CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202379Orig1s000

MEDICAL REVIEW(S)

Clinical Review

Application Type	NDA
Submission Number	202379
Submission Code	None
Letter Date	Dec. 20, 2010
Stamp Date	Dec. 23, 2010
PDUFA Goal Date	June 19, 2011
Efficacy Reviewer	Yangmin M. Ning, M.D., Ph.D.
Safety Reviewer	Paul Kluetz, M.D.
Cross-Discipline Team Leader	Ke Liu, M.D., Ph.D.
Review Completion Date	April 26, 2011
Established Name	Abiraterone
Used Trade Name	Zytiga™
Therapeutic Class	Androgen Biosynthesis Inhibitor
Applicant	Centocor Ortho Biotech, Inc.
Priority Designation	Priority Review

Formulation:	Tablets of 250 mg for oral administration
Dosing Regimen:	Four tablets of 250 mg administered orally once daily (b) (4) (b) (4) without food
Proposed Indication:	"*Zytiga ™ is indicated with prednisone for the treatment of metastatic* (b) (4) (b) (4) (b) (4) *(castration resistant prostate cancer) in patients who have received prior chemotherapy containing a* (b) (4)

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Commonly Used Abbreviations in this Review

Abbreviation	Full Term
AA	Abiraterone Acetate
ADT	Androgen Deprivation Therapy
AE	Adverse Event
AI	Adrenocortical Insufficiency
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AR	Androgen Receptor
BPI-SF	Brief Pain Inventory-Short Form
CRF	Case Report Form
CTC	Circulating Tumor Cell
DLT	Dose-Limiting Toxicity
GS	Gleason Score
ITT	Intent-to-Treat
MTD	Maximum Tolerated Dose
OS	Overall Survival
PFS	Progression Free survival
PR	Partial Response
PSA	Prostate specific antigen
RECIST	Response evaluation criteria in solid tumors

1. Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on the findings described in this clinical review of the new drug application for abiraterone acetate (NDA 202379), the reviewers recommend regular approval of abiraterone acetate for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) who have received prior chemotherapy containing docetaxel.

The recommended indication differs from the applicant's originally proposed indication: "*Zytiga™ is indicated with prednisone for the treatment of metastatic* (b) (4) *(castration resistant prostate cancer) in patients who have received prior chemotherapy containing a* (b) (4) ," (b) (4) However, it is necessary to point out that the evidence found in the NDA review suggests that pre-treatment with docetaxel is not a prerequisite for abiraterone acetate to exert its antitumor activity, most likely secondary to the distinctive mechanism of action of abiraterone acetate from that of taxanes (see Sections 2.6 and 4). (b) (4)

In accordance with the provision of 21 Code of Federal Regulations 201.57 (c), our recommended indication for approval reflects the study patient population in which the efficacy and safety of abiraterone acetate was demonstrated.

1.2 Risk Benefit Analysis

The key clinical study supporting this NDA is a randomized, double-blind, placebo-controlled, multicenter phase 3 trial that evaluated the efficacy and safety of abiraterone acetate in patients with mCRPC who had previously received docetaxel-based chemotherapy. 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). Treatment continued until disease 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.

Efficacy

The protocol pre-specified interim analysis of overall survival was conducted with 69% of the 797 deaths required for the planned final analysis. The results from this analysis demonstrated a statistically significant improvement in overall survival in patients on the abiraterone arm compared to patients on the placebo arm (HR=0.646; 95% CI: 0.543, 0.768; p<0.0001). The median survival for patients in the abiraterone arm was 14.8 months compared to 10.9 months for patients 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. This overall survival benefit was consistently demonstrated in an updated survival analysis (with 97% of the required number of events for final analysis), sensitivity analyses and subgroup analyses.

Evaluable secondary endpoints that demonstrated the antitumor activity of abiraterone in the phase 3 trial included percentage of patients with PSA declines of ≥50% and objective tumor response evaluated by Response Evaluation Criteria in Solid Tumors (RECIST criteria). Confirmed PSA responses, as assessed with the central laboratory measurement of PSA levels, were detected in 29% of patients on the abiraterone arm compared to 6% in patients on the placebo arm, favoring

abiraterone acetate treatment and corroborating the previously reported antitumor activity in the same patient population in two previous Phase 2 trials conducted by the applicant. In addition, confirmed radiographic tumor response rate, assessed by investigators according to the RECIST criteria in 48% of patients with measurable disease at baseline, was higher in the abiraterone acetate arm (14%) than in the placebo arm (3%). Although being exploratory in nature (see Section 6.1.5), these results demonstrated the anti-tumor activity of abiraterone acetate and appear to support its treatment effect on overall survival.

Safety

Adverse reactions reported in >10% patients and more frequently in the abiraterone acetate arm were joint swelling/discomfort, muscle discomfort, edema, hot flush, diarrhea, urinary tract infection and cough. The majority of these adverse reactions were Grade 1 or 2 according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.

Adverse reactions associated with mineralocorticoid excess occurred more frequently in the abiraterone acetate 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 acetate 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) 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.

Review of 4-month safety update to the NDA did not identify new safety signals.

Risk-Benefit Analysis

The efficacy and safety findings from the clinical review of this NDA provide substantial evidence for the effectiveness of abiraterone acetate in the intended patient population, in which treatment with abiraterone acetate was associated with a 3.9-month improvement in median overall survival compared to placebo, and with an acceptable toxicity profile. Distinct from myelosuppression-related toxicities (e.g., severe neutropenia and/or febrile neutropenia) that are commonly observed with cytotoxic chemotherapy in the treatment of patients with mCRPC (see Sections 2.2 and 2.6), abiraterone acetate has unique toxicities that include 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, the clinical reviewers concluded that abiraterone acetate treatment offers a highly favorable risk-benefit profile for patients with mCRPC who have received prior chemotherapy containing docetaxel.

1.3 Recommendations for Risk Evaluation and Mitigation Strategies

No safety signals were identified for REMS

1.4 Recommendations on Post Marketing Requirements/Phase 4 Commitments

No clinical requirements or commitments identified for the proposed indication.

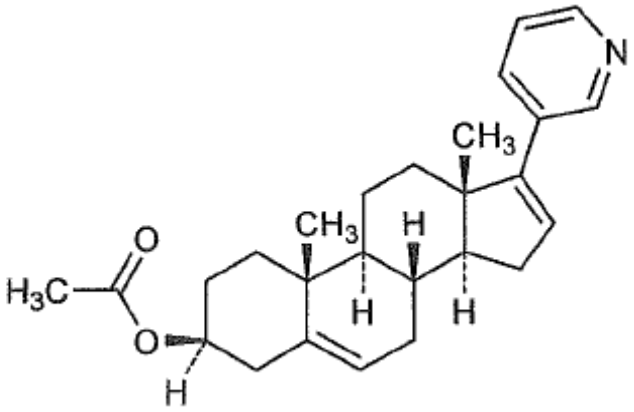
See clinical pharmacology review for relevant Post Marketing Requirements.

2 Introduction and Regulatory Background

2.1 Product Information

Abiraterone acetate (AA) is the active ingredient of ZYTIGA™ and is chemically designated as (3β)-17-(3-pyridinyl) androsta-5, 16-dien-3-yl acetate. Its molecular formula is $C_{26}H_{33}NO_2$, with a molecular weight of 391.55 and a structural formula shown in Figure 1:

Figure 1: Chemical Structure of Abiraterone Acetate



The inactive ingredients of the ZYTIGA™ tablets are lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate, magnesium stearate and colloidal silicon dioxide.

ZYTIGA™ (abiraterone acetate) is provided with white to off-white, oval-shaped tablets, debossed with "AA250" on one side. This means that each ZYTIGA™ tablet contains 250 mg of abiraterone acetate.

Abiraterone inhibits both 17-α-hydroxylase and C17, 20-lyase activities of CYP17 in the synthesis pathway of steroids, resulting in further decreases in testosterone levels in patients who have already been castrated. (See Section 4 for more information on its clinical pharmacology.

2.2 Currently Available Treatments for Proposed Indication

Cabazitaxel (Jevtana®) in combination with prednisone is the only product that received FDA approval in June 2010 for the treatment of patients with mCRPC who have previously received chemotherapy containing docetaxel. The treatment was associated with a 2.4-month improvement in median overall survival, but also associated with severe toxicities such as Grade 3 or 4 neutropenia, leukopenia, anemia, febrile neutropenia, diarrhea, fatigue, and asthenia. Other life-threatening or fatal cabazitaxel toxicities included neutropenic complications (febrile neutropenia and infection), renal failure, hematuria, and cardiac toxicity. Cabazitaxel treatment related deaths, occurring within 30 days of the last dose but not directly attributed to disease progression, were reported in about 5% of patients treated with cabazitaxel (see Section 2.6 for more information).

Other products such as mitoxantrone, ixabepilone, satraplatin or other platinum agents, used either alone or in combination, have been studied in the post-docetaxel mCRPC setting, but are associated with limited antitumor activity.[1] No survival benefit has been detected with any of the studied regimens, and none of them have been approved for the treatment of mCRPC progressing on or after docetaxel.

2.3 Availability of Proposed Active Ingredient in the United States

No abiraterone or abiraterone-like product is commercially available at the time of evaluation of this NDA.

2.4 Important Safety Issues with Consideration to Related Drugs

Drugs that affect the ability of the adrenal glands to synthesize corticosteroids and testosterone can lead to unique toxicities. When blocked for the synthesis of androgens and their precursors, the adrenal glands also reduce production of corticosteroids. This reduction decreases their feedback inhibition on ACTH, leading to increased ACTH produced by the pituitary gland, which in turn drives the over-production of mineralocorticoids in the adrenal glands (see Figure 2). Additionally, decreasing the ability to regulate corticosteroid production can lead to adrenal insufficiency. The clinical data for abiraterone acetate provided in this NDA submission did reveal adverse events (AEs) related to mineralocorticoid excess as well as adrenocortical insufficiency [see 7.3.4.2 Mineralocorticoid-related Adverse Events and 7.3.5.2 Adrenocortical Insufficiency (AI)].

Ketoconazole, a drug related to abiraterone acetate, targets androgen synthesis and has been investigated in the treatment of patients with CRPC[2]. However, its mechanism of action differs from abiraterone acetate in that it targets cytochrome P450 14a-demethylase. Adrenal insufficiency has also been seen with ketoconazole and hydrocortisone is co-administered with this compound. Some patients have difficulty tolerating ketoconazole-associated toxicities including nausea and vomiting, neuropathy, ototoxicity, malaise, fatigue and hepatic toxicity. Furthermore, ketoconazole has significant potential for drug-drug interactions.

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1 Aragon-Ching JB and Dahut WL (2007): Chemotherapy in Androgen-Independent Prostate Cancer (AIPC): What's next after taxane progression? *Cancer Ther*. 5(A): 151–160

2 Small EJ, Halabi S et al (2004): Antiandrogen Withdrawal Alone or in Combination With Ketoconazole in Androgen-Independent Prostate Cancer Patients: A Phase III Trial (CALGB 9583) Jour Clin Onc. 22(6): 1025-1033.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 1 summarizes key pre-submission regulatory activities with the FDA during the development of abiraterone for the treatment of progressive mCRPC following docetaxel-based chemotherapy.

Table 1: Key Regulatory Activities during Clinical Development of Abiraterone for Treatment of mCRPC following Docetaxel-Based Chemotherapy

Milestone	Date	Comments from clinical perspectives
Initial IND (71023)	Dec. 2005	Phase 1 studies determined a dosing schedule of 1000 mg QD for further clinical studies and Phase 2 studies showed antitumor activity, associated with a PSA response rate of approximately 50% in patients with mCRPC after docetaxel-based chemotherapy.
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 an overall survival benefit with abiraterone. The IDMC recommended unblinding of the study and crossing over of patients initially assigned on placebo. FDA concurred with 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 PDUFA date is on June 19, 2011.

2.6 Other Relevant Background Information

Docetaxel in combination with prednisone has been the standard of care for patients with metastatic castration-resistant prostate cancer (mCRPC) since its approval in 2004. The approval was based on the demonstrated efficacy from the TAX327 trial [3-4] that randomized 1,006 patients to compare two dosing schedules of intravenous docetaxel to a control arm of intravenous mitoxantrone with the following dosing schedules: docetaxel 75 mg/m^2 every 3 weeks (a cycle) for up to 10 cycles or docetaxel 30 mg/m^2 weekly for 5 weeks of every 6 weeks (a cycle) for 5 cycles, or mitoxantrone 12 mg/m^2 ever 3 weeks (a cycle) for up to 10 cycles. Oral prednisone 5 mg was administered twice daily in each treatment arm. The results showed a statistically significant improvement in the primary endpoint OS with the every three weeks docetaxel arm compared to the mitoxantrone arm (estimated median OS 18.9 vs. 16.5 months; HR = 0.76, 95% CI: 0.62 -0.94, stratified log-rank P-value = 0.009). In contrast, there was no statistically significant improvement in survival with the weekly docetaxel regimen when compared to the mitoxantrone arm (estimated median OS 17.4 vs. 16.5 months; HR = 0.91, 95% CI: 0.75 -1.11, P-value = 0.36). The rate of PSA declines of ≥50% from baseline, one of secondary endpoints, was 45% with the every three weeks docetaxel arm and 48% with the weekly docetaxel arm, respectively, as compared to a rate of 22% with the mitoxantrone arm, suggestive of better antitumor activity of docetaxel compared to mitoxantrone. However, the similar PSA response rates between the two docetaxel arms did not correlated with the above findings on improvements in survival, highlighting that PSA response rate alone is limited in its usefulness to predict survival. The approval evaluation of docetaxel considered the PSA response rate and other secondary endpoints as exploratory,[2] mainly because of no statistical plan pre-specified for adjustment for multiplicity or hierarchical ordering of secondary endpoints and the use of proportions of patients for the analyses conducted. Nevertheless, docetaxel-based chemotherapy is not a cure and the disease may progress through or after treatment with docetaxel. [1,5]

Treatment of mCRPC following progression on or after docetaxel-based treatment represented an unmet medical need until the approval of cabazitaxel in 2010.[6]

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3 Dagher R, et al (2004): Approval Summary: Docetaxel in Combination with Prednisone for the Treatment of Androgen-Independent Hormone-Refractory Prostate Cancer. *Clinical Cancer Research 10: 8147–8151*

4 Tannock IF, et al (2004): Docetaxel plus Prednisone or Mitoxantrone plus Prednisone for Advanced Prostate Cancer. *N Engl J Med 2004;351:1502-12*

5 Seruga B, et al (2011): Drug resistance in metastatic castration resistant prostate cancer. *Nat. Rev. Clin. Oncol.* 8, 12–23

6 Cabazitaxel Approval Reviews: at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/201023s000TOC.cfm Accessed as

Cabazitaxel is a novel taxane, active in docetaxel-resistant tumor cell lines and xerograft models. Its clinical efficacy was demonstrated in the EFC6193 trial designed to evaluate the efficacy and safety of cabazitaxel in patients with mCRPC previously treated with docetaxel-containing chemotherapy.[7] The trial randomized 755 patients 1:1 to receive either cabazitaxel 25 mg/m2 intravenously every three weeks in combination with prednisone 10 mg daily or a control: mitoxantrone 12 mg/m2 intravenously every three weeks in combination with prednisone 10 mg daily. Patients continued treatment until disease progression, death, unacceptable toxicity, or completion of 10 cycles of therapy. The primary endpoint was OS. Compared to the control, treatment with cabazitaxel showed a clinically significant improvement in OS [HR 0.70 (95% CI 0.59-0.83), log-rank p<0.0001], with a median survival of 15.1 with the cabazitaxel arm and of 12.7 months with the control, respectively. Key secondary endpoints that assessed antitumor activity of cabazitaxel in the post-docetaxel mCRPC setting also showed an improvement in PSA response rate in approximately 87% of the total patients (39.2 % on the cabazitaxel arm vs. 17.8% on the mitoxantrone arm) and an improvement in measurable disease by RECIST criteria per investigator assessment of approximately 53% of the total patients (14.4 % for cabazitaxel-treated vs. 4.4% for mitoxantrone-treated patients). For the similar reasons as mentioned above, these findings in the secondary endpoints were considered exploratory but were important in revealing cabazitaxel's antitumor activity. The investigator-assessed tumor response rates are included in the product's packaging insert.[8]

Both docetaxel and cabazitaxel are cytotoxic agents, associated with infusion reactions and frequent incidences of severe bone marrow suppression such as Grade 3 or 4 neutropenia, leukopenia, and anemia that frequently require aggressive supportive care or management. Both also can cause fatigue, mucositis, diarrhea, and asthenia. Life-threatening or fatal toxicities reported to be associated with these agents include neutropenic complications (febrile neutropenia and infection) and/or renal failure.

In addition to the two cytotoxic agents, development and studies of other targeted agents for effective treatment of mCRPC have been vigorous in the last decade. One important approach is to target androgen-androgen receptor (AR) signaling pathway.

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of April 3, 2011.

7 De Bono JS et al (2010) Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. *Lancet 376: 1147–54*

8 Cabazitaxel Label (2010): available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/201023lbl.pdf Accessed as of April 3, 2011.

Mounting evidence has shown that the progression of castration-resistant prostate cancer still depends on the activity of AR signaling pathway[9-10] despite castrate levels of androgens after androgen deprivation therapy (ADT) with either orchiectomy or continuous administration of a GnRH analog.

To date, three androgen-AR targeted agents have been investigated in Phase 3 trials in patients with mCRPC progressing on or after treatment with a docetaxel-containing regimen. Abiraterone is one of the three agents and its effectiveness and safety are evaluated in this NDA submission. The other two agents are TAK700 and MDV3100.

TAK-700 is similar to abiraterone in terms of mechanism of action, but appears to be a selective inhibitor of 17, 20 lyase activity.[11] The preliminary report[10] from a Phase 1-2 study showed that 11 of 26 patients treated with the agent had PSA reductions of ≥ 50%. Its efficacy and safety is being studied in a Phase 3 trial in patients with mCRPC that has progressed during or following docetaxel-based therapy (ClinicalTrials.gov ID: NCT00974311).

Unlike abiraterone and TAK700, MDV3100 is a new form of AR antagonist that blocks androgen binding to AR in the cytoplasm and interferes with the translocation of androgen-AR complex to the nucleus where the complex exerts its targeted gene transactivations and promotes tumor growth.[12] Its antitumor activity has been demonstrated in a Phase 1-2 study,[13] which showed a RECIST response rate of 22% and PSA declines of ≥50% from baseline in 56% of the study patients. A phase 3 trial is currently ongoing to assess its efficacy and safety in patients with mCRPC who have been previously treated with docetaxel-based chemotherapy (ClinicalTrials.gov ID: NCT00974311).

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9 Zhu W, et al (2010): Treatment of castration-resistant prostate cancer: updates on therapeutics targeting the androgen receptor signaling pathway *Am J Ther.* 17(2):176-81.

10 Attard G, et al (2009): Steroid hormone receptors in prostate cancer: a hard habit to break? *Cancer Cell 16: 458-62*

11 Dreicer R et al (2010): Safety, pharmacokinetics, and efficacy of TAK-700 in castration-resistant, metastatic prostate cancer: A phase I/II, open-label study. *The 2010 Genitourinary Cancers Symposium: Abstract 103.*

12 Tran C et al (2009): Development of a second-generation antiandrogen for treatment of advanced prostate cancer. *Science 324: 787-90*

13 Scher HI, et al (2010): Antitumour activity of MDV3100 in castration-resistant prostate cancer: a phase 1-2 study. *Lancet 375: 1437-46*

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality and integrity of the submitted data in the NDA were found adequate and acceptable. The applicant submitted safety and efficacy datasets in raw form for both the placebo-controlled pivotal phase 3 clinical trial and the integrated safety population, allowing the reviewers to verify efficacy and safety findings. Datasets in general corresponded to submitted CRFs and information contained in the datasets was found to be consistent. However, some clinical or statistical issues, as listed below, were identified during the review and conveyed to the applicant to clarify. All issues had been addressed and resolved satisfactorily.

- Your Dataset "FU" contained information collected from 848 study subjects. We understood that there were 276 subjects actively on study at the time of the interim analysis. This means that 71 study subjects who were supposed to be included in Dataset FU had no follow-up information in the dataset after discontinuation of study treatment. Please specify where the follow-up information for the 71 patients can be found in your submission or explain why if the information was not submitted or missed.
    - *Applicant responded that those patients had not reached their first scheduled FU visit (scheduled every 3 months) as of the clinical data cutoff.*

- Provide reasons as to why survival follow-up information was not available for the following 5 subjects who were censored within 2 months after randomization: Subject ID 124-0008, 600-0035, 604-0023, 126-0003, and 615-0002.
    - *Applicant responded that those patients were censored at the time of analysis because one patient withdrew consent and four patients did not receive study medication.*

- For Study Patient 116-0001, an abiraterone dose modification occurred directly from 1000 mg daily to 250 mg daily according to the information contained in both CRF and Dataset EX. There were no intermediate dose reductions between the above two doses. Please verify the accuracy of the reported dose reduction information in this patient and/or provide clinical reasons as to why this patient had an abrupt 75% dose reduction, which appeared not consistent with the protocol specified dosing modification plan.

- *Applicant responded that the study site updated the information for the patient, who did not undergo a dose reduction but rather had study agent withheld due to an adverse event.*

- For Study Subject 116-0005, the reported total dose of previous docetaxel use was 58492 mg in the CRF and Dataset CONMED. That dose seems implausible for the patient based on his BSA of 2.23 M^2 and the documented docetaxel treatment period between 2/21/06-2/5/08. The reviewer estimated that the total docetaxel dose might be 5849.2 mg. Please clarify what was the total docetaxel dose the patient actually received before enrollment.
  - *Applicant responded that the site was queried and updated the cumulative docetaxel dose for Subject 116-0005's 35 Cycles to 5850.7 mg on 23 MAR 2011. The previous value of 58492 mg was due to a transcription error.*

- We note that 2 patients in the Phase 3 trial and 3 patients in the pooled Phase 1/2 safety data experienced adrenal insufficiency. We have been unable to locate the narratives for these events. Please direct us to these narratives or submit narratives if they do not exist.
  - *Applicant provided a narrative for one patient and specified the location of narratives for the other four patients in the submission.*

- During FDA inspections of site #600 at Royal Marsden Hospital (Dr. de Bono PI) and site #601 at University College Hospital (Dr. Harland PI), it was noted that the data with respect to adverse event reporting and causality attribution as recorded in source documentation and Case Report Forms for all subject records reviewed did not match the respective data listings submitted to the NDA for Study COU-AA-301. 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.
  - *Applicant provided clarification as to how the FDA's Division of Scientific Investigation- (DSI) identified systematic error regarding the attribution of adverse events to either abiraterone or prednisone*

occurred. The clinical safety review verified the clarification and found that the AE data listings submitted to the IND for the 5 sites that the DSI used during the inspections were different than the AE data listings submitted to the NDA. The column headings Causality (Abiraterone) and Causality (Prednisone/Prednisolone) were reversed in the IND submission due to a programming error. The safety reviewer also verified that the resubmitted corrected IND AE data listings matched those in the NDA submission. The DSI reviewer confirmed that the discrepancy between AE datalisting and the source documents at the sites could be explained by this programming error for the IND datalisting.

3.2 Compliance with Good Clinical Practices

Sites that participated in COU-AA-301 enrolled from 1 to 49 men per site. Five sites listed in Table 2 below were identified for inspection after careful considerations of efficacy and safety information as well as protocol violations reported for each site.

The reasons for having 5 sites inspected were as follows: a) Regulatory action for this application depends solely on the results from a single Phase 3 trial halted prior to its completion and planned final analysis due to the IDMC recommendation that the pre-specified interim analysis had demonstrated an improvement in overall survival in the abiraterone treatment arm compared to placebo arm; b) the Applicant identified that original sites monitoring was inadequate, which then necessitated their undertaking an extensivere-monitoring program to ensure the reliability of data submitted.

Table 2: DSI Inspected Sites

Site # (Name,Address, Phone number, email, fax#)	Number of Subjects	Median OS at Site (Range)
Site #139 Christopher J Logothetis, M.D. Cancer Center Dept. of Genitourinary Medical Oncology, 1155 Pressler St., Unit 1374 Houston, TX 77030 Phone: 713-563-7210 Fax: 713-745-9101 Email: clogothe@mdanderson.org	48	433 days (87, 529+)
Site #159 Mansoor Saleh, M.D. 1835 Savoy Drive Suite 300 Atlanta, GA 30341 Phone: 770-496-9403 Fax: 770-496-9497 Email: mansoor.saleh@gacancer.com	15	267 days (60, 432+)
Site #600 Johann de Bono, M.D.* Royal Marsden Hospital NHS Foundation Trust, Downs Road, Sutton, Surrey, SM2 5PT United Kingdom Phone: 44 2087224028 Fax: 44 2086427979 Email: jdebono@icr.ac.uk	49	433 days (2+, 529+)
Site #601 Stephen Harland, M.D. MB BX, FRCP 18 NE (55, 459+) 13 6 University College Hospital 1st Floor Central, Oncology 250 Euston road, London NW1 2PQ United Kingdom Phone: 44 207 380 9287 Fax: 44 207 380 9055 Email: stephen.harland@uclh.nhs.uk	18	NE (55, 459+)
Site #701 Cora Sternberg, M.D. Hospital San amillo Forlanini O.U. Medical Oncology New pavilions, 4th floor Circonvallazione Gianicolense 87 Rome, 00152 Italy Phone: 39 06 58704262 Fax: 39 06 663 0771 Email: csternberg@scamilloforlanini rm.it	17	500 (45, 500)

Inspection of the sponsor was also conducted.

The information from DSI as of April 14, 2011 indicated that the inspections of all sites have been completed and that no issues impacting data reliability were identified. Some minor deviations were recognized but were considered not significant in terms of data integrity. In the final inspection summary review dated April 15, 2011, the DSI recommended that the submitted data be considered reliable in support of the proposed indication. Please see the detailed final DSI summary of inspection findings in the approval package.

In addition, FDA's Office of Compliance made an overall recommendation "acceptable" from establishment evaluation.

3.3 Financial Disclosures

Disclosure of financial interests of the investigators involved in the clinical studies supporting this NDA was submitted in the FDA form 3454. The disclosure was certified for the applicant by Robyn Sterner, Pharm.D, North American Regional Therapeutic Leader of Johnson & Johnson L.L.C. Based on the financial interests collected, no investigator in the key trial COU-AA-301 disclosed a proprietary interest or a significant equity in the sponsor, or was the recipient of significant payments of other sorts. Financial disclosure information was not obtainable from eight associate investigators.

The primary endpoint for the key trial was overall survival, which apparently minimized the potential effects of financial conflicts, if any, on the outcome of the trial.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC review disclosed an outstanding deficiency related to dissolution acceptance criteria. This deficiency, identified by the ONDQA reviewer, was addressed satisfactorily with the applicant's agreement to the Agency's proposed dissolution specification and updated the specifications table. The ONDQA review concluded that

this NDA is acceptable from the Biopharmaceutics perspective and recommended approval from the CMC perspective.

4.2 Product Risk Management Plan

None

4.3 Preclinical Pharmacology/Toxicology

No clinically relevant issues reported.

4.4 Clinical Pharmacology

Abiraterone acetate is a prodrug that is converted after adsorption to abiraterone, a 17 α-hydroxylase/C17,20-lyase (CYP17) inhibitor that exerts its antitumor activity by targeting two enzymatic steps critical for the synthesis of testosterone and thereby decreasing levels of testosterone further in patients who have been already castrated. Figure 2 shows a schematic diagram illustrating the mechanism of abiraterone action.

Please refer to the final product packaging insert for detailed clinical pharmacology information.

14 Adapted from Attard G. et al (2008): Phase I Clinical Trial of a Selective Inhibitor of CYP17, Abiraterone Acetate, Confirms That Castration-Resistant Prostate Cancer Commonly Remains Hormone Driven. J. Clin. Oncol. 26:4563-71

During the review, the clinical pharmacology reviewers raised a question about whether it is clinically meaningful to investigate the pharmacokinetics of abiraterone in individuals with severe hepatic impairment. Since patients with moderate or severe hepatic dysfunction were excluded from clinical studies of abiraterone, the clinical team considered it necessary to understand the pharmacokinetics in individuals with severe hepatic impairment, which will help determine a safe abiraterone acetate dose for patients with mCRPC who have severe hepatic impairment but who may benefit from abiraterone acetate. A trial in patients with severe hepatic impairment will be conducted as a post-marketing requirement.

With regard to use of abiraterone in patients with moderate hepatic impairment, the clinical pharmacology reviewers recommended a starting abiraterone dose of 250 mg once daily. This dosing schedule is based on the PK results from a study of a single dose in individual with moderate hepatic impairment. Frequent monitoring of hepatic function during treatment was also recommended. From safety perspective, this recommendation would allow patients with moderate hepatic impairment to be treated with abiraterone acetate.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

Clinical studies related to use of abiraterone acetate for the proposed indication in the current NDA are listed in Table 3. Important information about their study phase, design and major findings is also summarized. Clearly, the key study that forms the basis to support the proposed indication is COU-AA-301.

No additional clinical studies were submitted as supplemental evidence during the review.

Table 3: Clinical Studies in Support of the Abiraterone Acetate NDA

Phase	Study ID (Period)	Study Population	Key Objectives	Key Design Elements	Major Findings
Phase 1/2*	COU-AA-001 (11/2005-11/2008)	Patients with chemotherapy-naïve CRPC with a rising PSA (N=54)	Safety and tolerability evaluation; Dosing determination; PK/PD	Open-label, dose-escalation (250, 500, 750, 1000, 2000 mg) daily for DLT evaluation in the first 28 days.	No DLTs at all dose levels studied Observed important AEs: hypokalaemia, hypertension, and peripheral edema.

Phase	Study ID (Period)	Study Population	Key Objectives	Key Design Elements	Major Findings
			analyses	Continued daily dosing in an extension cohort.	PSA declines of ≥50% from baseline observed in 60% of the patients A significant difference observed between the administration of drug with or without food
	COU-AA-002 (07/2006-01/2010)	Patients with CRPC with or without prior ketoconazole therapy (N=66)	MTD Determination; Safety and tolerability evaluation PK/PD analyses	Open-label, dose-escalation (250, 500, 750, 1000 mg) for MTD determination; Evaluation of the need for supplementation with corticosteroids during therapy with abiraterone acetate	No MTD determined because of no DLTs observed. Frequent AEs: hypertension, hypokalaemia Confirmed PSA declines of ≥50% from baseline observed at week 12 in 58% of all the patients and in 47% of the patients with prior ketoconazole therapy
Phase 2	COU-AA-003 (11/2006-01/2010)	patients with metastatic advanced prostate cancers who failed docetaxel-based chemotherapy (N=47)	Anti-tumor effects of abiraterone acetate in the docetaxel treated mCRPC	Open-label, single arm study of once daily abiraterone acetate at 1000 mg in combination with prednisone (5 mg twice daily) or dexamethasone (0.5 mg once daily) Treatment continued through 12 cycles (28 days a cycle) or until documented disease progression, lack of disease response after 6 evaluable cycles of treatment, or unacceptable toxicity	In the 47 patients, 45% of them had confirmed PSA decreases from baseline of ≥50%; 15% had a confirmed decrease in PSA from baseline of ≥90%. The most frequently reported adverse event of interest: hypokalemia, peripheral edema, and hypertension.

Phase	Study ID (Period)	Study Population	Key Objectives	Key Design Elements	Major Findings
				Responding patients allowed to continue after 12 cycles in UK (an extension study)	
Phase 2	COU-AA-004 (06/2007-01/2008)	Patients with advanced (metastatic) CRPC who have failed androgen deprivation and docetaxel-based chemotherapy (N=58)	Antitumor effects and safety of abiraterone acetate in combination with prednisone	Open-label, single arm study of once daily abiraterone acetate at 1000 mg. Treatment continued through 12 cycles (28 days a cycle) or until documented disease progression or unacceptable toxicity	Confirmed PSA declines of ≥50% from baseline observed at week 12 in 38% of the 58 patients; Three patients (6%) had PR in measurable disease. Commonly observed AEs with an incidence rate of >20%: Fatigue, peripheral edema back pain, constipation, AST elevation, anemia, and arthralgia. Adverse event of special interest (fluid retention or edema, liver function abnormalities, cardiac disorders, hypertension, and hypokalemia) observed in 62% of the patients. The majority of the AEs were <Grade 3 in severity.
Phase 3	COU-AA-301 (05/2008-cutoff 01/2010)	Patients with mCRPC who have failed docetaxel-based chemotherapy (N=1195)	To assess whether abiraterone acetate improves overall survival in men with progressive mCRPC after 1 or 2 chemotherapy regimens, one of which had to contain docetaxel	Randomized (2:1), double-blind, placebo-controlled trial comparing the survival of patients treated with abiraterone at 1000 mg daily or placebo in combination with prednisone at 5 mg twice daily. Treatment continued until documented disease progression,	The protocol prespecified interim analysis showed a significant improvement in overall survival with abiraterone compared with placebo (HR=0.646; 95% CI: 0.543, 0.768; p<0.0001). The median overall survival in the abiraterone arm was 14.8 months compared to a median overall survival of 10.9 months in the placebo group arm. Key safety information: the most commonly reported AE was fatigue

Phase	Study ID (Period)	Study Population	Key Objectives	Key Design Elements	Major Findings
				unacceptable toxicity, or for initiation of new antitumor therapy.	in both arms. Compared to the placebo arm, patients in the abiraterone arm had more incidences of peripheral edema, hypokalemia, hypertension, and muscular discomfort. (see detailed review findings in Sections 6 and 7)
* The applicant's described Phase 2 part represented an extension cohort to assess the activity of continuous daily abiraterone acetate dosing.					

5.2 Review Strategy

The review focused on the key study that supports the proposed use of abiraterone acetate in patients with mCRPC who have received prior docetaxel-based chemotherapy. The reviewers evaluated the submitted data and study report, assessed both accuracy and internal consistency of the information contained in relevant datasets against information documented in case narratives and/or case report forms, and verified survival events or censoring with information across all relevant datasets. Discrepancies or issues indentified during the review were investigated and conveyed to the applicant for clarification and/or correction. Newly submitted information or data during the review was also examined or verified against that originally submitted information, if applicable, to determine its acceptability, consistency and reliability. The reviewers, with the help of statistical review team, conducted independent analyses of the efficacy and safety of abiraterone acetate in appropriate analysis populations, mainly including ITT population, subgroup populations, and safety population.

The reviewers also examined the consistency of abiraterone acetate's antitumor activity demonstrated between the above key study and the early Phase 2 studies in patients with mCRPC who have received prior docetaxel-based chemotherapy. Relevant to the proposed indication for abiraterone acetate, the reviewers also scrutinized numerous literature publications or review reports on product(s) approved or being developed for the same indication, and intended to better evaluate and understand the clinical meaningfulness of abiraterone acetate in the treatment of mCRPC following docetaxel-based chemotherapy.

5.3 Discussion of Individual Studies

The phase 3 trial COU-AA-301 is the key study supporting the efficacy claim for abiraterone in this NDA. Its design, conduct, and results are reviewed comprehensively in Sections 6 and 7.

The other Phase 1 and 2 studies listed in Table 3 provided support for the dosing schedule of abiraterone used in the key study as well as the scientific justification for investigating the efficacy and safety in patients with mCRPC following docetaxel-based chemotherapy.

As shown in Table 3, the two Phase 1 studies, COU-AA-001 and -002, were designed to evaluate the tolerability and to determine the MTD in patients with chemotherapy-naïve CRPC, but did not have an MTD defined because of no DLTs observed at the studied dose levels (250, 500, 750, 1000, 2000 mg daily) within the first 28 days. Based on the finding along with the pharmacokinetics and its effects on adrenal steroid synthesis, a dosing schedule of 1000 mg daily for abiraterone acetate was selected for further clinical studies.

Using the selected 1000 mg daily dosing schedule, the two open-label, single-arm Phase 2 studies as shown in Table 3 explored the antitumor activity and safety of abiraterone acetate in patients with progressive mCRPC following docetaxel-based chemotherapy. The results as summarized in the Table 3 showed that in each study, approximately 40% of the patients had confirmed PSA declines of ≥50% from baseline and that a few patients with measurable disease also had PR based on the RECIST criteria as assessed by the investigator. These results, obtained from approximately 100 patients, suggested that abiraterone acetate is active to exert its antitumor activity in patients with progressive mCRPC who have received prior docetaxel-based treatment. Nevertheless, these antitumor activity results are not considered as key evidence to demonstrate the efficacy of abiraterone in this disease setting. In addition, the two Phase 2 studies revealed adverse reactions of interest such as hypokalemia, hypertension, and peripheral edema, which were likely secondary to abiraterone acetate treatment-induced mineralocorticoid excess.

6 Review of Efficacy

6.1 Indication

The initial proposed indication for abiraterone acetate in this NDA submission was as follows: "Zytiga™ is indicated with prednisone for the treatment of metastatic (b) (4) (castration resistant prostate cancer) in patients who have received prior chemotherapy containing a (b) (4)

Reviewer's Comments: (b) (4)

6.1.1 Methods

For the proposed indication for abiraterone acetate in the current NDA, the efficacy review focused on examining the results from the randomized, placebo-controlled study (COU-AA-301).

The reviewers evaluated the original study protocol and its amendments during study to critically assess whether efficacy or safety assessments were affected by the amendments (See the details below in this Section). To evaluate the reliability of important efficacy endpoints, especially for the primary endpoint, the reviewers randomly examined the accuracy of information between CRFs and relevant datasets and verified the completeness of the datasets and analyses reported by the applicant. Discrepancies identified during the review were conveyed to and clarified with the applicant. The efficacy reviewer also participated in clinical inspection of one study site in the USA and scrutinized the consistency of the reported data with the documented clinical information at the study site.

Factors that may affect efficacy analyses and results interpretation, such as protocol deviations, adjustment for multiplicity, central assessment of efficacy endpoints, and percentage of the patients in each analysis were also considered as appropriate based on the protocol and applicant's study report.

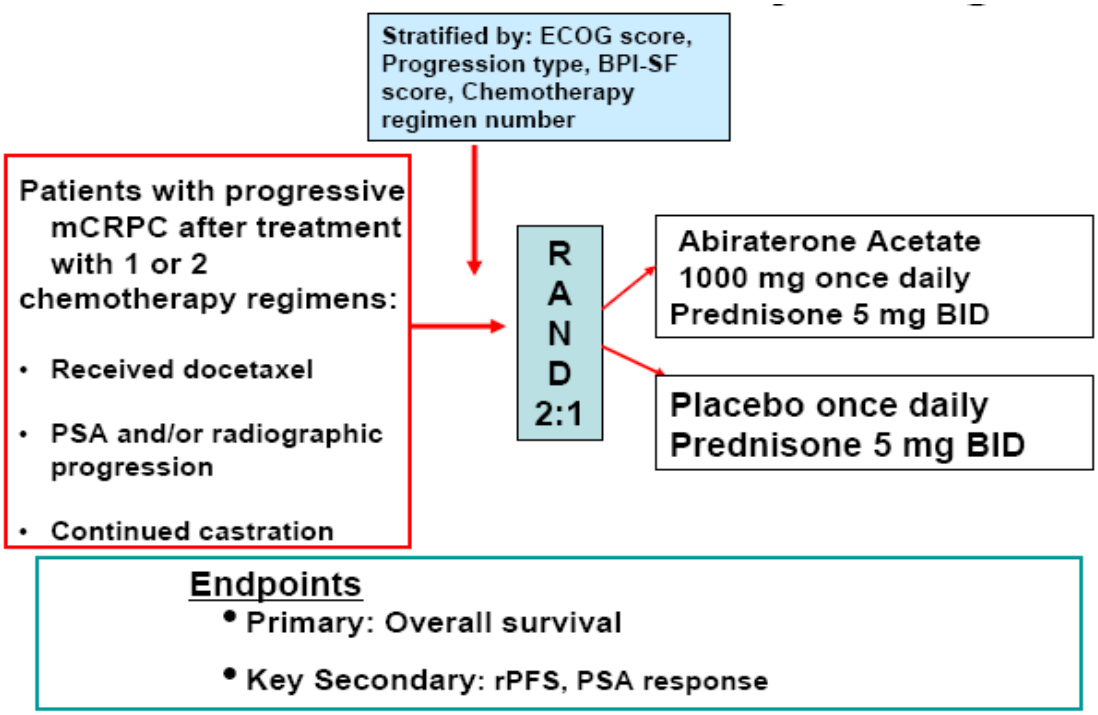
Differences in data tabulations or analyses between the review and the applicant's study report were specified and discussed with the statistical reviewers assigned for the NDA. Sensitivity analyses were also conducted whenever indicated to assess the reliability of the study results and/or conclusions. Importance and clinical implications of the efficacy results were also evaluated and discussed in reviewer's comments with reference to the current understanding and appropriate management of mCRPC.

Protocol Review for Study COU-AA-301

Study Design

COU-AA-301 was a randomized, double-blind, placebo-controlled, multicenter Phase 3 trial to compare the efficacy and safety of once daily dosing of abiraterone acetate plus prednisone with placebo plus prednisone in patients with mCRPC whose disease had progressed on or after 1 or 2 chemotherapy regimens, one of which was docetaxel-based. Patients had to have documented evidence of disease progression by PSA and/or radiographic scans despite castrate levels of testosterone. Consented eligible patients were stratified according to four factors, as shown in Figure 3, 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 or placebo orally once daily plus prednisone 5 mg orally twice daily. The primary endpoint was overall survival. Treatment continued until patients experienced unacceptable toxicity, disease progression as defined in the protocol, death, or withdrawal. An external IDMC was formed prior to the study initiation to monitor the safety during study and evaluated efficacy and safety results at the time of the protocol-specified interim analysis. Figure 3 summarizes the study design and its key elements.

Figure 3: Study Design of COU-AA-301



Note: Placebo tablets matching the abiraterone tablets

Protocol Amendments

The study was initiated in May 2008. Since then, there were 3 protocol amendments as summarized in Table 4.

Table 4: Protocol Milestones and Amendments during COU-AA-301

Milestone	Date	Major Changes or Comments
Original Protocol	02/07/2008	Status post Special Protocol Assessment
Protocol Initiation	05/08/2008	First patient enrolled
Amendments 1	07/30/2008	• Clarification of safety reporting after completion of treatment phase of the study • Clarification of how to manage study treatment in patients with hypokalemia, hypertension, edema/fluid retention, and non-mineralcorticoid-based side effects
Amendment 2	01/12/2009	• Provided guidance to investigators on dose reduction and management of study drug-related hepatotoxicity

Milestone	Date	Major Changes or Comments
		• Increase routine monitoring of liver function tests during the first 12 weeks • Provide guidance to investigators on dose reduction and patients management of the study drug-related events
IDMC Recommendation	8/20/2010	• Unblinding the study after the pre-specified interim analysis showed a survival benefit with abiraterone • The data cutoff for the interim analysis was in January 2010.
Amendment 3	08/26/2010	• Termination of the blinded portion of the study • Allowed patients in the placebo arm to receive abiraterone acetate provided that they met the criteria specified in the amended protocol • Continuation of treatment until disease progression as determined by the investigator
Updated survival analyses	09/20/2010	• Unplanned, but with 97% of the planned number of deaths for final analysis
NDA-submission	12/20/2010	• Priority Review designated

Reviewer's Comments: *The above listed amendments had no significant impact on the assessment of the primary endpoint. Instead, most of the amendments helped better manage adverse reactions associated with study agent.*

Endpoints

Primary:

- To compare overall survival of patients treated with abiraterone acetate plus prednisone to those treated with placebo plus prednisone.

Key Secondary:

- Proportion of patients achieving a PSA decline ≥50% according to protocol-specific PSA Working Group (PSAWG) criteria
- Time-to-PSA progression based on protocol-specific PSAWG criteria
- Proportion of patients with objective tumor response by modified RECIST
- Progression-free survival (PFS) based on imaging studies

Reviewer's Comments: *Other secondary endpoints measured but not listed above and not evaluated in the review included proportion of patients experiencing pain palliation using BPI-SF and analgesic score, time to pain progression, time to first skeletal-related event. Reasons for not including them in the review are as follows: a) only a portion (<50%) of patients had data for the endpoints not listed as key secondary endpoints; b) measuring the endpoints was less objective, and their regulatory acceptability had not been evaluated by the Agency in terms of reliability, validity, ability to detect change, and interpretability in the study patient population; c) since use of bisphosphonate is standard of care for patients with mCRPC and was allowed prior to or during the study (Section 6.1.3 shows that 48% of the patients used bisphosphonates), its effect on the bone can considerably affect interpretation of skeletal-related events in relation with abiraterone acetate; d) no pre-specified plan for multiple comparisons adjustment; e) changes in these endpoints do not constitute a basis for marketing approval or disapproval of abiraterone acetate for the proposed indication.*

In contrast, the above listed key secondary endpoints were based on objective laboratory or radiographic assessments and will be evaluated or discussed further in the review (Section 6.1.5). One laboratory based endpoint "Proportion of patients achieving a decline in CTCs/7.5ml to less than 5" was discussed below in Efficacy Assessments but not evaluated in Section 6.1.5 because of concerns about its definition and reproducibility as well as a small portion (~30%) of data availability (see Efficacy Assessment).

Nevertheless, these objective secondary endpoints are considered exploratory because of the lack of validation, no central independent review, no adjustment for multiplicity, and/or only a small portion of patients evaluable for some of the endpoints.

Key Inclusion Criteria

- Patients with progressive mCRPC who had met all of the following:
    - Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell histology
    - Had received 1-2 cytotoxic chemotherapy regimens for mCRPC and one of the regimens had contained docetaxel. Docetaxel-containing chemotherapy used more than once was considered as one regimen.
    - Documented prostate cancer progression as assessed by the investigator with PSA progression according to PSAWG criteria or radiographic progression in soft tissue or bone regardless of PSA levels
    - Continued androgen deprivation with serum testosterone < 50 ng/dL (< 2.0 nM)
- An ECOG performance score of ≤2
- Adequate bone marrow (hemoglobin ≥ 9.0 g/dL independent of transfusion, and platelet count ≥100,000/μL) and renal function (serum creatinine < 1.5 x ULN or a calculated creatinine clearance ≥ 60 mL/min)
- Serum albumin ≥ 3.0 g/dL
- Serum potassium ≥ 3.5 mmol/L
- Willing and able to provide written informed consent

Exclusion criteria

- Serious or uncontrolled co-existent non-malignant disease, including active and uncontrolled infection
- Known brain metastasis
- History of gastrointestinal disorders (medical disorders or extensive surgery) which may interfere with the absorption of the study drug
- Prior use of ketoconazole for prostate cancer
- Active or symptomatic viral hepatitis, chronic liver disease, or abnormal hepatic function test results of > Grade 1 [Serum bilirubin ≥ 1.5 x ULN (except for patients with documented Gilbert's disease), AST or ALT ≥ 2.5 x ULN (for patients with known liver metastasis, AST or ALT ≤ 5 x ULN is allowed)]

- History of pituitary or adrenal dysfunction
- Uncontrolled hypertension or major cardiovascular conditions or LVEF < 50% at baseline
- Prior therapy with CYP17 inhibitor(s) or investigational agent(s) targeting the androgen receptor for metastatic prostate cancer
- Not willing to comply with the procedural requirements of this protocol

Reviewer's Comments: *The above eligibility criteria were acceptable for the intended study population. On the other hand, the efficacy and safety of abiraterone acetate in patients meeting the exclusion criteria remain unknown. Therefore, it is important to realize that the results described in this review, especially the risk-benefit profile of the product, may not be extrapolated to patients who have had a condition listed in the exclusion criteria.*

Study Conduct

Upon completion of all required screening assessments, as shown in Table 5, eligible patients were stratified according to baseline ECOG performance status (0-1 versus 2), presence or absence of pain [a brief pain inventory-short form (BPI-SF) score for worst pain of at least 4 versus < 4], number of prior chemotherapy regimens (1 versus 2), and type of prostate cancer progression at entry (PSA progression only versus radiographic progression in bone or soft tissue regardless of PSA levels).

Randomization was carried out using a centralized Interactive Web Response System (IWRS) that assigned each patient a unique patient identification number and a treatment number at randomization. The unique identification number determined patient's treatment assignment and was used on all study-related documents including case report forms (CRFs). The treatment number served as the link between a patient's CRF and blinded treatment group assignment. All study persons were blinded to the patient treatment assignments and all necessary precautions such as not reporting post-treatment values of testosterone, steroid metabolites, PK, and CTCs to the investigators or patients, were taken to ensure that blinding was adequately maintained throughout the study. Treatment continuation and clinical assessments were according to the protocol pre-specified study calendar shown in Table 5.

Table 5: Study Calendar of COU-AA-301 (Adapted from Applicant)

		Treatment Phase						Follow-Up Phase
Evaluation	Screening Day -14 to 1	Cycle 1 Day 1 [a]	Cycle 1 Day 15	Cycle 2, 3, 5, 6, 8, 9, 11, 12 Day 1[a]	Cycle 2 and 3 Day 15	Cycle 4, 7, and 10 Day 1[a] and at Treatment Discontinuation[b]	End of Study Visit[c]	Q3 Months up to Month 60
Procedures								
Signed consent form[d]	X							
Medical history, prior prostate therapies	X							
FACT-P		X				X[e]		
BPI-SF, analgesic usage	X	X	X	X		X		
BFI, Fatigue	X	X	X	X		X		
Physical examination and weight[f]	X		X	X		X	X	
Vital signs[f]	X	X	X	X		X	X	
ECOG	X	X	X	X		X	X	
12-lead ECG[g]	X					X	X	
MUGA scan or cardiac ECHO	X					X[h]	X	
Dosing compliance			X	X		X	X	
Concomitant medications	X	X	X	X		X	X	
Adverse events	X[i]	X	X	X		X	X[j]	
Laboratory Assessments								
CBC	X	X		X		X	X	
Coagulation factors - PT/PTT (INR)	X	X	X	X		X	X	
Serum chemistry, electrolytes[r]	X	X	X	X	X	X	X	
Fasting glucose[k]	X					X	X	
Serum lipids	X					X	X	
PSA[l]	X	X				X	X	
Serum testosterone and other androgens	X					X		
Urinalysis (dipstick)	X							
CTC assessments	X	X		X[m]		X[m]		

		Treatment Phase						Follow-Up Phase
Evaluation	Screening Day -14 to 1	Cycle 1 Day 1 [a]	Cycle 1 Day 15	Cycle 2, 3, 5, 6, 8, 9, 11, 12 Day 1[a]	Cycle 2 and 3 Day 15	Cycle 4, 7, and 10 Day 1[a] and at Treatment Discontinuation[b]	End of Study Visit[c]	Q3 Months up to Month 60
Tumor Assessments								
CT / MRI /other imaging procedure Chest x-ray[n]	X					X		
Bone scan[n]	X					X[o]		
Disease progression assessment						X		
Overall survival								X[p]
Pharmacokinetics[q] and Additional ECG Sampling at Select Study Centers								
Predose pharmacokinetics		X		X[q]				
In-clinic dosing of study treatment for pharmacokinetics[q]		X		X				
1st postdose pharmacokinetics		X		X[q]				
2 hr postdose ECG[g]		X						
2nd postdose pharmacokinetics		X						

a If subjects continued on study without disease progression or discontinuation of treatment beyond Cycle 12, they were to continue visit assessments as indicated for every third cycle starting with Cycle 13 and were to restart to every first and second cycle visit assessments following.
b The treatment discontinuation visit could occur at any scheduled or unscheduled visit, when applicable. At this visit,
documentation to confirm progressive disease was required.
c The end-of-study visit was to be scheduled to collect safety assessments 15 to 28 days after the subject stopped treatment. Subjects were to enter the Follow-up Phase at that time.
d Written informed consent must have been obtained within 30 days prior to Cycle 1 Day 1.
e After Cycle 10, assessments were to be collected every 6 cycles up to the treatment discontinuation visit.
f Weight was to be recorded at every visit. Height was to be measured at the screening visit only. Vital signs were to include upright blood pressure, heart rate, respiratory rate, and oral or aural body temperature.
An ECG should have been obtained prior to the Day 1 visit, every 3 cycles, and at the end-of-study visit except for subjects in the pharmacokinetic sampling portion of the protocol who also were to have ECGs collected at approximately 2 hours postdose on Cycle 1. ECGs were not to be obtained when serum potassium was <3.5 mg/mL. Hypokalemia was tobe corrected prior to ECG collection.
h A MUGA scan was to be obtained at baseline and at the end -of-study visit in all subjects. Subjects who had prior mitoxantrone were also to have a MUGA scan at every 3 cycles. A cardiac ECHO could be used if MUGA was not available or when ECHO was standard of care at the study site.
I Pretreatment SAEs were to be reported from the time a subject signed an informed consent form up to Day 1 treatment administration.
j Adverse event follow up was required for 30 days following last dose to determine if any new or ongoing drug-related AE or any SAE regardless of relationship to drug had occurred. Follow-up could have been conducted by sites via telephone attempts and were to be documented in source notes.
k Fasting glucose could have been measured as part of the chemistry panel run by the central laboratory when possible or as a pre-test run by the site local laboratory to the full chemistry panel if a subject had not fasted. If the local laboratory was used, the results were to be collected on the supplemental laboratory CRF.
l If a subject underwent a DRE, PSA was to be sampled prior to the DRE.
m Blood samples for assessment of CTCs were to be collected from subjects at select centers at screening, Cycle 1 Day 1, and then Cycle 2, 3, and 4 Day 1, and at the time of disease progression. CTC enumeration was to be run on all samples collected; molecular characterization was to be performed on samples when subjects provide a signed informed consent form for molecular testing.
n Scans (CT, MRI, and bone) performed up to 28 days prior to Study Day 1 could be used for baseline assessments. If a

status of partial or complete response was made, changes in tumor measurements had to be confirmed by repeat assessments that were to be performed no less than 4 weeks after the criteria for response were first met. If a chest CT or MRI was performed as part of the imaging evaluation, then the chest x-ray was optional and was not required to be performed.
o Bone scans after screening were to be conducted as part of the response assessment.
p Overall survival could be collected by telephone interview or chart review.
q Selected study centers only: Pharmacokinetic blood samples were to be collected pre- and postdose on Cycle 1 Day 1 (2 postdose samples on Cycle 1), Cycle 2, and Cycle 5. Subjects were asked to withhold their daily dose and take study treatment following the pre-sample pharmacokinetic collection. Additional ECG assessments were to occur at approximately 2 hours postdose on Cycle 1.
r At Cycle 2 Day 15 and Cycle 3 Day 15, chemistry was limited to liver function tests: AST, ALT, alkaline phosphatase, and total bilirubin.

Adapted from Page 35 of the study report

Treatment Plan

Randomized patients received 4 tablets of study agent, either abiraterone acetate or placebo orally at least 1 hour before a meal or 2 hours after a meal any time up to 10 pm every day. Patients also took 5-mg prednisone twice daily. Each treatment cycle consisted of 28 consecutive days.

Dose-reduction secondary to an adverse reaction was allowed but only up to 2 dose reductions. Each dose reduction consisted of removal of one tablet of study agent. Detailed dose delay and modifications for adverse reactions related to mineralocorticoid excess or hepatic dysfunction were pre-specified in the protocol. For other adverse reactions, general guidelines were also specified in the protocol. If toxicity recurred despite two dose level reductions and aggressive medical management, discontinue study agent.

Supportive care medications were permitted during the study. These included continuation of a GnRH analog for castration, use of additional systemic glucocorticoid such as "stress dose" for a life-threatening medical condition if clinically indicated, use of bisphosphonates, transfusions or use of hematopoietic growth factors as clinically indicated.

Restricted concomitant therapy during the study included any of the following:

- 5α-reductase inhibitor
- Chemotherapy
- Immunotherapy
- Ketoconazole, diethylstilbestrol, PC-SPES, and other preparations such as saw palmetto thought to have endocrine effects on prostate cancer

- Radiopharmaceuticals such as strontium (^{89}Sr) or samarium (^{153}Sm)
- Aldactone, Spironol (spironolactone)

Efficacy Assessments

For the primary endpoint, OS was measured from the date of randomization to the date of death (whatever the cause). Survival time of living patients was censored on the last date a patient was known to be alive or lost to follow-up.

For the following secondary endpoints, assessment was dependent on the study calendar and varied with the definition for each of them:

a) Proportion of patients achieving a PSA decline ≥50% represents PSA response rate according to protocol-specific PSAWG criteria. It was assessed based on central laboratory measurements of PSA at 12-week intervals that coincided with assessment of response using radiographic scans. If a ≥50% PSA decline from baseline was detected, confirmation of the decline was required with an additional central laboratory measurement obtained 4 or more weeks later. If the decline remained a ≥ 50% decrease from baseline, the PSA response was considered confirmed.

b) Time-to-PSA progression based on protocol-specific PSAWG criteria: Time-to-PSA progression was the time from the date of randomization to the date of PSA progression, as defined in the PSAWG criteria. Briefly, PSA progression occurred if PSA increased 50% above the nadir and with a minimum increase of 5ng/mL for patients who had achieved a ≥50% decrease from the baseline PSA or if PSA had a ≥25% increase from the baseline PSA for patients who had not achieved a PSA decrease of ≥50%, including no decrease, from the baseline.

c) Proportion of patients with objective tumor response by modified RECIST: Tumor responses in patients with measurable disease were assessed using the RECIST criteria with a modification that only baseline lymph nodes of ≥2 cm in at least one dimension were considered as target lesions. CT/MRI scans were performed at a 12 week interval and at treatment discontinuation and were assessed by the investigator at study sites.

d) Progression-free survival (PFS) based on imaging studies:

Progression-free survival was determined based on imaging studies and was defined as the time interval from the date of randomization to the date of radiographic disease progression, as assessed by the investigator, or death. If no event or on-study assessment existed at the time of analysis, PFS was to be censored at the last disease assessment on study or at randomization.

Radiographic progression was defined as follows:

For measurable soft tissue disease, progression was determined by modified RECIST criteria (baseline lymph node size must be ≥2.0 cm to be considered a target lesion);

For non-measurable bone metastases, progression was defined with ≥2 new lesions (not consistent with tumor flare) by bone scans, confirmed ≥6 weeks later by bone scan showing ≥1 additional new lesion.

Radiographic scans were also performed at a 12 week interval and at treatment discontinuation and were assessed by the investigator at study sites

e) Proportion of patients achieving a decline in CTCs/7.5ml to less than 5:

CTCs were collected in select study centers at screening, Cycle 1 Day 1, and then Cycle 2, 3, and 4 Day 1, and at time of disease progression, as shown in the Study Calendar. CTC enumeration was processed using Veridex CellSearch™ on all samples collected. A responder was defined as a CTC decline to below 5 at any post-baseline visit if the baseline CTC was ≥5.

Reviewer's Comments: *None of the secondary endpoints described above have been shown to have a good correlation with clinical benefit such as overall survival. However, these endpoints may be able to demonstrate the antitumor activity of a study product.*

The definition of disease progression by bone scan was protocol-specified, but not consistent with the 2008 Prostate Cancer Clinical Trials Working Group (PCWG2)

recommendations[15], which do not require at ≥1 additional new bone lesions in a confirmatory scan.

The criteria for defining a responder in CTC were not clear. According to the study plan, a patient could have 4 post-baseline visits for CTC enumeration if he had >4 cycles of treatment. A responder was defined as "A CTC decline to below 5 at ANY post-baseline visit". This definition did not clarify whether a patient with a CTC number of <5 at one visit was a responder if he also had a CTC number of ≥5 at other visits. Reproducibility of the results obtained with the current definition, as well as the sensitivity and specificity of Veridex CellSearch™ in predicting treatment effect in this disease setting remains to be further investigated.

Statistical Methods

The trial sample size was calculated under the following assumptions: a median overall survival of 15 months for the abiraterone acetate arm and a median overall survival of 12 months for the placebo arm; a 2-tailed significance level of 0.05; an enrollment period of approximately 13 months; and a study duration of approximately 30 months to observe the required 797 death events.

The planned sample size of approximately 1158 patients (772 on abiraterone acetate and 386 on placebo) would provide 85% power to detect a 20% decrease in the risk of death for the abiraterone acetate-treated arm (hazard ratio [HR]=0.80). One interim analysis at 67% of the required 797 death events (alpha-level 0.0124, O'Brien-Fleming boundary) and one final analysis were planned to be performed after the pre-specified number of death events reached.

All randomized patients were included in the intent-to-treat (ITT) population, regardless of the actual treatment received. Primary efficacy analyses were conducted in the ITT population. In contrast, safety population consisted of all patients who receive at least one dose of study drug.

For the details, please see the statistical review for this NDA.

15 Scher HI et al (2008): Design and End Points of Clinical Trials for Patients with Progressive Prostate Cancer and Castrate Levels of Testosterone: Recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol 26:1148-1159

6.1.2 Accrual, Demographics, and Analysis Populations

A total of 1195 patients were randomized in the trial: 797 to the abiraterone arm and 398 to the placebo arm. The study patients were recruited from 147 study centers in 13 countries. Their enrollment by geographic region is summarized in

Table 6. Forty-two percent of patients were enrolled from the United States.

Table 6: Geographic Distribution of Study Patients in COU-AA-301

Geographic Region	AA (N=797)	Placebo (N=398)
USA Canada	336 97	162 57
Europe*	295	144
Australia	69	35
* Including Austria, Belgium, France, Germany, Hungary, Italy, Netherlands, Ireland, Spain, United Kingdom		

The patient demographics are shown in
Table 7. The median age was 69 years. Ninety-three percent of the patients were White and 3% were Black.

Table 7: Baseline Demographics of the Patients in COU-AA-301

	AA (N=797)	Placebo (N=398)
Age		
Median (yrs) (range)	69 (42, 95)	69 (39, 90)
Race		
Caucasian	743 (93%)	368 (93%)
Black	28 (4%)	15 (4%)
Other	25 (3%)	14 (3%)
Body Surface Area (m^2)		
Median (range)	2.01 (1.3, 3.2)	2.00 (1.5, 2.8)

Baseline disease characteristics of the randomized patients were examined and key findings are shown in Table 8. Overall, the characteristics listed were balanced between the arms. As shown in the table, seventy percent of patients had radiographic

evidence of disease progression and 30% had PSA-only progression. Approximately 90% of patients had metastases in bone and 30% had visceral involvement. The percentages of patients with soft tissue disease involved in lymph nodes or visceral organs were about 5% less in the placebo arm compared to those in the abiraterone arm. In contrast, the percentage of patients with a Gleason score of ≥8 at initial diagnosis was slightly higher in the placebo arm than that in the abiraterone arm.

In addition, important baseline laboratory parameters that may be associated with disease outcome were also examined. These included levels of baseline hemoglobin, lactate dehydrogenase (LDH), and alkaline phosphatase (ALP). These parameters were balanced between the two arms. In both arms, the overall median hemoglobin level were 11.8 g/dL (range: 7.2, 16.5), the median LDH level 227 IU/L (range: 84, 5125), and the median ALP level 134 IU/L (range: 20, 4896).

Table 8: Disease Related Characteristics of the Patients in COU-AA-301

	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 (patient's reported worst pain over last 24 hours)

Regarding prior use of cytotoxic chemotherapy, the number of regimens was balanced between the two arms. As shown in Table 9, approximately 30% of patients received 2 cytotoxic chemotherapy regimens and 70% received one chemotherapy regimen.

Nevertheless, all patients had received docetaxel-based chemotherapy. A few patients, about 1.7%, also received treatment with paclitaxel or cabazitaxel.

Table 9: Prior Use of Cytotoxic Chemotherapy in COU-AA-301

	AA (N=797)	Placebo (N=398)
Prior Chemotherapy Regimen #		
One	558 (70%)	275 (69%)
Two	239 (30%)	123 (31%)
Prior Taxane Type		
Docetaxel [a]	797	397
Paclitaxel [b]	6	4
Taxane not specified [c]	8	2

a: One patient (ID *126-0003) in the placebo arm who was randomized in error and who did not have information about prior use of docetaxel in the dataset or CRF.*
b: Patients received paclitaxel in addition to docetaxel.
c: Specified as XRP6258 (cabazitaxel)

Prior docetaxel usage information was also evaluated based on the submitted, retrospectively collected data. Table 10 summarizes the cumulative dosage of docetaxel and the docetaxel treatment times relevant to the initiation of study treatment in the trial. The tabulations as shown in this table were balanced between the two arms, suggestive of equal exposure of patients to docetaxel between the arms prior to enrollment in the trial.

Table 10: Prior Docetaxel Usage in Study COU-AA-301

	AA (N=797)	Placebo (N=398)
Total Dosage [a] (mg) Median (range)	906 (50-5849)	895 (29-5610)
Time from the FIRST docetaxel treatment to study initiation[b] (mos) Median (range)	13.1 (1.2, 110.1)	12.6 (2.4, 97.3)
Time from the LAST docetaxel treatment to study initiation[b] (mos) Median (range)	5.3 (0.6, 65.9)	5.4 (0.5, 85.4)

a: Reported docetaxel dosing information in 65% of the patients in the AA arm and 62% of the patients in the placebo arm, respectively. Numbers of treatment cycles were used for some patients. These numbers were not transformed to usage in mg in the tabulation.
b: Information reported in 99.3% of the patients enrolled.

The ITT population included all randomized patients in the trial and was used for efficacy analyses of the primary endpoint. Populations used for sensitivity analyses or exploratory analyses, as described in Section 6.1.4, were determined as appropriate to each analysis.

Reviewer Comments:
All characteristics listed above appear to be balanced between the two arms. These include some important characteristics such as baseline pain, visceral involvement, anemia, and radiographic progression (e.g. bone scan progression), which appear to represent prognostic factors in the docetaxel treatment era based on a recently published retrospective study.[16]

Importantly, the extent of prior docetaxel usage may also affect survival outcomes of the study patients. The tabulations as shown in Table 10 suggest that the previous exposure was similar between the two arms. On the other hand, an imbalance between the two arms would make the results of the trial difficult to be interpreted.

6.1.3 Patient Disposition

Overall patient disposition at the pre-specified interim analysis of the trial was examined and the main findings are shown in Table 11. More patients were actively on treatment in the abiraterone acetate arm than in the placebo arm. In contrast, more treatment discontinuation and more deaths were in the placebo arm than in the abiraterone acetate arm. Key reasons for treatment discontinuation were also shown in this Table. These reasons appeared balanced between the two arms. Interestingly, more patients discontinued treatment because of adverse events in the placebo arm with a rate of 18% compared to a rate of 12% in the abiraterone acetate arm.

Table 11: Patients Disposition in COU-AA-301

	AA (N=797)	Placebo (N=398)
On Treatment	222 (28%)	54 (14%)
Treatment Discontinued	569 (72%)	340 (86%)
Death	333 (42%)	219 (55%)
Key Reasons for Discontinuation	219 (28%)	112 (28%)
Disease Progression	107 (14%)	64 (16%)
New Treatment Initiated	98 (12%)	70 (18%)
Adverse Events	70 (9%)	40 (10%)
Consent Withdrawal	36 (5%)	27 (7%)
Investigator's Discretion		

16 Armstrong AJ, et al (2010): The development of risk groups in men with metastatic castration-resistant prostate cancer based on risk factors for PSA decline and survival. *Eur. J. Cancer 46: 517-525.*

Major protocol violations and/or deviations were found in approximately 16-17% in each arm. These are summarized in
Table 12 with a detailed list of major violation/deviation types in the footnote of the Table.

Table 12: Major Protocol Violations/Deviations in COU-AA-301

	AA (N=797)	Placebo (N=398)
Eligibility Criteria not Met [a]	50	21
Prohibited Concurrent Medicine [b]	40	17
Docetaxel Use during the Study [c]	12	4
Other [d]	37	27
Total [e]	130 (17%)	63 (16%)

a: Important deviations included >2 prior chemotherapies, not on a LHRH analogue or with high levels of testosterone of >50 ng/dL, absence of metastatic disease, use of disallowed medicines such as ketoconazole.
b: Included radiation therapy, dexamethasone, bicalutamide, flutamide, cyproterone acetate, PC-SPES, dutasteride, finasteride, ketoconazole.
c: Included use of the last dose of docetaxel within 30 days prior to the initiation of study treatment
d: Included no performance of required tests, not withdrawn when withdrawal was indicated, dosing errors, uncontrolled hypertension or decreased LVEF less than 50% at baseline.
e: Some patients had >2-3 violations and/or deviations.

Use of bisphosphonates was not considered as a protocol deviation since it was allowed before or during the study. According to the protocol, an addition of a bisphosphonate or change to the type of bisphosphonate was only allowed if a new skeletal-related event or bone progression was documented. The pre-study use of bisphosphonates was reported in 29 (4%) patients assigned to the abiraterone acetate arm and in 16 (4%) patients assigned to the placebo arm. In contrast, the on-study use of bisphosphonates was documented in 345 (43%) patients receiving abiraterone acetate and in 195 (49%) patients receiving placebo. These on-study bisphosphonate use rates are much higher than the discontinuation rate of 28% for disease progression (Table 11) in the two arms.

Reviewer Comments:
The impact of the protocol deviations/violations on survival was examined and the result is shown below in Section 6.1.4 Sensitivity Analyses. In addition, use of bisphosphonates, one standard care for patients with mCRPC, was remarkably different between the pre-study and on-study periods and the percentages of concomitant bisphosphonate use during study was considerably higher than those of disease progression documented in both arms, making it difficult to evaluate any effect

of abiraterone acetate on the incidence of skeletal-related event or time to first skeletal-related event in the trial.

6.1.4 Analysis of Primary Endpoint(s)

Analysis of Primary Endpoint

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 13 summarizes the results and

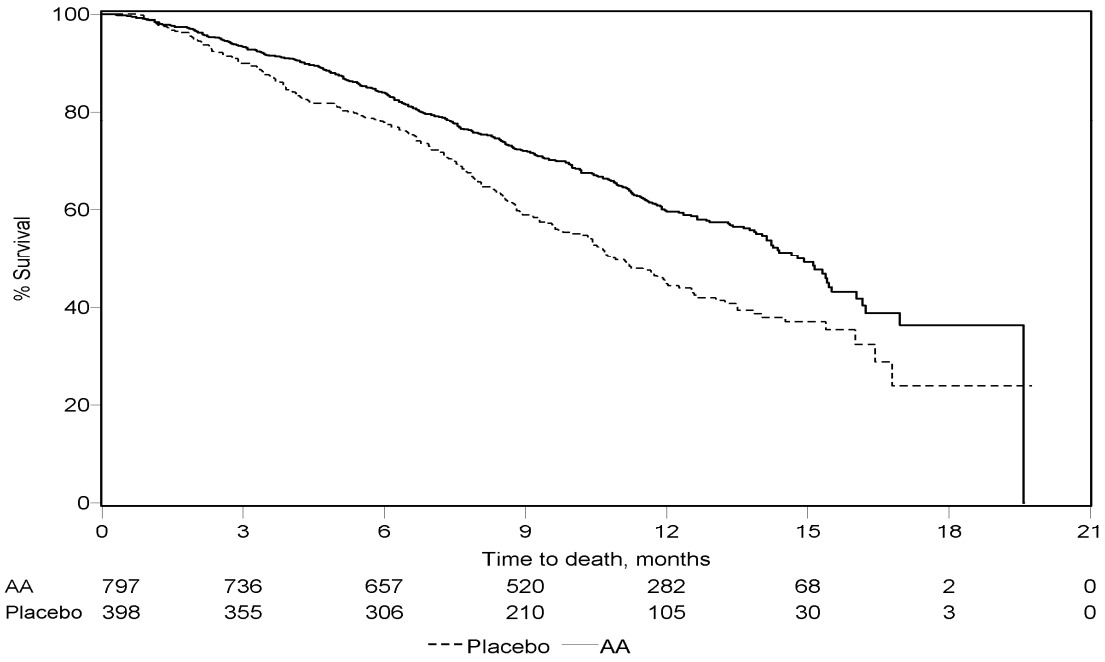
Figure 4 shows the Kaplan-Meier overall survival curves from this interim analysis. Compared to placebo, treatment with abiraterone acetate had a 35% decreased risk of death in patients with progressive mCRPC who had received prior docetaxel-based chemotherapy (HR=0.646; 95% CI: 0.543, 0.768; p<0.0001). 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 13: 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)	

[a] *P-value is derived from a log-rank test stratified by ECOG performance status score (0-1 vs 2), pain score (absent vs present), number of prior chemotherapy regimens (1 vs 2), and type of disease progression (PSA only vs radiographic).*

Figure 4: Kaplan-Meier Overall Survival Curves ((Pre-specified Interim Analysis in ITT)



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 additional survival analysis was performed with the updated number of events. The results of the updated analysis, as summarized in

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Table 14, 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.

Table 14: Updated Primary Endpoint Analysis Results in ITT

	AA (N=797)	Placebo (N=398)
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) [a]	0.740 (0.638, 0.859)	

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

Sensitivity Analyses of the Primary Endpoint

Protocol violations/deviations may affect the reliability of the primary endpoint analysis results. To examine whether the protocol violations/deviations as listed in Table 12 impact the survival results in the trial, a sensitivity analysis was conducted with exclusion of patients with the violations/deviations from the above interim analysis. The results of the sensitivity analysis, as shown in

Table 15, were similar to the interim analysis results, suggesting that the survival benefit demonstrated was not driven by those protocol violations/deviations.

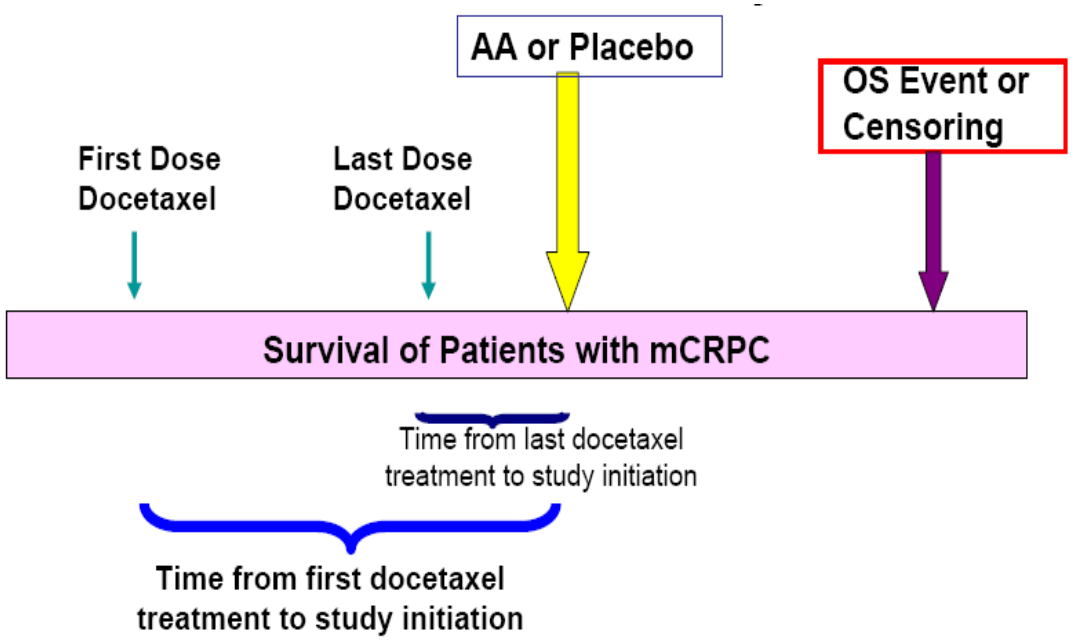
Table 15: Sensitivity Analysis of the Impact of the Protocol Violations/Deviations on Survival

	AA (N=667*)	Placebo (N=335*)
Deaths (%)	273 (41%)	183 (54%)
Median survival (months)	14.8	10.7
(95% CI)	(14.1, 15.4)	(9.8, 12.5)
Hazard ratio (95% CI) [a]	0.644 (0.533, 0.779) p<0.0001	

[*] Not including the patients with protocol violations and/or deviations.
[a] Hazard Ratio is derived from a stratified long rank test

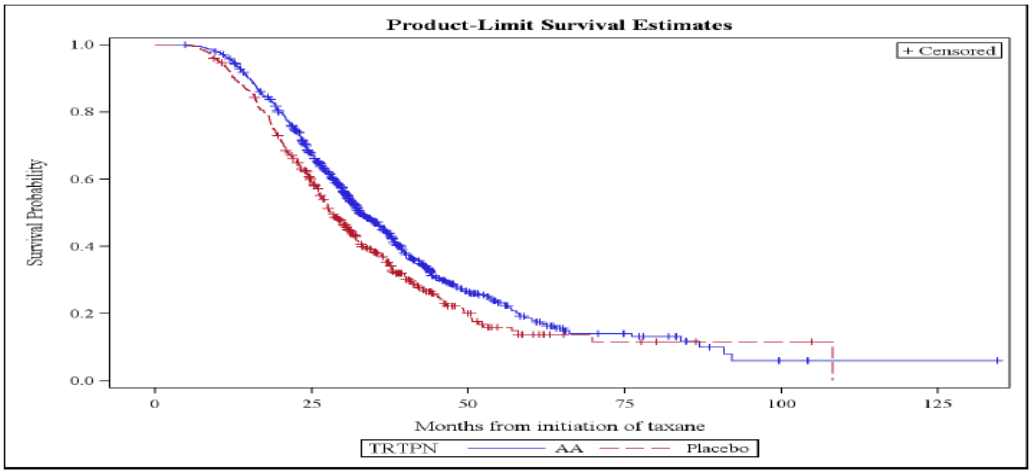
To further examine the robustness of the primary survival results, two more sensitivity analyses were performed to investigate whether the timing of docetaxel treatment had any impact on the overall survival. The first analysis considered the timing from the prior docetaxel treatment initiation (first dose) to the occurrence of either deaths or censoring and the second analysis dealt with the discontinuation (last dose) to either death or censoring. To help better understand the results from the two sensitivity analyses, Figure 5 illustrates the prior docetaxel use time points (first and last doses) and two time periods relative to study treatment or randomization of the trial. As shown in Table 10, the two time periods of prior docetaxel use relative to study randomization were found to be balanced between the two arms, along with the prior total dose of docetaxel.

Figure 5: Schematic Diagram Illustrating the Timing of Docetaxel Treatment to Study Treatment (Abiraterone or Placebo)



The results of the analysis conducted from the initiation of prior docetaxel treatment in the ITT population are shown in Figure 6. The Kaplan-Meier estimated median overall survival was 32.7 months (95% CI: 31.2 to 35.9) for patients in the abiraterone acetate arm compared with a median overall survival of 28.1 months (95% CI: 26.5- 30.7) in the placebo arm. The hazard ratio was 0.79 (95% CI: 0.68, 0.92), with a nominal p value of 0.0017. These results also provide information on how long patients with mCRPC may survive from initiation of docetaxel treatment for metastatic castration-resistant prostate cancer.

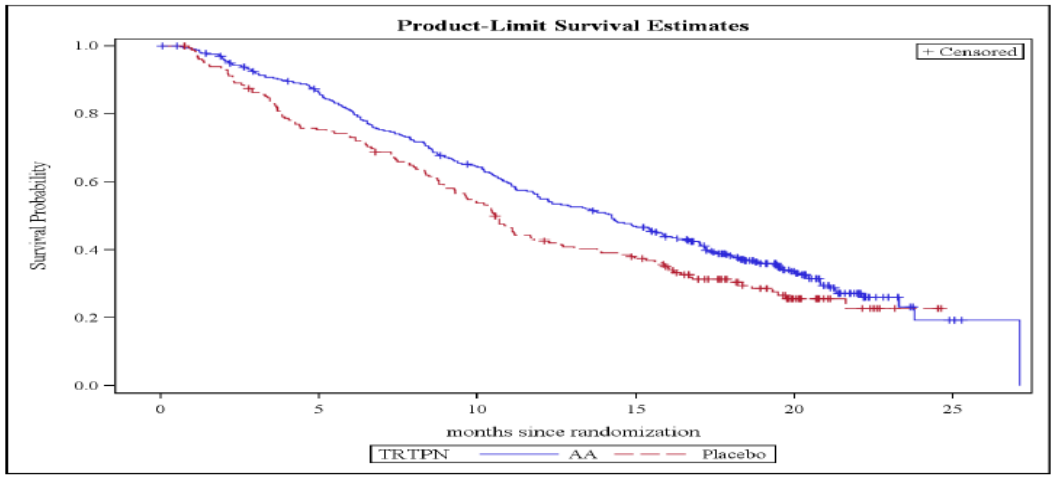
Figure 6: Sensitivity Survival Analysis from the Initiation of Prior Docetaxel Treatment



	Median mos (95% CI)	Nominal P-value
AA	32.7 (31.2, 35.9)	0.0017
Placebo	28.1 (26.5, 30.7)	

Figure 7 shows the results of the sensitivity analysis from the time of last docetaxel treatment in the ITT population. The Kaplan-Meier estimated median overall survival was 23.9 months (95% CI: 22.7 to 25.4) in the AA arm and 20.2 months (95% CI: 18.6- 21.4) in the placebo arm. The hazard ratio was 0.77 (95% CI: 0.66, 0.89), with a nominal p value of 0.0004. These results also suggest how long patients with mCRPC may survive after discontinuation of docetaxel treatment for metastatic castration-resistant prostate cancer.

Figure 7: Survival Analysis from the Discontinuation of Prior Docetaxel Treatment



	Median mos (95% CI)	Nominal P-value
AA	23.9 (22.7, 25.4)	0.0004
Placebo	20.2 (18.6, 21.4)	

The results of these two sensitivity analyses, based on the prior docetaxel use initiation or discontinuation, suggest that the survival benefit associated with abiraterone acetate treatment in the trial was preserved from both initiation and discontinuation of prior docetaxel treatment. Compared to the placebo arm, the magnitude of improvements in median overall survival for patients on the abiraterone acetate arm remains approximately 4 months, consistent with the demonstrated 3.9-4.6 month improvement in median overall survival with abiraterone acetate from study randomization in the pre-specified interim analysis or the updated survival analysis. This consistency demonstrates the robustness of primary survival analysis results.

Reviewer's Comments

The above primary endpoint analyses, including the pre-specified interim analysis, updated survival analysis and three sensitivity analyses, demonstrate a robust survival improvement associated with abiraterone acetate treatment in the study population as compared to placebo. The improvement in median overall survival was approximately 4 months with abiraterone acetate treatment.

Having considered differences in the adverse reactions between abiraterone acetate (see Section 7 of the review) and cabazitaxel (see Section 2 or cabazitaxel labeling[17]), the benefit-risk profile of abiraterone acetate appears more favorable than that of cabazitaxel in patient with mCRPC who have received prior docetaxel-based chemotherapy. The median overall survival time observed in the abiraterone acetate arm was about 15 months, comparable with that observed in the cabazitaxel arm in the cabazitaxel trial (discussed in Section 2.6) that supported the approval of cabazitaxel in patients with mCRPC previously treated with docetaxel-containing chemotherapy. Compared to study control, the abiraterone acetate treatment associated 4 month improvement in median overall survival appears longer than the 2.4 month improvement in median survival in the cabazitaxel trial. Please note that differences in the study population and control treatment or other factors between the two trials make it difficult to generate a convincing conclusion because of the inherent problems with cross-study comparisons.

Moreover, the abiraterone acetate survival benefit demonstrated in the COU-AA-301 trial was maintained from the initiation of prior docetaxel treatment for the disease. If

17 Cabazitaxel Label (2010): available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/201023lbl.pdf Accessed as of April 3, 2011.

one considers that the initiation of docetaxel treatment for patients with mCRPC in the study population was random in regular clinical practice prior to their enrollment onto the trial, the preserved survival benefit would suggest that the abiraterone acetate treatment effect is sustained during treatment of mCRPC. Since the mechanism of action of abiraterone acetate is different from that of the cytotoxic agent docetaxel, it is reasonable to envision that abiraterone acetate conferred its treatment effect independent of prior docetaxel use. This assessment is supported by four Phase 1-2 studies (see Section 5) that demonstrated similar antitumor activities of abiraterone acetate in patients with mCRPC who had been previously treated with or without docetaxel-based chemotherapy, suggesting that docetaxel treatment is not prerequisite for abiraterone to exert its antitumor activity. In contrast, the available evidence as shown in Table 3 seems to suggest that use of abiraterone before docetaxel appeared to be more active than after docetaxel in terms of PSA declines of ≥50% from baseline.

Furthermore, as an oral hormonal agent, abiraterone acetate appears to have a more favorable risk-benefit profile as compared to docetaxel (see Section 7 and the product labeling for docetaxel), which conferred a 2.4 improvement in median overall survival compared to mitoxantrone treatment, but was associated with severe adverse reactions such as Grade 3 or 4 neutropenia (32%) and febrile neutropenia (3%) that generally require aggressive medical management.

Taken together, the above primary endpoint analysis results provide convincing evidence for the effectiveness of abiraterone acetate in the intended patient population. Its overall benefit-risk profile in the treatment of patients with mCRPC appears to be better compared to that of cytotoxic products used for the treatment of this devastating disease. This may be seen with the information shown in

Table 16, *which summarizes key efficacy and safety findings based on the controlled Phase 3 studies in support of marketing approval of three products in the treatment of*

	Docetaxel	***Cabazitaxel***	***Abiraterone***
Approval Year	*2004*	*2010*	*2011*
Drug Class	*Cytotoxic*	*Cytotoxic*	*Hormonal*
Trial Supporting Approval	*TAX327*	*EFC6193*	*COU-AA-301*
Study Disease Setting *Study Control** *Study Size (# to treatment arm)*	*mCRPC*** *Mitoxantrone* *1006 (335)*	*mCRPC s/p Docetaxel* *Mitoxantrone* *755 (378)*	*mCRPC s/p Docetaxel* *Placebo* *1195 (797)*
Survival Difference*** *HR (95% CI)* *Improvement in Median OS (mos)*	*0.76 (0.619, 0.936)* *2.4*	*0.70 (0.59-0.83)* *2.4*	*0.65 (0.543, 0.768)* *3.9*
Key Toxicity Profile *Infusion Reaction* *Boxed Warnings*	*Yes* *Yes*	*Yes* *Yes*	*N/A* *No*
Severe Toxicity (Grade 3/4) *Neutropenia (%)* *Febrile Neutropenia (%)* *Infection or UTI (%)* *Fluid Retention/Edema (%)* *Hepatic ALT/AST (%)* *Neutopathy (%)*	*32%* *3%* *6%* *1%* *NS* *4%*	*82%* *7%* *2%* <*1%* *1%* <*1%*	*NS* *NS* *2%* *2%* *2%* *NS*
Adverse Reaction of Interest (Grade 3/4) *Hypokalemia (%)* *Hypertension (%)* *Adrenocortical Insufficiency*	*NS* *NS* *NS*	*NS* *NS* *NS*	*5%* *1%* <*1%*

** All treatment was in combination with prednisone 5 mg BID*
*** About 50% patients with pain.*
**** Compared to Study Control in each trial*
N/A denotes not applicable.
NS denotes "not specified", meaning not found in relevant product's label or the review.
All the trials showed a statistically significant improvement in OS as compared to control.
Only the products relevant to this NDA are shown in the Table.

mCRPC. Please note that neither improvements in median overall survival nor

incidence rates of adverse reactions as listed in this table should be compared directly to each other because of the inherent problems with cross-study comparisons.

Table 16: Key Efficacy and Safety Information from Trials in Support of Three Drug Products for the Treatment of Patients with mCRPC (Reviewer Benefit-Risk Evaluation Table)

	Docetaxel	***Cabazitaxel***	***Abiraterone***
Approval Year	*2004*	*2010*	*2011*
Drug Class	*Cytotoxic*	*Cytotoxic*	*Hormonal*
Trial Supporting Approval	*TAX327*	*EFC6193*	*COU-AA-301*
Study Disease Setting *Study Control** *Study Size (# to treatment arm)*	*mCRPC*** *Mitoxantrone* *1006 (335)*	*mCRPC s/p Docetaxel* *Mitoxantrone* *755 (378)*	*mCRPC s/p Docetaxel* *Placebo* *1195 (797)*
Survival Difference*** *HR (95% CI)* *Improvement in Median OS (mos)*	*0.76 (0.619, 0.936)* *2.4*	*0.70 (0.59-0.83)* *2.4*	*0.65 (0.543, 0.768)* *3.9*
Key Toxicity Profile *Infusion Reaction* *Boxed Warnings*	*Yes* *Yes*	*Yes* *Yes*	*N/A* *No*
Severe Toxicity (Grade 3/4) *Neutropenia (%)* *Febrile Neutropenia (%)* *Infection or UTI (%)* *Fluid Retention/Edema (%)* *Hepatic ALT/AST (%)* *Neutopathy (%)*	*32%* *3%* *6%* *1%* *NS* *4%*	*82%* *7%* *2%* <*1%* *1%* <*1%*	*NS* *NS* *2%* *2%* *2%* *NS*
Adverse Reaction of Interest (Grade 3/4) *Hypokalemia (%)* *Hypertension (%)* *Adrenocortical Insufficiency*	*NS* *NS* *NS*	*NS* *NS* *NS*	*5%* *1%* <*1%*

** All treatment was in combination with prednisone 5 mg BID*
*** About 50% patients with pain.*
**** Compared to Study Control in each trial*
N/A denotes not applicable.
NS denotes "not specified", meaning not found in relevant product's label or the review.
All the trials showed a statistically significant improvement in OS as compared to control.
Only the products relevant to this NDA are shown in the Table.

6.1.5 Analysis of Secondary Endpoints(s)

Rate of PSA Declines of ≥50%

As discussed in Section 6.1.1 protocol review, PSA response was assessed based on the central laboratory measurement of PSA levels during the trial and a response with a ≥50% decline from baseline was confirmed with an additional central laboratory measurement obtained 4 or more weeks later. A total of 98% of patients had at least one PSA value after enrollment. Patients with PSA declines of ≥50% are summarized in Table 17. The response rates appeared comparable with the responses rates in the early Phase 2 studies (see Section 5) in patients with mCRPC following treatment with docetaxel-containing chemotherapy, suggestive of the antitumor activity of abiraterone acetate.

Table 17: Patients with PSA Declines of ≥50% from Baseline

	AA (N=797)	Placebo (N=398)
Number of Patients with the PSA response (%)	303 (38%)	40 (10%)
Confirmed Response (%)	232 (29%)	22 (6%)
Unconfirmed Response (%)	71 (9%)	18 (5%)

Time-to-PSA progression

At the time of interim analysis, PSA progression was documented in approximately 30% of patients in each arm while 70% of patients were censored for the analysis of the secondary endpoint. The limited numbers of patients with the event make it difficult to reliably assess the endpoint besides the concern about clinical meaningfulness of the endpoint. Thus, no further analysis of the endpoint was conducted in this review.

Tumor Response by RECIST Criteria

Patients with measureable disease at baseline were also assessed by the investigator for response by RECIST criteria. No central independent review was planned or conducted. A total of 574 patients had measurable disease at baseline, 393 in the abiraterone arm and 181 in the placebo arm. Their confirmed, objective RECIST responses are shown in Table 18. All the responses were partial response. The response rate was 14% in the abiraterone acetate arm, greater than a response rate of 3% in the placebo arm.

Table 18: Tumor Response by RECIST Criteria

	AA (N=797)	Placebo (N=398)
Number of Patients with Measurable Disease (%)	**393***	**181**
Number of Responder (%)	55 (14%)	5 (3%)

**Including one patient with baseline measurable disease who did not have on-study scans*

Progression-Free Survival (PFS) based on imaging studies

PFS was defined as the time interval from the date of randomization to the date of radiographic disease progression or death. Radiographic progression was assessed by the investigator based on both RECIST criteria and the protocol specified bone scan progression criteria, without central review.

The PFS events at the time of the interim analysis are summarized in Table 19. The investigator documented radiographic progression events represented only about 27-30% of the randomized patients, implicating that the applicant intended evaluation of imaging studies based PFS was heavily driven by the number of deaths. Therefore, the subjective of measuring radiographic PFS could not be satisfactorily evaluated with the limited data. Further analysis of this secondary endpoint became irrelevant to this review.

Table 19: Distribution of PFS Events at the Interim Analysis

	AA (N=797)	Placebo (N=398)
Total PFS Event (%)	**577 (72%)**	**327 (82%)**
Death	333 (42%)	219 (55%)
Radiographic Progression	244 (30%)	108 (27%)
Censored (%)	**220 (28%)**	**5 (18%)**

Reviewer Comments:

The results from the evaluable objective secondary endpoints are considered exploratory because of lack of validation, absence of central independent review, and no adjustment for multiplicity. Nevertheless, the observed PSA or RECIST response rate in the abiraterone acetate arm was higher than that in the placebo arm, demonstrating the antitumor activity of abiraterone acetate. It is important to reiterate

that neither PSA nor RECIST response rate has been shown to be correlated with an improvement in overall survival in patients with mCRPC.

The objective secondary endpoints that only included a small proportion (<1/3) of patients who had documented events were not considered evaluable in the review since the results would be unreliable in estimating a median progression time and thus could not be interpreted.

6.1.6 Subpopulations

Multiple subgroup analyses were performed to examine the treatment effect of abiraterone acetate in various subpopulations that may affect the interpretation of the primary endpoint analysis results. The results of the subgroup analyses, as shown in Figure 8, were generally consistent with the overall primary analysis results, favoring the abiraterone acetate arm, except for in the subgroup of ECOG score 2. This discrepancy may be related to the small number of patients (10% in each arm) in the trial. Of note, the abiraterone acetate survival benefit appeared to be present in patients with visceral disease, pain at baseline, or radiographic disease progression. In addition, Table 20 shows that the abiraterone acetate survival effect was detected in patients with a Gleason score of 8-10 at the initial diagnosis.

Figure 8: Subgroup Analyses of Overall Survival

Variable	Subgroup	Median(days) AA	Median(days) Placebo	HR	95% C.I.	Events/N AA	Events/N Placebo
All subjects	ALL	450.0	332.0	0.66	(0.56, 0.79)	333/797	219/398
Baseline ECOG	0-1	466.0	356.0	0.64	(0.53, 0.78)	273/715	184/353
	2	222.0	212.5	0.81	(0.53, 1.24)	60/82	35/45
Baseline BPI	<4	492.0	397.0	0.64	(0.50, 0.82)	151/440	105/219
	>=4	385.0	270.0	0.68	(0.53, 0.85)	182/357	114/179
No. prior chemo regimens	1	469.0	350.0	0.63	(0.51, 0.78)	218/558	147/275
	2	427.0	315.0	0.74	(0.55, 0.99)	115/239	72/123
Type of progression	PSA only	NE	373.0	0.59	(0.42, 0.82)	79/238	64/125
	Radiographic	433.0	318.0	0.69	(0.56, 0.84)	254/559	155/273
Age	<65	436.0	341.0	0.66	(0.46, 0.91)	92/232	63/119
	>=65	450.0	325.0	0.67	(0.55, 0.82)	241/565	156/278
	>=75	454.0	282.0	0.52	(0.38, 0.71)	91/220	72/111
Visceral disease at entry	YES	385.0	257.0	0.70	(0.52, 0.94)	125/252	66/101
	NO	469.0	342.0	0.62	(0.50, 0.76)	208/545	153/297
Baseline PSA above median	YES	391.0	268.0	0.65	(0.52, 0.81)	194/391	131/200
	NO	494.0	403.0	0.69	(0.53, 0.90)	139/406	88/198

Adapted from Applicant after statistical reviewer's verification
Note: No adjustment for multiple comparisons

Table 20: Subgroup Analysis of Overall Survival by Gleason Score Group

Gleason Score at Diagnosis	AA (N=797)	Placebo (N=398)
GS ≤7	(N=342)	(N=161)
Median survival (months) (95% CI)	15.1 (14.1, 17.0)	12.0 (10.4, NE)
Hazard ratio (95% CI)	0.715 (0.543, 0.942)	
Nominal P value	0.0171	
GS≥8	(N=356)	(N=189)
Median survival (months) (95% CI)	14.3 (12.7, 16.2)	10.2 (8.7, 11.1)
Hazard ratio (95% CI)	0.588 (0.462, 0.748)	
Nominal P value	<0.0001	

Reviewer Comments: *Without a pre-specified statistical analysis plan, the above subgroup analysis results are considered exploratory. However, the information may be clinically relevant in helping make treatment decisions suitable for patient's disease condition.*

6.1.7 Analysis of Clinical Information Relevant to Dosing Recommendations

As discussed in Section 5, there was no MTD determined in early phases of development. The recommended dose for further clinical development was 1000 mg once daily, which was used in the key study supporting the NDA. Use of abiraterone acetate at a dose of >1000 mg once daily is not recommended with the current safety and efficacy findings from the studies submitted to this NDA.

With regard to dose modification for adverse reactions, the reviewer examined whether the abiraterone acetate treatment effect was affected after dose reductions. A total of 28 patients (3.5%) treated with abiraterone acetate had dose reductions during the trial. Twenty-one had a dose reduction to 750 mg and 11 patients had a maximum dose reduction to 500 mg. The median overall duration of treatment at the reduced doses was 36 days, with a range of 4 to 262 days in 25 patients who had relevant information at the time of the interim analysis.

To explore whether dose reductions affected the treatment effect or antitumor activity of abiraterone acetate, differences in PSA response rates between treatment periods at the original dose level and the reduced dose levels were analyzed. Because the percentage of patients who had dose reductions was only 3.5% of the total 797 patients in the abiraterone acetate arm, survival analysis comparing patients with and without dose reductions would be unlikely to generate a reliable estimate. Evaluation of changes in the central laboratory-measured PSA levels may help understand the clinical relevance of the applicant's dosing reduction recommendations.

Table 21 shows the PSA response information in patients with the dose reductions. The results suggest that the dose reductions were associated with similar PSA responses compared to the PSA responses observed prior to the reductions in these patients. In addition, PSA declines of 50% also occurred or continued at the dose level of either 750 mg or 500 mg, suggesting that the antitumor activity remained with a dose reduction in patients responding to abiraterone acetate treatment. This finding also supports that the proposed dose reduction recommendations in the product label.

Table 21: Effect of Dose Reductions on PSA Response

	Pre-Dose Reduction	**Post-Dose Reduction**
PSA Declines of 50%	7/28 (25%)	10*/28 [a] (36%)
Number of Patients Who Continued PSA Declines of 50% after Dose Reduction	n/a	5
Number of Patients With PSA Declines of 50% Occurring after Dose Reduction	n/a	5
** including 6 patients whose dose reduction reached to 500 mg once daily while the PSA response remained observed.* *a: Two patients (ID 604-0020 and 902-0009) had no PSA information after dose reduction*		

6.1.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

The median treatment duration in the abiraterone acetate arm was about 32 weeks compared to a median duration of 16 weeks in the placebo arm (see Section 7.2.1). This difference in median treatment duration was consistent with the observation that more patients continued treatment in the abiraterone acetate arm than in the placebo arm after 4 cycles of treatment. Some responding patients had a prolonged response to

abiraterone acetate for more than one year while being treated with abiraterone acetate. It remains to be investigated why these patients had sustained responses to abiraterone acetate.

Given that the estimated median survival for patients who have received docetaxel-based therapy is about one year, the current information about the persistence of antitumor activity of abiraterone acetate seems very encouraging. On the other hand, mechanisms underlying the failure or resistance to abiraterone acetate treatment also remain to be investigated. To the efficacy reviewer's best knowledge, one possible mechanism may be that prostate cancer cells are or become dependent on signaling pathways that either enhance the androgen-AR signaling pathway despite a very low level of androgens or stimulate cancer cell proliferation irrespective of the AR signaling pathway.

6.1.9 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

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 appears to offer a reasonable safety profile when compared to placebo plus prednisone. Several categories of 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 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, severe adverse events (SAE) or TEAEs leading to discontinuation or death when compared to placebo. In pivotal study 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 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/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, both had pre-existing liver conditions (metastases and gallstones) and elevated alkaline phosphatase. Elevated hepatic enzymes led to dose

modifications/reductions/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 4-month safety update did not identify new safety signals.

7.1 Methods

7. 1.1 Studies/Clinical Trials Used to Evaluate Safety

A total of 1873 patients have been enrolled in 19 phase 1 or 2 clinical trials in both prostate cancer patients and healthy volunteers as well as the pivotal phase 3 placebo-controlled clinical trial. The safety population includes any subject who received at least part of the planned 1000 mg dose of AA or placebo during a study period (N=1464) and includes integrated data from 1185 patients of the phase 3 trial (COU-AA-301) and pooled data from 279 patients treated with 1000 mg of AA in studies COU-AA-004, -003, -003EXT, -BMA, -001, 001EXT, -002 and -BE (Figure 9).

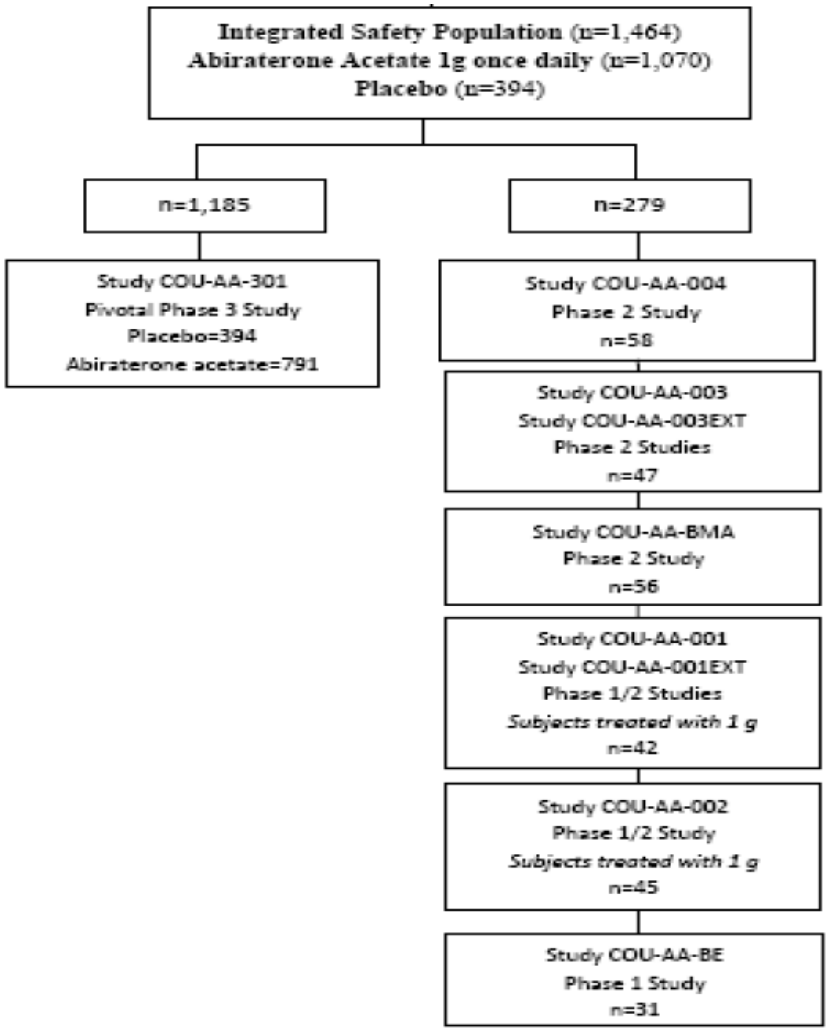


Figure 9: Safety population

(Modified from the applicants Figure 1: page 10 of the summary of clinical safety)

Data from 100 subjects/patients were excluded from the integrated safety analysis. These patients were either treated with doses other than 1000 mg AA or had no extended dosing or safety data available by the January 22, 2010 data cutoff date. Another 309 patients without prostate cancer (PK studies and hepatic and renal impairment studies) were not included in the integrated safety analysis.

7.1.2 Categorization of Adverse Events

Adverse events were captured in subject reports, physical examinations and laboratory evaluations. Please see section 6.1.2 for the schedule of screening and follow up for COU-AA-301 (

Table 5). TEAEs were defined as those occurring or worsening in toxicity on or after the first dose and within 30 days after the last dose of study agent. The applicant

provides data on causality and defined a drug-related AE as an AE with a relationship to the drug listed as "unlikely", "possible" or "related". Adverse events were graded for severity based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (NCI CTCAE) v3.0. Adverse events were captured on CRF and investigators were informed to include disease progression as an AE according to the protocol.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

As mentioned above, the integrated safety data included pooled data from several phase 1/2 studies using 1000 mg of abiraterone acetate once daily in patients with CRPC (Figure 9). A comparison of AEs seen in the abiraterone arm of the phase 3 pivotal trial with the pooled phase 1-2 population was presented by the applicant. This table was verified by the reviewer and reveals no significant difference in patients taking 1000 mg of abiraterone acetate across trials with the exception of a higher incidence of mineralocorticoid excess seen in the phase 1-2 population. The ten most frequent adverse events that were reported in patients taking abiraterone in the pivotal trial compared to the pooled phase 1-2 trials is shown below in Table 22.

Table 22: The 10 Most Frequent Adverse Events reported in COU-AA-301 Compared to Pooled Phase 1 and 2 Study Population Regardless of Attribution.

Abiraterone Arm (AA) COU-AA-301 (N=791)			Pooled Phase 1/2 Trials (N=279)		
	All Grade	Grade 3-4		All Grade	Grade 3-4
Fatigue	43.7%	8.3%	Fatigue	43.7%	4.7%
Nausea	29.5%	1.8%	Hypokalemia	34.8%	2.5%
Back pain	29.5%	6.2%	Oedema peripheral	28.3%	0.3%
Arthralgia	27.2%	4.2%	Arthralgia	24.4%	3.6%
Constipation	26.0%	1.0%	Constipation	22.6%	0.4%
Oedema peripheral	25.2%	1.6%	Nausea	22.6%	1.4%
Bone pain	24.5%	5.7%	Hypertension	21.9%	1.4%
Anemia	22.6%	7.5%	Hyperglycemia	21.5%	1.4%
Vomiting	21.2%	1.9%	Back Pain	21.5%	3.6%
Hot flush	19.0%	0.3%	Anemia	20.4%	3.6%

Reviewer Comment: *The subset of patients (N=279) pooled from phase 1 and 2 studies was somewhat unique in that prednisone was not uniformly used and, thus, the frequency of mineralocorticoid events (shaded cells) was higher.*

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations

The integrated safety database was chosen based on patients with CRPC who had received 1000 mg of abiraterone acetate once daily. This includes 791 patients from the pivotal phase 3 trial in addition to 279 patients from the pooled phase 1 and 2 studies for a total of 1070 patients exposed to 1000 mg of AA. Table 23 shows the duration of treatment. Patients in both the abiraterone arm of trial COU-AA-301 and the overall abiraterone safety population received a median of approximately eight 28-day cycles (32 weeks). The placebo arm of trial COU-AA-301 had a median treatment duration of 15.5 weeks, less than half that of the overall abiraterone population. The treatment compliance was high with 90.9% of patients in the overall AA group receiving 90% or more of their scheduled treatment doses. There were only 6 patients in the overall AA group that discontinued treatment secondary to medication non-compliance (0.6%). Approximately 4% of the overall abiraterone acetate population had dose reduction and thus the majority of patients were treated at the 1000mg dose level.

Table 23: Treatment Duration in Weeks

	COU-AA-301 AA (N=791)	COU-AA-301 Placebo (N=394)	Pooled Phase 1-2 (N=279)	Overall AA (N=1070)
Mean	32.5	23.1	38.2	34.0
Median	32.1	15.5	28.3	31.9
Range	0.7 - 80.7	0.6 - 82.3	0.3 - 147.9	0.3 - 147.9
Std Dev	20.0	17.7	31.5	23.7
25%-75%	13.0 - 48.3	11.4 - 32.3	12.3 - 49.6	12.9 - 48.5

Source: dataset ADSL analyze distribution DURTRT

Reviewer Comment: The overall exposure to the drug was adequate to assess its safety.

7.2.2 Explorations for Dose Response

Not Applicable.

7.2.3 Special Animal and/or In Vitro Testing

Please see pharmacology/toxicology review.

7.2.4 Routine Clinical Testing

As is illustrated in

Table 5, routine laboratory values and physical exams were obtained at screening, each cycle and at the end of the study. A liver panel was obtained every 2 weeks for the first

3 cycles. Cardiac evaluation with MUGA or TTE was obtained at screening and at the end of the study for all patients. Patients with prior mitoxantrone use also had MUGA or TTE every three cycles. An EKG was obtained at screening, every 3 cycles and at end of study.

7.2.5 Metabolic, Clearance, and Interaction Workup

The terminal elimination half-life for abiraterone in plasma is 12 ± 5 hours (mean ± SD), and it has an accumulation ratio of 2.0. As discussed in the clinical pharmacology review, the plasma concentrations of abiraterone are increased significantly when taken concomitantly with food, with a Cmax increase of up to 17-fold when given with a high fat meal. Given this finding, AA is to be taken under modified fasting conditions (1 hour before or 2 hours after meal).

Following oral administration, AA is hydrolyzed to abiraterone (active metabolite). The conversion is likely through esterase activity and is not mediated by CYP isozymes. Abiraterone is metabolized to two main inactive metabolites, which account for about 43% of exposure each. CYP3A4 and SULT2A1 are the enzymes involved in the formation of these two inactive metabolites. Inhibition of CYP3A4 by the concomitant use of strong CYP3A4 inhibitors may lead to an increase in abiraterone concentrations and a risk of toxicity. Induction of CYP3A4 by the concomitant use of potent CYP3A4 inducers can decrease abiraterone concentrations and lead to efficacy concerns. Abiraterone acetate is an inhibitor of the hepatic drug-metabolizing enzyme Cytochrome P450 (CYP) 2D6. In a CYP2D6 drug-drug interaction trial, the Cmax and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1000 mg daily and prednisone 5 mg twice daily. Therefore, AA should be used in caution when administered concomitantly with drugs metabolized by CYP2D6, drugs that are strong CYP3A4 inhibitors, and drugs that are potent CYP3A4 inducers. Refer to the clinical pharmacology review for details of these interactions with their conclusions and recommendations for further studies.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Abiraterone, the active metabolite of the abiraterone acetate, selectively inhibits CYP17 alpha. This inhibition results in increased mineralocorticoid production from the adrenal glands, likely from decreased feedback inhibition and a subsequent increase in ACTH levels. It is this mineralocorticoid excess that produces many adverse events unique to this drug. Another adrenal inhibitor used in the treatment of prostate cancer is

ketoconazole. While ketoconazole has not shown a survival benefit, and is not FDA approved for this indication, it is frequently used off-label to treat metastatic prostate cancer which has become castration-resistant. Ketoconazole was studied in a phase 3 trial (CALGB 9583) of 260 CRPC patients randomized to anti-androgen withdrawal alone (AAWD) or AAWD with 400 mg TID of oral ketoconazole. While ketoconazole did provide evidence of antitumor activity including a PSA decline of ≥50% in 27% of patients and a 20% objective response rate, there was no survival benefit, although the results were possibly confounded due to an 82% rate of crossover. Twenty-one percent of patients in the ketoconazole arm developed grade ≥3 toxicity (compared with 7% AAWD alone) with most frequent AEs including motor neuropathy and ototoxicity, malaise, fatigue, and hepatic toxicity. The drug must also be used with hydrocortisone. Furthermore, ketoconazole has significant potential for drug-drug interactions as it is a strong inhibitor of CYP450.

7.3 Major Safety Results

7.3.1 Deaths

AEs with an outcome of death were reported in 14.7% of the placebo arm versus 11.8% of the abiraterone arm in the AE dataset for COU-AA-301. A listing of AEs with an outcome of death is provided in Table 24. There were no hepatotoxicity-related AEs that resulted in death in the abiraterone arm. The most common AE with an outcome of death was disease progression (8.5%), followed by cardiorespiratory arrest (0.8%) and infection (0.6%).

Table 24: AEs with an Outcome of Death at any Time during Study or Survival Follow-up for COU-AA-301

	Abiraterone acetate 1000 mg daily every 4 weeks with prednisone 10 mg daily (n=791)		Placebo once daily every 4 weeks with prednisone 10 mg daily (n=394)	
TOTAL DEATHS	93	11.8%	58	14.7%
General disorders and administration site conditions				
Disease Progression	67	8.5%	38	9.6%
Death	3	0.4%	0	0.0%
Multiorgan Failure	1	0.1%	0	0.0%
General Physical Health Deterioration	2	0.3%	2	0.5%
Cardiac disorders				
Cardiorespiratory Arrest	6	0.8%	2	0.5%
Arrythmia	1	0.1%	0	0.0%
Congestive Heart Failure	1	0.1%	1	0.3%

Myocardial Infarction / Ischemia	1	0.1%	2	0.5%
Sudden Death	1	0.1%	0	0.0%
Infections and infestations	5	0.6%	3	0.8%
Respiratory, thoracic and mediastinal disorders	4	0.5%	4	1.0%
Renal Failure	2	0.3%	2	0.5%
Gastrointestinal Hemorrhage	1	0.1%	1	0.3%
Injury, poisoning and procedural complications	1	0.1%	2	0.5%
Lung neoplasm malignant	1	0.1%	3	0.8%
Hemorrhage intracranial	1	0.1%	1	0.3%

Reviewer Comments: No significant clustering of deaths was apparent in the trial COU-AA-301.

7.3.2 Nonfatal Serious Adverse Events (SAE)

Overall, nonfatal serious adverse events occurred more frequently in the placebo arm when compared to both the abiraterone arm of the pivotal trial and the pooled phase 1-2 patients receiving abiraterone in the safety population. SAEs in body system class "cardiac disorders" occured in 3%, 2.9% and 1.3% of patients in the AA arm, Placebo arm, and pooled phase 1-2 patients respectively. Table 25 lists the most commonly reported SAEs and their frequencies.

Table 25: Nonfatal Serious Adverse Events Occurring in >0.5% of the Abiraterone Acetate Arm of COU-AA-301 Compared With Placebo and Pooled Phase 1-2 Patients

	COU-AA-301 AA (N=791)	**COU-AA-301 Placebo (N=394)**	**Phase 1-2 1g AA (N=279)**
Preferred Term	%	%	%
Total	**37.5**	**41.4%**	**36.6%**
Anaemia	2.8%	3.3%	4.3%
Spinal cord compression	2.5%	4.3%	2.5%
Pneumonia	1.9%	1.0%	2.5%
Urinary tract infection	1.8%	0.8%	2.9%
Bone pain	1.8%	3.3%	0.4%
Vomiting	1.5%	2.3%	2.2%
Dehydration	1 5%	1.3%	1.8%
Disease progression	1.4%	0.5%	0.0%
Hydronephrosis	1.4%	0.8%	0.0%
Sepsis	1 1%	0.5%	2.2%
Haematuria	1 1%	2.8%	1.4%
Fatigue	0.9%	1.5%	2.2%
Urinary retention	0 9%	1.3%	0.0%
Dyspnoea	0.9%	1.0%	2.9%
Thrombocytopenia	0.8%	0.3%	1.1%
Hypokalaemia	0.8%	0.0%	2.5%
Back pain	0.8%	2.8%	3.2%
Renal failure acute	0.8%	0.5%	1.8%

Myocardial infarction	0.6%	0.3%	0.4%
Abdominal pain	0.6%	0.5%	1.8%
Constipation	0.6%	0.8%	1.1%
Nausea	0.6%	0.8%	2.5%
Asthenia	0.6%	0.3%	0.7%
Pyrexia	0.6%	2.3%	1.8%

Reviewer Comments: Urinary tract infection and sepsis were reported more commonly as SAEs in the abiraterone acetate groups. A plausible mechanism for this finding is not readily apparent and its clinical significance is uncertain. Severe adverse events occurring secondary to cardiac disorders as a grouped body system were seen more frequently in abiraterone acetate-containing arms. A full discussion of cardiac findings is provided in section 7.3.4.4 Cardiac Toxicity.

7.3.3 Treatment Discontinuations

Table 26: Most Frequent Adverse Events Leading to Treatment Discontinuation in COU-AA-301

	AA (N=791)		Placebo (N=394)	
Patients with any AE leading to discontinuation	**149**	**18.8%**	**88**	**22.3%**
Disease progression	48	6.1%	21	5.3%
Spinal cord compression	7	0.9%	8	2.0%
Vomiting	6	0.8%	1	0.3%
Fatigue	5	0.6%	4	1.0%
Back pain	5	0.6%	4	1.0%
Cardio-respiratory arrest[1]	4	0.5%	2	0.5%
Asthenia	4	0.5%	3	0.8%
Aspartate aminotransferase increased	**4**	**0.5%**	**1**	**0.3%**
Myocardial infarction	3	0.4%	2	0.5%
Pneumonia	3	0.4%	3	0.8%
Urosepsis	**3**	**0.4%**	**1**	**0.3%**
Alanine aminotransferase increased	**3**	**0.4%**	**0**	**0.0%**
Cardiac failure [2]	**3**	**0.4%**	**0**	**0.0%**
Renal failure acute	3	0.4%	0	0.0%

[1] Includes terms "Cardiac arrest" and "Cardio-respiratory arrest"

[2] Includes terms "Cardiac failure", "Cardiac failure congestive", "Left ventricular dysfunction", "Cardiogenic shock", "Cardiomegaly", "Cardiomyopathy" and "Ejection fraction decreased"

Reviewer Comment: The most frequent adverse reactions (AEs thought possibly related to AA) leading to abiraterone acetate discontinuation were elevated aspartate aminotransferase, urosepsis, elevated alanine aminotransferase and cardiac failure (bolded in Table 26).

7.3.4 Significant Adverse Events

7.3.4.1 Adverse Reactions

The pivotal phase 3 placebo-controlled trial COU-AA-301 provided a comparison of adverse events reported for 791 patients taking abiraterone and 394 patients taking placebo. The adverse event rates were compared between the two groups and those adverse events which occurred more frequently in the abiraterone arm by an absolute frequency of 2% or greater were considered by the safety clinical reviewer as possibly related to abiraterone acetate treatment (adverse reaction). These adverse reactions as well as cardiac and mineralocorticoid excess adverse events of interest are presented in Table 27 below.

Adverse Events Standardized for Exposure

Because treatment duration in the abiraterone acetate arm was twice that of the placebo arm (32 weeks versus 15.5 weeks), the applicant performed an analysis of the COU-AA-301 data to standardize the adverse event rates by treatment exposure (AEs per 100 patient-years). Using an absolute difference of 5 or more events occurring in the abiraterone arm, peripheral edema (54 events/100 P-Y vs 44), hypokalemia (47 events/100 P-Y vs 29) and urinary tract infection (24 events/100 P-Y vs 18) were identified by the applicant as occurring more frequently in the AA arm. In general, this methodology attenuated the differences between the treatment arms.

It should be pointed out that this approach has never been used in oncology drug or biologic review to determine adverse reactions. Therefore, the FDA safety reviewer did not use the standardized data when determining adverse reactions for this submission.

Table 27: Adverse Reactions Occurring in ≥5% of Patients Taking Abiraterone Acetate in COU-AA-301

System/Organ Class Adverse reaction	AA with Prednisone (N=791) All Grades[1] %	 Grade 3-4 %	Placebo with Prednisone (N=394) All Grades %	 Grade 3-4 %
Musculoskeletal and connective tissue disorders				
Joint Swelling/ Discomfort[2]	29.5%	4.2%	23.4%	4.1%
Muscle discomfort[3]	26.2%	3.0%	23.1%	2.3%
General disorders				
Edema[4]	26.7%	1.9%	18.3%	0.8%
Vascular disorders				
Hot flush	19.0%	0.3%	16.8%	0.3%
Hypertension	8.5%	1.3%	6.9%	0.3%
Gastrointestinal disorders				
Diarrhea	17.6%	0.6%	13.5%	1.3%
Dyspepsia	6.1%	0	3.3%	0
Infections and infestations				
Urinary tract infection	11.5%	2.1%	7.1%	0.5%
Upper respiratory tract infection	5.4%	0	2.5%	0
Respiratory, thoracic and mediastinal disorders				
Cough	10.6%	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
Cardiac Disorders				
Arrhythmia[5]	7.2%	1.1%	4.6%	1.0%
Chest Pain or chest discomfort[6]	3.8%	0.5%	2.8%	0
Cardiac failure[7]	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 "Oedema", "Oedema peripheral", "Pitting oedema" and "Generalised oedema"
[5] Includes terms "Arrhythmia", "Tachycardia", "Atrial fibrillation", "Supraventricular tachycardia", "Atrial tachycardia", "Ventricular tachycardia", "Atrial flutter", "Bradycardia", "Atrioventricular block complete", "Conduction disorder", and "Bradyarrhythmia".
[6] Includes terms "Angina pectoris", "Chest pain", and "Angina unstable". Myocardial infarction or ischemia occurred more commonly in the placebo arm than in abiraterone (1.3% vs 1.1% respectively).
[7] Includes terms "Cardiac failure", "Cardiac failure congestive", "Left ventricular dysfunction", "Cardiogenic shock", "Cardiomegaly", "Cardiomyopathy" and "Ejection fraction decreased"

7.3.4.2 Mineralocorticoid-related Adverse Events

Due to the mechanism of action of abiraterone acetate, a decrease in the negative feedback inhibition of cortisol on the hypothalamic-pituitary axis may lead to increases in ACTH resulting in increased levels of mineralocorticoid mediated toxicities. This effect seemed to be attenuated with the routine use of 10 mg of prednisone given to patients in the COU-AA-301 trial. Table 28 lists mineralocorticoid related AE frequencies in the treatment and placebo arms of

the pivotal trial as well as the pooled phase 1 and 2 trials and the overall abiraterone acetate population. The mineralocorticoid effects seen in COU-AA-301 did not lead to treatment discontinuations and there were no deaths reported for AE terms of hypertension, edema or hypokalemia.

Table 28: Mineralocorticoid Adverse Events

	Placebo COU-AA-301 N=394		AA COU-AA-301 N=791		AA Pooled Phase 1/2 N=279		Overall AA N= 1070	
GRADE	All	3-4	All	3-4	All	3-4	All	3-4
Edema[1]	18.3%	0.8%	26.7%	1.9%	30.8%	0.4%	27.8%	1.5%
Hypokalemia	8.4%	0.8%	17.1%	3.8%	34.8%	2.5%	21.7%	3.5%
Hypertension	6.9%	0.3%	8.5%	1.3%	21.9%	1.4%	12.0%	1.3%

[1] Includes terms "Oedema", "Oedema peripheral", "Pitting oedema" and "Generalised oedema"

Reviewer Comment: There is a plausible mechanistic rationale for adverse events related to mineralocorticoid excess in patients taking abiraterone acetate. The relationship is supported by a higher level of mineralocorticoid-related events in the phase 1-2 studies, which did not uniformly require the use of concurrent corticosteroids.

Care should be taken to monitor for these adverse reactions. The recommended labeling text regarding these toxicities includes: "Control hypertension and correct hypokalemia before treatment. Monitor blood pressure, serum potassium and symptoms of fluid retention at least monthly."

7.3.4.3 Hepatotoxicity

There were several cases of significant hepatic transaminase elevations seen in patients taking abiraterone acetate. Table 29 below lists adverse event rates for elevated hepatic transaminases, bilirubin and alkaline phosphatase reported from the pivotal phase 3 trial and pooled phase 1-2 data.

Table 29: Adverse Events Related to Hepatic Toxicity Reported in the Phase 3 Placebo-Controlled Clinical Trial and Pooled Phase 1 and 2 Data

	Abiraterone (N=791)			Placebo (N=394)			Pooled Phase 1-2 (N=279)		
GRADE	ANY	3	4	ANY	3	4	ANY	3	4
Preferred Term	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)	N(%)
AST increased	31(3.9%)	7(0.9%)	1(0.1%)	15(3.8%)	3(0.8%)	1(0.3%)	38(13.6%)	2(0.7%)	0
ALT increased	21(2.7%)	7(0.9%)	0	5(1.3%)	1(0.3%)	1(0.3%)	22(7.9%)	3(1.1%)	0
Hyperbilirubinemia	10(1.3%)	3(0.4%)	0	7(1.8%)	2(0.5%)	1(0.3%)	15(5.4%)	0	0
Alk Phos increased	33(4.2%)	10(1.3%)	1(0.1%)	16(4.1%)	5(1.3%)	1(0.3%)	27(9.7%)	15(5.4%)	1(0.4%)

The applicant presented their table of liver-related adverse events reported for the pivotal trial COU-AA-301 which was verified by the FDA review. This table is presented below (Table 30).

Table 30: Liver-Related Adverse Events Reported in the Phase 3 Trial COU-AA-301

Adverse Event	AA (N=791)	Placebo (N=394)
LFT abnormalities	82 (10.4%)	32 (8.1%)
Blood alkaline phosphatase increased	33 (4.2%)	16 (4.1%)
Aspartate aminotransferase increased	31 (3.9%)	15 (3.8%)
Alanine aminotransferase increased	21 (2.7%)	5 (1.3%)
Hyperbilirubinaemia	10 (1.3%)	7 (1.8%)
Hypoalbuminaemia	6 (0.8%)	4 (1.0%)
Hepatomegaly	5 (0.6%)	1 (0.3%)
Gamma-glutamyltransferase increased	2 (0.3%)	2 (0.5%)
Jaundice	2 (0.3%)	1 (0.3%)
Abnormal faeces	1 (0.1%)	0
Cholestasis	1 (0.1%)	2 (0.5%)
Hepatic enzyme increased	1 (0.1%)	0
Hepatic pain	1 (0.1%)	1 (0.3%)
Hepatotoxicity	1 (0.1%)	0
Ischaemic hepatitis	1 (0.1%)	0
Liver tenderness	1 (0.1%)	0
Varices oesophageal	1 (0.1%)	0
Hepatic encephalopathy	0	1 (0.3%)
Hepatitis	0	1 (0.3%)
Hepatosplenomegaly	0	1 (0.3%)
Liver function test abnormal	0	1 (0.3%)

Table taken from applicants study report COU-AA-301 Clinical Study Report Table 38 page 113.

The safety reviewer analyzed the laboratory dataset, *LABS1*, from COU-AA-301 for liver-related laboratory abnormalities. While the numbers of all-grade AST, ALT and bilirubin elevations were found to be higher, the number of grade 3 or 4 elevations continued to be seen in less than or equal to 2.1% of patients. (Table 31)

Table 31: Elevated Liver-Related Laboratory Values from the Placebo-Controlled Phase 3 Clinical Trial COU-AA-301

	Abiraterone (N=791)		Placebo (N=394)	
GRADE	ANY	3-4	ANY	3-4
AE Term				
High AST	30.6%	2.1%	36.3%	1.5%
High ALT	11.1%	1.4%	10.4%	0.8%
High total Bilirubin	6.6%	0.1%	4.6%	0.0%

Source: Labs1 dataset with VISIT and VISITS ≠ BL and LBNRIND=HIGH. LBORRESN column was selected for values > the cutoff for grade 3 (per CTCAE 3.0 criteria).
Denominator is number of patients with at least 1 post-baseline value

Importantly, there were no deaths attributed to liver failure seen in the integrated safety population. AST, ALT or Bilirubin elevations leading to treatment discontinuation occurred in 0.5% or less of the 1070 patients who received at least 1 gram of abiraterone acetate. AST or ALT elevations leading to dose modification, reduction or interruption were seen in less than 1% of patients taking AA.

Despite the low and relatively comparative numbers of grade ≥ AST/ALT elevations, two patients did experience significant AST and ALT elevations that were considered to be cases of drug-induced liver injury (DILI) by the applicant. A complete analysis of DILI using both Hy's law and eDISH criteria can be found in section 7.3.5.1 Hepatotoxicity: Hy's Law Analysis.

Reviewer Comment:
There is a signal for hepatoxicity seen with the use of abiraterone acetate. There were no deaths reported due to liver failure and the incidence of SAE or treatment interruptions, modifications or discontinuations was less than 1%. A more comprehensive analysis for drug induced liver injury can be found in section 7.3.5.1.

7.3.4.4 Cardiac Toxicity

Fluid retention secondary to mineralocorticoid excess provides a plausible mechanism for increased cardiac stress. While relatively low in incidence, the frequency of grouped AE terms for arrhythmias, chest pain or discomfort and cardiac failure was higher in the abiraterone arm of the placebo controlled trial COU-AA-301 (Table 27).

Arrhythmias:

The grouped term arrhythmias occurred in 7.2% of the abiraterone arm versus 4.6% of patients taking placebo. The grouped term is subdivided into its components in Table 32. The predominant preferred terms are tachycardia (21 patients) and atrial fibrillation (17 patients) in the abiraterone arm. The clinical significance of this finding is unclear given the nearly identical rate of grade 3-4 events (1.1% versus 1.0%). Additionally, there was minimal difference in sudden death and syncope between the two arms with 1 sudden death reported and 8 patients with syncope in the abiraterone arm versus 0 sudden deaths and 6 syncopal episodes in the placebo arm.

Table 32: Arrhythmias and Conduction Disorders Reported in COU-AA-301

	Abiraterone Acetate (N=791)	Placebo (N=394)
Tachycardia	21 (2.7%)	6 (1.5%)
Atrial fibrillation	17 (2.1%)	5 (1.3%)
Arrhythmia	9 (1.1%)	0
Bradycardia	4 (0.5%)	1 (0.3%)
Supraventricular tachycardia	2 (0.3%)	0
Arrhythmia supraventricular	1 (0.1%)	1 (0.3%)
Atrial tachycardia	1 (0.1%)	1 (0.3%)
Conduction disorder	1 (0.1%)	0
Ventricular tachycardia	1 (0.1%)	0
Atrioventricular Block Complete	1 (0.1%)	0
Atrial Flutter	0	1 (0.3%)
Bradyarrhythmia	0	1 (0.3%)
Clinical Signs of Significant Arrhythmia		
Cardiac Arrest	1 (0.1%)	2 (0.5%)
Sudden Death	1 (0.1%)	0
Syncope	8 (1.0%)	6 (1.5%)
Loss of Consciousness	5 (0.6%)	1 (0.3%)

Search Method: Dataset AE by TRTP searching AEDECOD for terms containing "tachycardia", "atrial", "arrhythmia", "conduction disorder", "atrioventricular block"

Chest Pain or Chest Discomfort:

Chest pain or chest discomfort occurred slightly more frequently in the abiraterone arm compared with placebo; however, myocardial infarction and unstable angina were seen at approximately the same frequency (Table 33). The increased frequency of chest pain or discomfort seen with abiraterone is largely due to the preferred term "angina pectoris" which occurred in 10 patients on abiraterone and 2 on placebo (1.3% versus 0.5%). Nonetheless, deaths due to myocardial infarction or ischemia were seen in 1 patient in the abiraterone arm and 2 patients in the placebo arm.

Table 33: Chest pain, Chest Discomfort and Myocardial Infarction or Ischemia Reported in COU-AA-301

	Abiraterone Acetate (N=791)	Placebo (N=394)
Musculoskeletal chest pain	24 (3.0%)	10 (2.5%)
Chest pain	20 (2.5%)	9 (2.3%)
Non-cardiac chest pain	18 (2.3%)	9 (2.3%)
Angina pectoris	10 (1.3%)	2 (0.5%)
Myocardial infarction	6 (0.8%)	3 (0.8%)
Acute myocardial infarction	2 (0.3%)	1 (0.3%)
Angina unstable	0	1 (0.3%)

Search Method: Dataset AE by TRTP searching AEDECOD for terms containing "chest pain", "angina", "infarction", "ischemia"

Cardiac Failure:

The grouped term "Cardiac failure" was seen more frequently in the abiraterone arm. Cardiac failure-related adverse event terms as well as possible clinical signs of heart failure are shown below in Table 34 . Cardiac failure and related AEs resulted in treatment discontinuation in 3 patients taking abiraterone compared to no patients on the placebo arm. There was 1 death reported due to cardiac failure in both the abiraterone and placebo arms.

Table 34: Cardiac Failure and related Adverse Events Reported in COU-AA-301

	Abiraterone Acetate (N=791)	Placebo (N=394)	Pooled Phase 1-2 (N=279)
Cardiac failure congestive	8 (1.0%)	(0.3%)	0
Ejection fraction decreased	7 (0.9%)	0	0
Pulmonary oedema	5 (0.6%)	0	0
Cardiac failure	3 0.4%)	2 (0.5%)	0
Acute pulmonary oedema	1 (0.1%)	0	0
Cardiogenic shock	1 (0.1%)	0	0
Cardiomegaly	1 (0.1%)	0	0
Left ventricular dysfunction	1 (0.1%)	1 (0.3%)	1 (0.4%)
Clinical Signs of Cardiac Failure			
Dyspnea	102 (12.9%)	49 (12.4%)	45 (16.1%)
Dyspnea Exertional	28 (3.5%)	17 (4.3%)	5 (1.8%)
Pleural effusion	17 (2.2%)	6 (1.5%)	4 (1.4%)
Dsypnea paroxysmal nocturnal	1 (0.1%)	0	0
Dyspnea at rest	1 (0.1%)	0	0

Search Method: Dataset AE by TRTP searching AEDECOD for terms containing "cardiac failure", "congestive", "cardiomegaly", "ejection fraction", "cardiogenic shock", "left ventricular", "cardiomyopathy", "pumonary oedema".
Search Method: Dataset AE by TRTP searching AEDECOD for terms containing, "dyspnoea".

Search Method: Dataset AE by TRTP searching AEDECOD for terms containing "cardiac failure", "congestive", "cardiomegaly", "ejection fraction", "cardiogenic shock", "left ventricular", "cardiomyopathy", "pumonary oedema".
Search Method: Dataset AE by TRTP searching AEDECOD for terms containing, "dyspnoea".

To assess clinical symptoms that may be associated with cardiac failure, an analysis of AE terms containing the word dyspnea was performed and the result

showed that dyspnea occurred at similar frequencies between the placebo and abiraterone acetate arm of COU-AA-301. There is a lack of cardiac failure reported in the phase 1-2 pooled data; however, it is noteworthy that the frequency of dyspnea reported in the phase 1-2 pooled data is higher than the abiraterone arm of COU-AA-301 (Table 34).

The dataset *MUGAECHO* was reviewed to further evaluate the effect of abiraterone acetate on cardiac function. There were 222 (28.1%) patients in the abiraterone arm and 119 (30.2%) patients in the placebo arm who had post-baseline cardiac function assessment with either echocardiography or MUGA. Table 35 presents the data for the abiraterone and placebo arm of the COU-AA-301 clinical trial.

Table 35: Post-baseline Cardiac Function Evaluated by Transthoracic Echo or MUGA

Patients with Post-Baseline LVEF Assessments	Abiraterone Acetate (N=222)	Placebo (N=119)
Any Post- Baseline LVEF <50%	17 (7.7%)	6 (5.0%)
LVEF 40 to <50	13 (5.9%)	5 (4.2%)
LVEF 30 to <40	3 (1.4%)	1 (0.8%)
LVEF 20 to <30	3 (1.4%)	0

Reviewer Comment: Cardiac failure is plausibly related to abiraterone acetate's mechanism of action secondary to the potential for fluid retention from mineralocorticoid excess. Albeit occurring in low frequency, clinically significant AEs related to cardiac failure including pleural effusion (2.2% versus 1.5%) pulmonary edema and acute pulmonary edema (6 cases versus 0) and paroxysmal nocturnal dyspnea (1 case versus 0) were seen more frequently in the abiraterone acetate arm.

Patients were excluded from study COU-AA-301 if their baseline ejection fraction was <50%. Despite the fact that the protocol specified that an end-of-study TTE or MUGA should be performed in all patients, analysis of the cardiac function assessments in the dataset MUGAECHO reveals that only 28.1% of AA and 30.2% of Placebo patients had a post-baseline cardiac function assessment. Based on the available data, the frequency of patients with a post-baseline ejection fraction (EF) less than 40% was quite low, but was seen more frequently in the AA arm (6 patients versus 1 patient in placebo). Abbreviated narratives for the 3 patients in the AA arm with significant EF reduction (documented post-baseline EF less than 30%) are listed below. Of note, case 3 appeared to have been a protocol violation based on his baseline MUGA EF of

<30%, indicating that this case may not represent a decreased EF from baseline.

NARRATIVES for PATIENTS WITH POST-BASELINE EF <30%
Case 1: Study COU-AA-301 Narratives: Subject ID Number 175-0001

Subject 175-0001 (Cause of death: Grade 5 cardio-respiratory arrest) (Serious adverse events: Grade 2 hypertension, Grade 2 failure to thrive, Grade 3 pneumonia, Grade 5 cardio-respiratory arrest) (Grade 3 or higher adverse events of special interest: Grade 3 cardiac failure congestive, Grade 5 cardio-respiratory arrest). 74-year-old white man who was initially diagnosed with prostate cancer approximately 18 years prior to study enrollment. At enrollment, the subject's baseline PSA was 378.9 µg/L and the sites of metastatic disease included bone, soft tissue, and viscera (lung). Previous prostate cancer treatments included chemotherapy with docetaxel. The subject received palliative radiation to an unknown site and to T3 for spinal cord compression. The subject's medical history included transurethral resection of the prostate, insulin-dependent diabetes mellitus treated with glargine and aspart insulin, pulmonary embolism, hypercholesterolemia, hypertension (no treatment reported), anemia, deep vein thrombosis treated with enoxaparin sodium, intermittent hematuria, nocturia, and urinary incontinence. At baseline, blood pressure was not elevated (110/70 mmHg). The **baseline ECG showed inferior infarction of indeterminate age, T-wave abnormality, anterolateral ischemia**, and prolonged QT, and was reported as abnormal but not clinically significant. **The LVEF was 58%.** The subject was randomly assigned to receive abiraterone acetate 1000 mg daily and prednisone/prednisolone 5 mg twice a day.

Grade 2 hypertension, a serious adverse event, and Grade 2 nausea were reported on Study Day 161 and assessed as possibly related to study medication and unlikely related to prednisone/prednisolone. The subject stated that he felt lightheaded, vomited and went to a walk-in medical clinic. His blood pressure was 150/100 mmHg. The clinic doctor advised him to go to the emergency room and he was admitted for observation for the hypertension. The subject was treated with sodium chloride infusion for the hypertension, and with ondansetron for the nausea. The hypertension and nausea resolved in 3 days. He was discharged on Study Day 163.

Grade 1 exertional dyspnea and Grade 1 paroxysmal exertional dyspnea were reported on Study Day 285 and were assessed as unrelated to study medication and prednisone/prednisolone. He received treatment with furosemide. The paroxysmal nocturnal dyspnea and exertional dyspnea were ongoing until his death.

The subject withdrew consent and received the last dose of study medication on Study Day 319.

Grade 2 failure-to-thrive-was reported as a serious adverse event on Study Day 322 and was assessed as unlikely related to study medication and unrelated to prednisone/prednisolone by the investigator. The subject reported he took only 5 mg of prednisone/prednisolone for 2 days and then discontinued it since at that time he felt very weak, and was not able to eat or drink due to loss of taste and appetite. His family decided to have the subject admitted to the hospital on Study Day 322. The subject was treated with prednisone 40 mg for 3 days for the failure to thrive. On Study Day 324, new pleural effusions were reported. Grade 1 atrial tachycardia was reported on Study Day 325 and assessed as unrelated to study medication and prednisone/prednisolone by the investigator. No heart rate value was reported. Grade 2 ejection fraction decreased (low ejection fraction 25%) was reported on Study Day 326 and was assessed as unlikely related to study medication and prednisone/prednisolone. During this time, his hemoglobin dropped to 7 requiring blood transfusion. The physician thought the subject likely had a silent cardiac ischemia. The subject received diltiazem hydrochloride for the atrial tachycardia, which resolved within 1 day and the failure to thrive resolved in 8 days. The left ejection fraction was 44% on Study Day 329, and he was discharged on that day.

On Study Day 337, the LVEF was 25%. The ECG showed left axis deviation, T-wave inversion in the inferolateral leads and borderline QT prolongation; the QT interval was 384 ms, QTcF was 442.803 ms, PR interval was 162 ms, QRS was 80 ms, and ventricular rate was 92 beats per minute. The neutrophil count on Study Day 337 was 7.31 x 109/L (normal range: 1.80-7.80 x 109/L).

Grade 3 pneumonia, a serious adverse event and Grade 3 congestive cardiac failure, and Grade 2 sepsis were reported on Study Day 341. These events were assessed as unrelated to study medication and prednisone/prednisolone by the investigator. The subject was taken to the hospital as he was short of breath and had diffuse pain, and was admitted on Study Day 341. The subject was found to

have pneumonia, sepsis, congestive heart failure, acute renal failure, and thrombocytopenia. He was treated with cefepime hydrochloride, ciprofloxacin, and vancomycin for the pneumonia and sepsis, and furosemide for the congestive cardiac failure.

While hospitalized, the subject had Grade 5 cardio-respiratory arrest on Study Day 344 that was assessed as unrelated to study medication and prednisone/prednisolone by the investigator. The subject died on Study Day 344 as a result of the cardio-respiratory arrest, 25 days after the last dose of study medication.

Case 2: Study COU-AA-301 Narratives: Subject ID Number 118-0003

Subject 118-0003 (Grade 3 or higher event of special interest: Grade 3 ejection fraction decreased) was a 68-year-old white man who was initially diagnosed with prostate cancer approximately 7 years prior to study enrollment. At enrollment, the subject's baseline PSA was 237.6 µg/L and the site of metastatic disease was bone. Previous prostate cancer treatments included prostatectomy; endocrine therapy with goserelin acetate (ongoing), flutamide, and cyproterone; and chemotherapy with docetaxel and patupilone. The subject received palliative radiation to femurs, right shoulder, pelvis, and sacrum, and to T10-L1. The subject also received ongoing prednisone. The subject's medical history included hypertension treated with valsartan (stopped Study Day -7) and atenolol (stopped on Study Day 15), gastric reflux treated with metoclopramide, bilateral lower leg edema, tingling of feet and toes, mid back pain, decreased hemoglobin (108 g/L at baseline; normal range: 125-170 g/L), fatigue, and shortness of breath. The subject had cardiac risk factors of hypertension and gender. The baseline ECG showed supraventricular premature beats and borderline left axis deviation, reported as abnormal and not clinically significant; QT interval was 428 ms, QTcF interval was 439.573 ms, PR interval was 176 ms, QRS interval was 23 ms, and ventricular rate was 65 beats per minute. The **baseline echocardiogram was reported as normal; the LVEF was 53%.** The subject was randomly assigned to receive abiraterone acetate 1000 mg daily and prednisone/prednisolone 5 mg twice a day.

Treatment with study medication was discontinued as the subject was starting a new anti-cancer treatment. The subject received the last dose on Study Day 57. The subject received palliative radiation to the skull and right tibia starting on

Study Day 58.

On Study Day 60, Grade 3 decreased ejection fraction (25%) was reported and assessed by the investigator as unrelated to study medication and prednisone/prednisolone. The ECG was reported as abnormal and clinically significant, no other details were reported; QT interval was 400 ms, QTcF interval was 425.063 ms, PR interval was 160 ms, QRS interval was 32 ms, and ventricular rate was 72 beats per minute. The event persisted.

The subject died from underlying disease 171 days after the last dose of study medication.

Case 3: Study COU-AA-301 Narratives: Subject ID Number 502-0002

Subject 502-0002 (Serious adverse events: Grade 4 renal failure acute, Grade 4 cardiac failure) (Adverse event leading to discontinuation: Grade 4 cardiac failure) (Grade 3 or higher adverse events of special interest: Grade 4 cardiac failure, Grade 3 hypokalemia) was a 73-year-old white man who was initially diagnosed with prostate cancer approximately 10 years prior to study enrollment. At enrollment, the subject's baseline PSA was 187.6 µg/L and the site of metastatic disease was bone. Previous prostate cancer treatments included prostatectomy; endocrine therapy with leuprorelin acetate (ongoing), bicalutamide, and cyproterone acetate; and chemotherapy with docetaxel and cyclophosphamide. The subject received palliative radiation to the back. The subject's **medical history included bone pain treated with oxycodone hydrochloride, dilated left ventricle and global hypokinesia** and renal insufficiency. The ECG at baseline was reported as normal. **The multiple gated acquisition scan was reported as not clinically significant and LVEF was 29%. At baseline,** potassium was 4.4 mmol/L (normal range: 3.5-5.5 mmol/L), blood urea nitrogen was 12.1 mmol/L (normal range: 1.8-9.3 mmol/L), creatinine was 133 µmol/L (normal range: 44-133 µmol/L), and creatinine clearance was 50 mL/minute (range lower limit: 91 mL/minute). The subject was randomly assigned to receive abiraterone acetate 1000 mg daily and prednisone/prednisolone 5 mg twice a day.

Grade 4 acute renal failure and Grade 4 cardiac failure (verbatim: decompensation cardiac) were reported as serious adverse events on Study Day 5 and were assessed as unrelated to study medication and prednisone/prednisolone by the investigator. The subject was hospitalized for

these events on Study Day 8. Per CIOMS, the subject was admitted for acute respiratory failure due to cardiopulmonary edema with acute renal failure. The subject had been oliguric for several days at home. On Study Day 9, the subject's clinical status worsened rapidly, and he abruptly decompensated with intense dyspnea, O2 saturation of 56%, pallor, and ocular disturbance. Creatinine was 390 µmol/L (normal range not provided). A chest x-ray revealed minimal pleural effusion. The differential diagnoses were pulmonary embolism or an infectious process. The subject was anticoagulated with unfractionated heparin, and started on amiodarone, ciprofloxacin, ceftriaxone, and supplemental O2 at 15 L/minute. An abdominal ultrasound revealed stable bilateral pyelocaliceal dilation compared to previous results. Treatment with study medication was discontinued on Study Day 9.

Grade 2 hyperkalemia (potassium: 5.9 mmol/L) was reported on Study Day 9, and he received oral sodium polystyrene sulfonate for 3 days. On Study Day 10, the hyperkalemia worsened in severity to Grade 3 (potassium: 6.0 mEq/L), treated with a single dose of IV sodium bicarbonate and furosemide 160 mg. No ECG information was reported; his blood pressure was 130/90 mmHg and heart rate was 102 beats per minute. Grade 1 hypokalemia was reported on Study Day 14 (potassium: 3.1 mmol/L) and the subject was treated with oral potassium chloride 8 IU daily from Study Day 14 through Study Day 21. These events of hyperkalemia and hypokalemia were assessed as unrelated to study medication and prednisone/prednisolone.

Anticoagulation with fluindione was started on Study Day 17 for pulmonary embolism. The hypokalemia worsened in severity to Grade 3 (potassium 2.5 mmol/L) on Study Day 17. Grade 3 hyperkalemia (potassium 6.1 mmol/L) was reported on Study Day 21 and assessed as unrelated to study medication and possibly related to prednisone/prednisolone. Treatment with potassium chloride was stopped on Study Day 21. An ECG on that day showed bundle branch block, reported as abnormal but not clinically significant. A multiple gated acquisition scan was reported as abnormal and clinically significant, no further information was reported; LVEF was 25%. His blood pressure was 120/80 mmHg and heart rate was 83 beats per minute. The Grade 3 hyperkalemia resolved in 2 days, and the acute renal failure and cardiac failure resolved in 24 days. Per CIOMS, on Study Day 21, creatinine was 11.0 mg/L. The subject was started on cyclophosphamide on that day. The subject was discharged on Study Day 28.

Treatment with study medication was discontinued as a result of the cardiac failure; the subject received the last dose on Study Day 8. The subject died 106 days after the last dose of study medication.

Reviewer Comment: While an infrequent occurrence, cardiac failure and arrhythmias were seen more commonly in the abiraterone acetate group than in placebo. The product labeling will reflect the fact that abiraterone acetate was not tested in patients with baseline EF<50% and that monitoring for signs and symptoms of cardiac failure is recommended. Specific wording added to the highlights section under warnings and precautions in the product labeling is provided below:

"Use ZYTIGA with caution in patients with a history of cardiovascular disease. The safety of ZYTIGA in patients with LVEF < 50% or NYHA Class III or IV heart failure is not established. Control hypertension and correct hypokalemia before treatment. Monitor blood pressure, serum potassium and symptoms of fluid retention at least monthly."

7.3.5 Review of Specific Primary Safety Concerns

7.3.5.1 Hepatotoxicity: Hy's Law Analysis

Because there were a small number of patients who experienced significant liver transaminase elevations, a Hy's Law analysis was performed in the COU-AA-301 dataset and reported in section 6.2.2.4 of the applicant's clinical study report. Hy's Law criteria per the FDA guidance for industry on drug-induced liver injury (FDA Guidance July 2009) includes three components: AST or ALT ≥ 3xULN, elevation of total Bilirubin to ≥2 xULN without signs of cholestasis (elevated Alkaline Phosphatase) and the absence of an alternative explanation for the combination of increased AST/ALT and tBili. This analysis is challenging in the mCRPC population given that the majority of patients have bone metastases and elevated alkaline phosphatase. As such, the applicant performed a Hy's Law analysis using both FDA criteria and using eDISH methodology which uses the same criteria but excludes alkaline phosphatase levels. The applicant's results were presented in the COU-AA-301 clinical study report, the excerpt is shown below (Table 36).

Table 36: Subjects Who Met Hy's Law or eDISH Criteria (Study COU-AA-301 Safety Population)

Criteria	Subjects Meeting Criteria
Hy's Law per FDA guidance	None
eDISH	Abiraterone acetate group: 113-0038 (total bilirubin = 2.0xULN) 158-0001 506-0007 907-0009 Placebo group: 125-0023 (total bilirubin = 2.0xULN) 614-0007 909-0007

eDISH= electronic tool for drug-induced serious hepatotoxicity; FDA=U.S. Food and Drug Administration; ULN=upper limit of normal

(Taken from applicant Clinical Study Report COU-AA-301 Page 118).

The clinical safety reviewer performed a query of the LABS1 dataset for trial COU-AA-301. A search for all patients who had an AST or ALT greater than or equal to 3 times the upper limit of normal (ULN) and a total bilirubin ≥ 2XULN resulted in the identification of 4 patients in the AA arm and 3 patients in the placebo arm (Table 37).

Table 37: Results from FDA search of LABS1 Dataset For Potential Hy's Law Cases

	Number of Patients With Laboratory Abnormality		
	AST or ALT >=3XULN	tBili >=2XULN	BOTH
AA (791)	47	5	4
Placebo (394)	20	4	3
SUBJECT IDs FOR PATIENTS MEETING BOTH CRITERIA			
Treament Arm	Subject ID		
AA	COU-AA 301-113-0038		
AA	COU-AA-301-125-0025		
AA	COU-AA-301-158-0001		
AA	COU-AA-301-506-0007		
Placebo	COU-AA-301-125-0023		
Placebo	COU-AA-301-614-0007		
Placebo	COU-AA-301-909-0007		

The clinical safety reviewer's Hy's Law analysis of trial COU-AA-301 returned the same set of patients that were identified by the applicant with two exceptions. Patient COU-AA-301-125-0025 was found in the AA arm in the

FDA analysis but not reported by the applicant. The second patient, COU-AA-301-909-0007 was reported by the applicant but not found during the FDA analysis. The narratives and laboratory values for these two patients are presented below.

Narrative: Patient COU-AA-301-125-0025:

A review of the patient's narrative reveals that he was a 72 yr old white male with CRPC metastatic to the bone and liver. His screening laboratory values (day -14) were notable for grade 1 AST and ALT elevation (Table 38). On study day 1 the patient had two sets of labs drawn with one set revealing an ALT of 172 in a laboratory with the upper limit of normal reported as 55 and thus the patient satisfied criteria for ALT over three times the upper limit of normal. That same day he had a bilirubin of 2.7 which was >2XULN. On study day 9 he experienced grade 3 bile duct obstruction and was treated with biliary drainage. On study day 16 he was again diagnosed with bile duct obstruction and study medication was interrupted secondary to elevated bilirubin (grade 3) and discontinued on day 21 due to elevated AST. This case does not satisfy Hy's law based on an elevated alkaline phosphatase and two alternative etiologies for liver laboratory abnormalities including hepatic metastases and bile duct obstruction.

Table 38: Liver Laboratory Abnormalities for Patient COU-AA-301-125-0025

	Lab Day			
	-14	1	16	85
AST (IU/L)	58	93,98	70,79	116
ALT (IU/L)	69	172, 175	125	118
Alk Phos (IU/L)	184	561, 625	325, 423	486
tBili (mg/dL)	0.6	2.2, 2.7	5.3, 6.0	0.6

Narrative: Patient COU-AA-301-907-0009:

The FDA analysis did not identify one patient (COU-AA-301-907-0009) whom the sponsor identified in their analysis. The day 32 laboratory value abnormalities for this patient were not included in the LABS1 dataset (accounting for our inability to pick up this case on our LABS1 analysis) and applicant notes that the labs were not present in the eCRF at the time of database lock. The narrative and laboratory data for this patient are presented below.

Subject 907-0009, who had known liver metastases at study entry, had baseline liver function test concentrations that were within normal limits except for an ALP concentration of 319 IU/L. This subject had a Grade 4 SAE of the preferred term, hepatoxicity, on Study Day 32; his ALT concentration was approximately 40 x ULN, his AST concentration was approximately 35 x ULN, and his ALP and total bilirubin concentrations were approximately 6 x ULN (Table 39). Note: The laboratory data documenting the ALT and AST concentrations during the course of the event were not present in the eCRF at the time of database lock. These data were available in the CIOMS and discussed with the Sponsor's medical monitor at the time of the event; the subject's status was followed closely and the event resolved. Viral hepatitis serologies, including Epstein-Barr virus and cytomegalovirus, were negative. Treatment was permanently discontinued. The subject died approximately 6 months later due to underlying prostate cancer.

Table 39: Liver Test Results for Subject 907-0009

Study Day	ALT Normal Range 0-55 IU/L	AST Normal Range 0-40 IU/L	ALP Normal Range 25-160 IU/L	Total Bilirubin Normal Range: 2-21 µmol/L
Day -7	9	23	319	5
Day 1	12	25	371	3
Day 15	11	24	351	10
Day 29[a]	313	235	378	15
Day 32	2252	1406 [5-40]	696/756 [30-115]	120 [3-20 µmol/L]
Day 62	27	35	424	10

ALT=alanine aminotransferase; ALP=alkaline phosphatase; AST=aspartate aminotransferase
Values on Study Day 32 reported in CIOMS; normal ranges in parentheses.
[a] Study medication was stopped on Study Day 30.

(Taken from Applicant Clinical Study Report COU-AA-301 page 119)

Reviewer Comment: Although this patient had significant elevation of liver function tests, the elevation of alkaline phosphatase and the presence of hepatic metastatic disease exclude the patient from meeting the definition for Hy's Law. Nonetheless, the applicant considered this a case of drug-induced liver injury (DILI) and the clinical safety reviewer concurs with that interpretation given the decrease in AST and ALT seen following treatment discontinuation on day 62.

Hy's Law Analysis of the Integrated Safety Population

The applicant also performed a Hy's Law analysis on the integrated safety population and found one more case of potential Hy's Law for a patient in study COU-AA-003, subject 600-031. The patient experienced grade 4 increase in

transaminases (AST 832 IU/L, ALT 822 IU/L) with elevated alkaline phosphatase 304 IU/L and an increased bilirubin of 2.28mg/dL on study day 309. Following treatment interruption, the events resolved and the patient was successfully rechallenged with abiraterone acetate. The narrative for this patient is presented below.

Narrative: Patient COU-AA-003-600-031:

Subject 1-31 (Serious adverse event and Grade 3 or higher adverse event of special interest: Grade 4 transaminases increased) was a 67-year-old white man who was initially diagnosed with prostate cancer approximately 5 years prior to study enrollment. At the time of the initial diagnosis his prostate cancer was staged as T4, N0 (M stage was not reported), with a total Gleason score of 8. Previous prostate cancer treatments included goserelin (ongoing), bicalutamide, diethylstilbestrol, dexamethasone, and cyproterone; radiation; and docetaxel. The subject also received an investigational agent CP-751871 (insulin-like growth factor type I receptor antibody) and was treated in a clinical trial investigating radium treatment. He did not undergo prostatectomy. The subject's medical history included hypertension, deep vein thrombosis, intermittent lack of appetite, emphysema, a urinary tract infection, and a gallstone (per CIOMS). At enrollment, sites of metastatic disease included bone, lymph node, and prostate. At baseline, the subject's weight was 77 kg, BSA was 1.9 m2, PSA was 423 ng/mL, and ECOG performance status was 0. The subject's baseline transaminase values were AST: 24.0 U/L and ALT: 13.0 U/L, bilirubin value was 0.64 mg/dL, and blood platelet count was 166,000/mm^3.

On Study Day 309, a serious adverse event of Grade 4 increased transaminases (AST: 832 U/L, ALT 822 U/L) and an adverse event of Grade 2 increased bilirubin (2.28 mg/dL) were reported; both events were assessed by the investigator as unlikely related to study medication. The subject was hospitalized for the elevated transaminase values, which lessened in severity to Grade 3 on Study Day 310, and then to Grade 1 on Study Day 315. The study treatment regimen was withheld due to elevated transaminases, and the events resolved within 9 days. Grade 1 bilirubin increase (per CIOMS: 20 µmol/L) recurred on Study Day 323, and was assessed by the investigator as unlikely related to study medication. The event resolved within 8 days. The subject completed 12 cycles of treatment.

The laboratories available in the ADLB dataset from the integrated safety database are presented below (Table 40).

Table 40: Patient COU-AA-003-600-031 Laboratory Values

Lab Day	AST (IU/L)	ALT (IU/L)	tBili (mg/dL)	Alk Phos (IU/L)
1	24	13	1.1	113
8	15	11	1.6	107
29	17	11	1.3	162
57	13	9	1.3	184
85	15	9	1.6	157
113	14	9	1.6	167
141	15	9	1.3	140
169	14	9	1.3	142
197	16	9	1.2	151
225	16	7	1.5	152
253	16	10	1.3	136
281	16	57	1.2	184
309	832	822	3.9	304
358	14	9	1.3	201

Reviewer Comment: This patient met the criteria for Hy's Law with the exception of an elevated alkaline phosphatase and possibly the history of a gallstone. As stated, this alkaline phosphatase elevation is difficult to interpret given the patients bone metastases from prostate cancer. It is reassuring to note that the patient was rechallenged with abiraterone acetate following resolution of his transaminases. Nonetheless, the dataset only includes one more set of labs on day 358 and so it appeared that the patient was only treated for one more cycle.

Overall Hy's Law Analysis:
Abiraterone acetate did produce a small signal for liver toxicity with two patients out of the 1070 receiving abiraterone having possible drug-induced liver injury (DILI). There were no cases of Hy's Law by strict definition secondary to the frequency of elevated alkaline phosphatase in most patients with prostate cancer and concurrent liver metastases seen in several patients. There were no deaths reported secondary to liver failure. Both of the episodes of DILI resolved following discontinuation of abiraterone and one patient was rechallenged with abiraterone acetate, although laboratory data following rechallenge is sparse (only one set of labs for day 358).

Given the overall survival benefit seen with abiraterone acetate, the prognosis of patients with metastatic castrate resistant prostate cancer who have received

docetaxel and the otherwise favorable toxicity profile of abiraterone acetate, it is the opinion of the clinical safety reviewer that the benefit-risk ratio remains favorable for abiraterone acetate in this population despite two possible cases of DILI.

7.3.5.2 Adrenocortical Insufficiency (AI)

Investigators reported adrenal insufficiency in 2 patients in the phase 3 clinical trial and three patients in the pooled phase 1-2 data. All events were grade 2 except one patient (COU-AA-003 Subject ID Number 160-105 (3-105). There was one dose interruption and one treatment discontinuation based on AE term adrenal insufficiency. There were no deaths reported as an outcome of AI. However, in review of the narratives, patient AA-301-153-0001 (case 2 below), had his AI ongoing at the time of his death. In addition, it appeared that adrenal insufficiency occurred not only following prednisone interruption, but also occurred while patients were on the recommended dose of prednisone in the setting of stress. In this scenario, most patients were experiencing some concurrent illness or AE. The abbreviated patient narratives for the 5 patients who experienced adrenal insufficiency are listed below:

AI Case 1: Study COU-AA-301: Subject ID Number 914-0005

This 71-year-old white man was initially diagnosed with prostate cancer approximately 15 years prior to study enrollment. Previous prostate cancer treatments included prostatectomy and radiation to the prostate bed; endocrine therapy with leuprorelin acetate (ongoing), bicalutamide, aminoglutethimide, and an unspecified investigational drug, and chemotherapy with docetaxel. The subject's medical history included gout treated with allopurinol, alopecia, nail changes, gastro esophageal reflux treated with rabeprazole, leg weakness, fragile skin, and cough. The subject was randomly assigned to receive abiraterone acetate 1000 mg daily and prednisone/prednisolone 5 mg twice a day

On Study Day 6, Grade 2 pyrexia, a serious adverse event, and adrenal insufficiency were reported. The pyrexia was assessed by the investigator as unrelated to study medication or prednisone/prednisolone, and the adrenal insufficiency was assessed as possibly related to study medication and unrelated to prednisone/prednisolone. The subject was febrile at 37.5°C on the day of his first dose. His chest was clear but **he had infected abrasions on his arm**. On

Study Day 6, his temperature was 39.5°C and he was sent to the local emergency room. He was admitted to the hospital for septic workup and antibiotics and was treated for a presumed respiratory tract infection. He received ceftazidime, ceftriaxone, and roxithromycin for the pyrexia and cough, and hydrocortisone for the adrenal insufficiency. The pyrexia resolved in 6 days and the adrenal insufficiency resolved in 4 days. The subject was discharged from the hospital on Study Day 11. As of the clinical cutoff date of 22 January 2010, the subject was still alive.

AI Case 2: Study COU-AA-301: Subject ID Number 153-0001

This 86-year-old white man was initially diagnosed with prostate cancer approximately 15 years prior to study enrollment. Previous prostate cancer treatments included prostatectomy; endocrine therapy with leuprorelin acetate (ongoing) and bicalutamide, and chemotherapy with docetaxel. The subject's medical history included right leg lymphedema, gall stones, and hypertension treated with lisinopril. The subject was randomly assigned to receive abiraterone acetate 1000 mg daily and prednisone/prednisolone 5 mg twice a day.

Grade 1 vomiting was reported on Study Day 114 resulting in an **interruption to study medication and prednisolone/prednisone** starting on Study Day 118. No treatment was reported. Grade 3 dehydration, hypotension, and urinary tract infection, serious adverse events, and Grade 2 cachexia were reported on Study Day 121. No vital signs were reported. The subject was hospitalized on that day for the dehydration, hypotension, and urinary tract infection. He was treated with potassium chloride and IV solutions for dehydration, and levofloxacin for the urinary tract infection. All of these events were assessed as unrelated to study medication and prednisolone/prednisone by the investigator. The dehydration, hypotension, and urinary tract infection resolved in 5 days, and the vomiting was ongoing.

Grade 2 adrenal insufficiency was reported on Study Day 122 and was assessed as unrelated to study medication and possibly related to prednisone/prednisolone by the investigator. The subject was treated with hydrocortisone for the adrenal insufficiency. Prednisone/prednisolone resumed at 20 mg daily on Study Day 123 and study medication resumed on Study Day 125. The subject was discharged on Study Day 125.

Treatment with study medication was discontinued at the discretion of the investigator as a result of PSA progression and liver progression. He received the last dose of study medication on Study Day 126.

Grade 2 asthenia, Grade 3 peripheral edema (verbatim: increased lower extremity edema) and Grade 1 peripheral edema (verbatim: left hand swollen) were reported on Study Day 134 and were assessed as unrelated to study medication and prednisolone/prednisone by the investigator. **The adrenal insufficiency, asthenia, and events of peripheral edema were ongoing at the time of his death.** Grade 5 disease progression was reported as a serious adverse event on Study Day 146 and the subject died at his home on that day from disease progression, 20 days after the last dose of study medication.

AI Case 3: COU-AA-003: Subject ID Number 160-105 (3-105)

This 72-year-old white man was initially diagnosed with prostate cancer approximately 14 years prior to study enrollment. Previous prostate cancer treatments included leuprorelin acetate (ongoing) and bicalutamide; a prostatectomy; and paclitaxel, carboplatin, estramustine, docetaxel, and clinical trials investigating 17-AAG and LBH589 treatments, respectively; and mitoxantrone. He did not undergo radiation. The subject's medical history included degenerative joint disease, hypertension, Lyme disease, coronary artery disease, congestive heart failure, elevated prothrombin time, elevated AST, atrial fibrillation, fatigue, right lower extremity weakness, neuropathy, edema, right hip pain, anemia, and hyperglycemia. At enrollment, sites of metastatic disease included bone, lymph node, and viscera. At baseline, the subject's weight was 104 kg, BSA was 2.4 m2, PSA was 45 ng/mL, and ECOG performance status was 1.

On Study Day 18, serious adverse events of Grade 3 adrenal insufficiency, Grade 3 pleural effusion, and Grade 2 pneumonitis, and an adverse event of Grade 1 hypokalemia, were reported; the investigator assessed the adrenal insufficiency and hypokalemia as possibly related, and the pleural effusion and pneumonitis as unrelated, to study medication. The subject was hospitalized for the adrenal insufficiency, pleural effusion and pneumonitis, and treatment included **broad spectrum antibiotics**. The hypokalemia resolved in 2 days, the **pneumonitis** and pleural effusion resolved in 9 days, and the adrenal insufficiency resolved in 40 days. Treatment with abiraterone acetate was

discontinued due to the adrenal insufficiency, pneumonitis, and pleural effusion. The subject received the last dose of abiraterone acetate on Study Day 18.

AI Case 4: COU-AA-003: Subject ID Number 600-033 (1-33)

Subject 1-33 (Serious adverse events: Grade 4 anemia, Grade 2 muscular weakness, Grade 2 adrenal insufficiency, Grade 2 diarrhea, Grade 2 sepsis) (Adverse event leading to discontinuation: Grade 2 sepsis) was a 71-year-old white man who was initially diagnosed with prostate cancer approximately 11 years prior to study enrollment. At the time of the initial diagnosis his prostate cancer was staged as N0, M0 disease (T stage was not reported). Previous prostate cancer treatments included goserelin (ongoing), bicalutamide, diethylstilbestrol, and prednisone; radiation; and docetaxel. He did not undergo prostatectomy. The subject's medical history included lower back pain, rib pain, general weakness, fatigue, and anemia. At enrollment, sites of metastatic disease included bone, prostate, and viscera. At baseline, the subject's weight was 92 kg, BSA was 2.2 m2, PSA was 6248 ng/mL, and ECOG performance status was 2. His baseline hemoglobin level was 9.7 g/dL.

On Study Day 111, a serious adverse event of Grade 2 muscular weakness was reported, led to subject's hospitalization, and was assessed by the investigator as unrelated to study medication. The event persisted.

Anemia was reported throughout the study as shown in the following table. The subject received the last dose of study medication on Study Day 167. On Study Day 168, serious adverse events of Grade 2 adrenal insufficiency, Grade 2 diarrhea, Grade 3 anemia, and Grade 2 sepsis were reported. These events led to the subject's hospitalization. On Study Day 169, an adverse event of Grade 2 gastrointestinal hemorrhage was also reported. The investigator assessed the adrenal insufficiency and diarrhea as unlikely related; and the anemia, sepsis, and gastrointestinal hemorrhage as unrelated, to study medication. Treatment included dexamethasone, 50% dextrose, normal saline, **amoxicillin and clavulanate** potassium, blood, loperamide, hydrocortisone, and prednisolone. Treatment with abiraterone acetate was discontinued due to **sepsis**. The adrenal insufficiency resolved in 5 days, the diarrhea resolved in 25 days, the anemia resolved in 16 days, the sepsis resolved in 6 days, and the gastrointestinal hemorrhage resolved in 11 days.

AI Case 5: Pooled Phase 1-2: COU-AA-0002: Subject 176-055

This 83 year-old white man was initially diagnosed with prostate cancer approximately 8 years prior to study enrollment. Previous prostate cancer treatments included radiation therapy to the prostate bed, and therapy with leuprolide, goserelin and bicalutamide. The subject's medical history included fatigue, degenerative disk disease, dyslipidemia, emphysema, neutropenia, and hyponatremia. He had a transurethral resection of the prostate for benign prostate hyperplasia. The subject had received abiraterone acetate 1000 mg daily.

Treatment with abiraterone acetate was discontinued on Study Day 315 due to rising PSA. Ongoing fatigue was reported throughout the study that had not improved after the abiraterone acetate discontinuation. Daily dexamethasone 1 mg was administered on Study Day 26, increased to 1.5 mg on Study Day 37, and decreased to 1 mg on Study Day 93. Laboratories obtained while the subject was taking daily dexamethasone 1 mg included an ACTH stim baseline 0.7 mg/dL (reference range: 7-18 mg/dL); ACTH stim 30 minutes 3.7 mg/dL; ACTH stim 60 min 5.3 mg/dL.

On Study Day 344, a non-serious AE of Grade 2 adrenal insufficiency was reported, and assessed by the investigator as possibly related to study medication. The subject's blood pressure was 155/87 mmHg. Review of systems was otherwise negative. Daily dexamethasone 1 mg was continued to treat subject's adrenal insufficiency and fatigue, both of which were ongoing at End-of-Study Visit.

Additional follow up information provided by the investigator (per site communication subsequent to 22 JAN 2010 data cutoff) indicated that the subject received subsequent therapy with docetaxel; at last contact on Study Day 699 he was referred to hospice.

Reviewer Comments: Adrenal insufficiency is mechanistically plausible and, despite the low incidence in this submission, is included in the warning/precautions section of the label. AI occurred both in the setting of prednisone interruption and while prednisone was being taken concomitantly. Most cases of AI occur in the setting of stress; frequently infection.

The recommendation for labeling includes the following text, "Use caution and monitor 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 Zytiga. If clinically indicated, perform appropriate tests such as an ACTH stimulation test to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations."

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Adverse events regardless of attribution were seen in 783 (99%) of the abiraterone arm and 392 (99.5%) of the placebo arm in the pivotal trial. The most common adverse events seen in the abiraterone arm regardless of attribution were fatigue, nausea, back pain, arthralgia and constipation. Table 41 below illustrates that many adverse events were seen more frequently in the placebo arm of the pivotal trial.

The applicant's adverse events table from the COU-AA-301 study report was verified by the clinical reviewer and is presented below as Table 42.

7.4.2 Laboratory Findings

Laboratory datasets LABS1 and LABS2 were analyzed. Laboratory abnormalities that were seen more frequently in the abiraterone arm of the pivotal randomized phase 3 clinical trial are listed in Table 43 below. As expected, the frequency of any grade of laboratory abnormalities was higher in the laboratory datasets than was reported as adverse events in the AE dataset. Nonetheless, the difference in the frequency of laboratory abnormalities between the AA and placebo arms was generally small. For those laboratory abnormalities that were seen more frequently in the abiraterone arm, the frequency of grade 3 or higher laboratory abnormalities is less than 1% in the majority of cases. Grade 3 or higher hypokalemia (5.3%), hypophosphatemia (7.2%), AST elevation (2.1%), ALT elevation (1.4%), leukopenia (1.5%) and low absolute neutrophil count (2.0%) were seen more commonly in the abiraterone arm.

7.4.3 Vital Signs

Vital signs were obtained at screening and during each follow up study visit. The vital signs dataset ADVS was used to verify the applicant's findings in their study report for COU-AA-301. The incidence of abnormalities in vital signs is presented in Table 44 below.

Table 41: Common Adverse Events Occuring in >10% of the Abiraterone Acetate Arm in the phase 3 trial COU-AA-301.

Preferred Term	AA (N=791) All Grades	PLACEBO (N=394) All grades
Fatigue	43.7%	42.9%
Nausea	29.5%	31.5%
Back pain	29.5%	32.7%
Arthralgia	27.2%	22.6%
Constipation	26.0%	30.7%
Oedema peripheral	25.2%	17.3%
Bone pain	24.5%	27.9%
Anaemia	22.6%	26.6%
Vomiting	21.2%	24.6%
Hot flush	19.0%	16.8%
Diarrhoea	17.6%	13.5%
Hypokalaemia	17.1%	8.4%
Pain in extremity	16.9%	20.1%
Anorexia	16.8%	18.3%
Musculoskeletal pain	14.8%	12.9%
Asthenia	13.3%	13.2%
Dyspnoea	12.9%	12.4%
Abdominal pain	12.0%	11.2%
Headache	11.9%	10.7%
Disease progression	11.6%	10.9%
Urinary tract infection	11.5%	7.1%
Weight decreased	10.7%	14.0%
Cough	10.6%	7.6%
Insomnia	10.4%	12.9%
Muscular weakness	10.1%	9.1%

Source: AE.xpt by TRPT, AEBODSYS, AECOD, SUBJID
(Events occurring more frequently in the abiraterone (AA) arm are highlighted.)

Table 42: Incidence of Adverse Events Reported in at least 5% in COU-AA-301

System Organ Class Preferred Term	AA (N=791)					Placebo (N=394)				
	Total	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 1	Grade 2	Grade 3	Grade 4
Number of subjects with a treatment-emergent adverse event	782 (98.9%)	102 (12.9%)	249 (31.5%)	347 (43.9%)	84 (10.6%)	390 (99.0%)	50 (12.7%)	110 (27.9%)	186 (47.2%)	44 (11.2%)
Musculoskeletal and connective tissue disorders	576 (72.8%)	185 (23.4%)	235 (29.7%)	148 (18.7%)	7 (0.9%)	291 (73.9%)	78 (19.8%)	117 (29.7%)	89 (22.6%)	7 (1.8%)
Back pain	233 (29.5%)	96 (12.1%)	90 (11.4%)	44 (5.6%)	3 (0.4%)	129 (32.7%)	45 (11.4%)	46 (11.7%)	37 (9.4%)	1 (0.3%)
Arthralgia	215 (27.2%)	89 (11.3%)	93 (11.8%)	33 (4.2%)	0	89 (22.6%)	30 (7.6%)	43 (10.9%)	16 (4.1%)	0
Bone pain	194 (24.5%)	73 (9.2%)	76 (9.6%)	42 (5.3%)	2 (0.3%)	110 (27.9%)	43 (10.9%)	38 (9.6%)	25 (6.3%)	4 (1.0%)
Pain in extremity	134 (16.9%)	70 (8.8%)	45 (5.7%)	18 (2.3%)	1 (0.1%)	79 (20.1%)	26 (6.6%)	33 (8.4%)	20 (5.1%)	0
Musculoskeletal pain	117 (14.8%)	63 (8.0%)	33 (4.2%)	20 (2.5%)	1 (0.1%)	51 (12.9%)	22 (5.6%)	21 (5.3%)	8 (2.0%)	0
Muscular weakness	80 (10.1%)	25 (3.2%)	37 (4.7%)	17 (2.1%)	1 (0.1%)	35 (8.9%)	15 (3.8%)	15 (3.8%)	4 (1.0%)	1 (0.3%)
Muscle spasms	68 (8.6%)	58 (7.3%)	9 (1.1%)	1 (0.1%)	0	37 (9.4%)	28 (7.1%)	9 (2.3%)	0	0
Groin pain	43 (5.4%)	24 (3.0%)	12 (1.5%)	7 (0.9%)	0	22 (5.6%)	8 (2.0%)	11 (2.8%)	3 (0.8%)	0
General disorders and administration site conditions	549 (69.4%)	229 (29.0%)	204 (25.8%)	110 (13.9%)	6 (0.8%)	262 (66.5%)	102 (25.9%)	95 (24.1%)	59 (15.0%)	5 (1.3%)
Fatigue	346 (43.7%)	143 (18.1%)	137 (17.3%)	64 (8.1%)	2 (0.3%)	169 (42.9%)	64 (16.2%)	66 (16.8%)	36 (9.1%)	3 (0.8%)
Oedema peripheral	197 (24.9%)	135 (17.1%)	50 (6.3%)	11 (1.4%)	1 (0.1%)	68 (17.3%)	48 (12.2%)	17 (4.3%)	3 (0.8%)	0
Asthenia	104 (13.1%)	48 (6.1%)	38 (4.8%)	18 (2.3%)	0	52 (13.2%)	19 (4.8%)	25 (6.3%)	7 (1.8%)	1 (0.3%)
Pyrexia	71 (9.0%)	46 (5.8%)	22 (2.8%)	3 (0.4%)	0	35 (8.9%)	21 (5.3%)	8 (2.0%)	5 (1.3%)	0
Gastrointestinal disorders	531 (67.1%)	277 (35.0%)	190 (24.0%)	59 (7.5%)	5 (0.6%)	264 (67.0%)	135 (34.3%)	96 (24.4%)	30 (7.6%)	2 (0.5%)
Nausea	233 (29.5%)	143 (18.1%)	77 (9.7%)	12 (1.5%)	1 (0.1%)	124 (31.5%)	77 (19.5%)	37 (9.4%)	10 (2.5%)	0
Constipation	206 (26.0%)	120 (15.2%)	78 (9.9%)	8 (1.0%)	0	120 (30.5%)	70 (17.8%)	46 (11.7%)	4 (1.0%)	0
Vomiting	168 (21.2%)	96 (12.1%)	58 (7.3%)	13 (1.6%)	1 (0.1%)	97 (24.6%)	61 (15.5%)	25 (6.3%)	11 (2.8%)	0
Diarrhoea	139 (17.6%)	94 (11.9%)	40 (5.1%)	5 (0.6%)	0	53 (13.5%)	34 (8.6%)	13 (3.3%)	5 (1.3%)	0
Abdominal pain	95 (12.0%)	59 (7.5%)	20 (2.5%)	16 (2.0%)	0	44 (11.2%)	26 (6.6%)	12 (3.0%)	6 (1.5%)	0
Dry mouth	55 (7.0%)	48 (6.1%)	7 (0.9%)	0	0	21 (5.3%)	18 (4.6%)	2 (0.5%)	1 (0.3%)	0
Dyspepsia	48 (6.1%)	37 (4.7%)	11 (1.4%)	0	0	13 (3.3%)	11 (2.8%)	2 (0.5%)	0	0
Metabolism and nutrition disorders	365 (46.1%)	164 (20.7%)	107 (13.5%)	87 (11.0%)	7 (0.9%)	164 (41.6%)	73 (18.5%)	49 (12.4%)	41 (10.4%)	1 (0.3%)
Hypokalaemia	135 (17.1%)	98 (12.4%)	7 (0.9%)	27 (3.4%)	3 (0.4%)	33 (8.4%)	28 (7.1%)	2 (0.5%)	3 (0.8%)	0
Anorexia	131 (16.6%)	58 (7.3%)	61 (7.7%)	12 (1.5%)	0	72 (18.3%)	33 (8.4%)	27 (6.9%)	12 (3.0%)	0
Decreased appetite	75 (9.5%)	54 (6.8%)	17 (2.1%)	4 (0.5%)	0	34 (8.6%)	25 (6.3%)	8 (2.0%)	1 (0.3%)	0
Hyperglycaemia	48 (6.1%)	19 (2.4%)	16 (2.0%)	13 (1.6%)	0	19 (4.8%)	10 (2.5%)	3 (0.8%)	6 (1.5%)	0
Nervous system disorders	339 (42.9%)	187 (23.6%)	87 (11.0%)	49 (6.2%)	16 (2.0%)	178 (45.2%)	82 (20.8%)	43 (10.9%)	43 (10.9%)	9 (2.3%)
Headache	94 (11.9%)	70 (8.8%)	16 (2.0%)	8 (1.0%)	0	42 (10.7%)	30 (7.6%)	9 (2.3%)	3 (0.8%)	0
Dizziness	75 (9.5%)	63 (8.0%)	10 (1.3%)	2 (0.3%)	0	38 (9.6%)	31 (7.9%)	6 (1.5%)	1 (0.3%)	0
Spinal cord compression	28 (3.5%)	1 (0.1%)	5 (0.6%)	11 (1.4%)	11 (1.4%)	20 (5.1%)	0	0	13 (3.3%)	7 (1.8%)
Infections and infestations	328 (41.5%)	112 (14.2%)	153 (19.3%)	56 (7.1%)	7 (0.9%)	134 (34.0%)	64 (16.2%)	49 (12.4%)	17 (4.3%)	4 (1.0%)
Urinary tract infection	91 (11.5%)	32 (4.0%)	42 (5.3%)	17 (2.1%)	0	28 (7.1%)	8 (2.0%)	18 (4.6%)	2 (0.5%)	0
Nasopharyngitis	45 (5.7%)	37 (4.7%)	8 (1.0%)	0	0	24 (6.1%)	24 (6.1%)	0	0	0
Upper respiratory tract infection	43 (5.4%)	25 (3.2%)	18 (2.3%)	0	0	10 (2.5%)	8 (2.0%)	2 (0.5%)	0	0
Respiratory, thoracic and mediastinal disorders	267 (33.8%)	173 (21.9%)	69 (8.7%)	18 (2.3%)	7 (0.9%)	116 (29.4%)	68 (17.3%)	26 (6.6%)	11 (2.8%)	10 (2.5%)
Dyspnoea	102 (12.9%)	61 (7.7%)	31 (3.9%)	8 (1.0%)	2 (0.3%)	46 (11.7%)	22 (5.6%)	14 (3.6%)	7 (1.8%)	2 (0.5%)
Cough	84 (10.6%)	68 (8.6%)	16 (2.0%)	0	0	30 (7.6%)	25 (6.3%)	5 (1.3%)	0	0
Vascular disorders	247 (31.2%)	124 (15.7%)	94 (11.9%)	27 (3.4%)	2 (0.3%)	123 (31.2%)	71 (18.0%)	47 (11.9%)	4 (1.0%)	1 (0.3%)
Hot flush	150 (19.0%)	101 (12.8%)	47 (5.9%)	2 (0.3%)	0	66 (16.8%)	45 (11.4%)	20 (5.1%)	1 (0.3%)	0
Hypertension	67 (8.5%)	20 (2.5%)	37 (4.7%)	10 (1.3%)	0	27 (6.9%)	10 (2.5%)	16 (4.1%)	1 (0.3%)	0
Investigations	242 (30.6%)	119 (15.0%)	76 (9.6%)	45 (5.7%)	2 (0.3%)	105 (26.6%)	50 (12.7%)	39 (9.9%)	12 (3.0%)	4 (1.0%)
Weight decreased	84 (10.6%)	50 (6.3%)	34 (4.3%)	0	0	55 (14.0%)	36 (9.1%)	17 (4.3%)	2 (0.5%)	0
Renal and urinary disorders	240 (30.3%)	119 (15.0%)	68 (8.6%)	44 (5.6%)	8 (1.0%)	111 (28.2%)	55 (14.0%)	32 (8.1%)	23 (5.8%)	1 (0.3%)
Haematuria	65 (8.2%)	35 (4.4%)	19 (2.4%)	11 (1.4%)	0	31 (7.9%)	15 (3.8%)	7 (1.8%)	9 (2.3%)	0
Pollakiuria	57 (7.2%)	40 (5.1%)	14 (1.8%)	2 (0.3%)	0	20 (5.1%)	14 (3.6%)	5 (1.3%)	1 (0.3%)	0
Nocturia	49 (6.2%)	41 (5.2%)	8 (1.0%)	0	0	16 (4.1%)	12 (3.0%)	4 (1.0%)	0	0
Blood and lymphatic system disorders	210 (26.5%)	45 (5.7%)	94 (11.9%)	57 (7.2%)	14 (1.8%)	116 (29.4%)	18 (4.6%)	64 (16.2%)	27 (6.9%)	7 (1.8%)
Anaemia	178 (22.5%)	31 (3.9%)	88 (11.1%)	51 (6.4%)	8 (1.0%)	104 (26.4%)	15 (3.8%)	60 (15.2%)	23 (5.8%)	6 (1.5%)
Psychiatric disorders	194 (24.5%)	108 (13.7%)	68 (8.6%)	17 (2.1%)	1 (0.1%)	104 (26.4%)	61 (15.5%)	36 (9.1%)	7 (1.8%)	0
Insomnia	82 (10.4%)	58 (7.3%)	23 (2.9%)	1 (0.1%)	0	50 (12.7%)	36 (9.1%)	13 (3.3%)	1 (0.3%)	0
Anxiety	45 (5.7%)	28 (3.5%)	17 (2.1%)	0	0	21 (5.3%)	11 (2.8%)	10 (2.5%)	0	0
Depression	37 (4.7%)	16 (2.0%)	15 (1.9%)	6 (0.8%)	0	20 (5.1%)	13 (3.3%)	7 (1.8%)	0	0
Injury, poisoning and procedural complications	174 (22.0%)	100 (12.6%)	47 (5.9%)	23 (2.9%)	3 (0.4%)	56 (14.2%)	35 (8.9%)	17 (4.3%)	2 (0.5%)	2 (0.5%)
Contusion	53 (6.7%)	48 (6.1%)	5 (0.6%)	0	0	21 (5.3%)	19 (4.8%)	2 (0.5%)	0	0
Reproductive system and breast disorders	41 (5.2%)	17 (2.1%)	17 (2.1%)	7 (0.9%)	0	39 (9.9%)	15 (3.8%)	14 (3.6%)	10 (2.5%)	0
Pelvic pain	17 (2.1%)	5 (0.6%)	9 (1.1%)	3 (0.4%)	0	22 (5.6%)	6 (1.5%)	6 (1.5%)	10 (2.5%)	0

(continued)

(Taken from Applicant's Clinical Study Report COU-AA-301, pages 96-98)

Table 43: Selected Laboratory Abnormalities in the Phase 3 Placebo-Controlled Clinical Trial

		Abiraterone (N=791)			Placebo (N=394)		
Preferred Term		Any Grade %*	Grade 3-4 %	Other %	Any Grade %	Grade 3-4 %	Other %
Lipid Profile							
High LDL[1]		n/a	n/a	-	n/a	n/a	-
	> ULN	-	-	64.0%	-	-	57.4%
	>200mg/dL	-	-	2.8%	-	-	1.5%
High Triglyceride		62.5%	0.4%	-	53%	0	-
High Cholesterol		55.6%	0.4%	-	48.5%	0.3%	-
Basic Metabolic Profile							
Low Cr Clearance[2]		n/a	n/a	-	n/a	n/a	-
	< LLN	-	-	67.5%	-	-	60.2%
	< 30	-	-	3.2%	-	-	2.0%
Low Potassium		28.3%	5 3%	-	19.8%	1.0%	-
Low Phosphorus		23.8%	7.2%	-	15.7%	5.8%	-
High Creatinine		13.4%	0.5%	-	10.4%	0.3%	-
Liver Panel							
High AST		30.6%	2.1%	-	36.3%	1.5%	-
High ALT		11.1%	1.4%	-	10.4%	0.8%	-
High total Bilirubin		6.6%	0.1%	-	4.6%	0.0%	-
Hematologic Profile							
Low WBC		18.7%	1.5%	-	14.5%	0.8%	-
Low ANC		7.1%	2.0%	-	3.3%	0.8%	-

ULN- Upper Limit of Normal, LLN - Lower Limit of Normal

Laboratory values from baseline visits are not included.

[1] There is no CTCAE v3.0 grading for high LDL

[2] There is no CTCAE v3.0 grading for low creatinine clearance

Reviewer Comment: Of note, the applicant presented a table of laboratory abnormalities, Table TLAB02: Hematology and Chemistry Central Laboratory Tests - Worst Toxicity Grade During Study. The result from an analysis performed by the clinical safety reviewer was similar to the findings by the applicant with the exception of hypokalemia. The applicant reported an overall 19% rate of all grade low potassium with 2.8% grade 3 and 0.1% grade 4. The clinical safety reviewer's findings were higher with 28.3% all grade and 5.3% grade 3-4 low potassium. This discrepancy does not alter the overall benefit-risk to an appreciable level.

Table 44: Incidence of Abnormalities in Vital Signs

Parameter	AA (N=791)	Placebo (N=394)
Temperature		
Total no. subjects with baseline and any postbaseline measurement	761(96.2%)	375(95.2%)
>38 C and with >=1 C increase from baseline	13(1.7%)	5(1.3%)
Pulse		
Total no. subjects with baseline and any postbaseline measurement	773(97.7%)	385(97.7%)
>120 bpm and with >30 bpm increase from baseline	8(1%)	3(0.8%)
<50 bpm and with >20 bpm decrease from baseline	6(0.8%)	2(0.5%)
Systolic blood pressure		
Total no. subjects with baseline and any postbaseline measurement	773(97.7%)	385(97.7%)
>180 mmHg and with >40 mmHg increase from baseline	15(1.9%)	4(1%)
<90 mmHg and >30 mmHg decrease from baseline	10(1.3%)	7(1.8%)
Diastolic blood pressure		
Total no. subjects with baseline and any postbaseline measurement	773(97.7%)	385(97.7%)
>105 mmHg and with >30 mmHg increase from baseline	8(1%)	2(0.5%)
<50 mmHg and with >20 mmHg decrease from baseline	5(0.6%)	1(0.3%)

Note: Percentages for abnormal rows are calculated with the total number subjects with baseline and any postbaseline measurement as denominator.

(Taken from Applicant's Clinical Study Report COU-AA-301, page 1417).

7.4.4 Electrocardiograms (ECGs)

While not intended to be a QTc study, the QTc interval was increased in patients receiving abiraterone versus placebo in the pivotal study AA-301. Based on the QTcF method, 16% of subjects in the abiraterone acetate group and 10% of subjects in the placebo group had a QTc interval prolongation of >30 ms and 5% and 2% of subjects in the abiraterone acetate and placebo groups, respectively, had a QTc interval prolongation of>60 ms.

Despite the above finding, preclinical data and the dedicated modified QTc study COU-AA-006 revealed no significant effect of AA on the QTc interval. Study AA-006 obtained pharmacokinetic and time-matched ECGs in 33 patients with metastatic CRPC. The upper bound of the two sided 90% CI for the baseline-adjusted mean change in QTcF duration across all post dose time points were below 10 msecs, below the threshold considered acceptable by ICH-E14 guidelines. An FDA review performed by the interdisciplinary review team for QT studies verified that the modified QTc study drug exposure was adequate and that the following labeling recommendations should be considered for section 12.2 Pharmacodynamics:

"The effect of abiraterone acetate (1000mg p.o. q.d.) in combination with prednisone (5 mg p.o. b.i.d) on QTc interval was evaluated in a multi-center, open-label, single-arm

study in 33 evaluable patients with metastatic castration resistant prostate cancer (CRPC) up to Day 2 Cycle 2. No large changes in QTc interval (i.e., >20 ms) from baseline were detected in the trial. However, small increases in QTc interval (i.e., <10 ms) with the use of abiraterone acetate cannot be excluded due to study design limitations."

Reviewer Comment: There appears to be no significant QT prolongation in the submitted application.

7.4.5 Immunogenicity

Not Applicable.

7.4.6 4-Month Safety Update

The applicant submitted a 4-month safety update to this NDA on 4-18-2011. The clinical safety reviewer reviewed the submission and did not identify any significant new safety signals when compared to the original submission. No Grade 3 or 4 AEs increased at an incidence >1% between the NDA and the updated safety analysis. There were 2 more cases of adrenal insufficiency (both grade 3) that occurred on the abiraterone arm:

Case 1: An 86 year old Asian male was diagnosed with grade 3 adrenal insufficiency, failure to thrive, general weakness, wasting and cachexia on study day 402. His treatment was discontinued as a result of adrenal insufficiency and he was treated with several doses of corticosteroids. He was discharged from the hospital on study day 412 to a nursing home/hospice and died on study day 522 of unknown causes.

Case 2: A 72 year old male who had grade 4 osteonecrosis of the left hip on study day 525 and underwent left total hip arthroplasty the same day. He was discharged on study day 529. He presented with generalized weakness, nausea and vomiting on study day 539 as well as low blood pressure. Prednisone/prednisolone was interrupted starting on study day 543. Grade 3 adrenal insufficiency was reported on study day 549 and subject was admitted and he resumed prednisone at a dose of 30mg per day on study day 550 returning back down to 10mg per day on study day 552. Patient was discharged and as of 9/20/2010 subject was still alive.

There were no other significant changes in the adverse reactions of special interest. While there were a few more cases of elevations in liver transaminases, the number of subjects
who met eDISH criteria (repeat eDISH / Hy's Law analysis) remained the same between the NDA and the updated safety analysis.

shows the overall safety profile comparing the NDA submission and the 4-month safety update.

Table 45: Overall Safety Profile of NDA Submission Compared to 4-Month Safety Update

	NDA		4MSU	
Summary of Adverse Events	AA (N=791)	Placebo (N=394)	AA (N=791)	Placebo (N=394)
Treatment-Emergent Adverse Events	782 (98.9%)	390 (99.0%)	784 (99.1%)	390 (99.0%)
Drug-related[a]	604 (76.4%)	303 (76.9%)	610 (77.1%)	305 (77.4%)
Grade 3-4 Treatment-Emergent Adverse Events	431 (54.5%)	230 (58.4%)	478 (60.4%)	240 (60.9%)
Drug-related[a]	161 (20.4%)	74 (18.8%)	182 (23.0%)	76 (19.3%)
Treatment-Emergent Serious Adverse Events	297 (37.5%)	163 (41.4%)	335 (42.4%)	172 (43.7%)
Drug-related[a]	70 (8.8%)	39 (9.9%)	88 (11.1%)	41 (10.4%)
Grade 3-4	254 (32.1%)	139 (35.3%)	288 (36.4%)	148 (37.6%)
Treatment-Emergent Adverse Events Leading to Treatment Discontinuation	148 (18.7%)	90 (22.8%)	162 (20.5%)	93 (23.6%)
Drug-related[a]	38 (4.8%)	25 (6.3%)	43 (5.4%)	27 (6.9%)
Treatment-Emergent Adverse Events Leading to Death	92 (11.6%)	58 (14.7%)	105 (13.3%)	61 (15.5%)
Drug-related[a]	4 (0.5%)	10 (2.5%)	8 (1.0%)	11 (2.8%)
All deaths within 30 days of last dose	84 (10.6%)	52 (13.2%)	97 (12.3%)	55 (14.0%)
Underlying Disease	60 (7.6%)	39 (9.9%)	64 (8.1%)	41 (10.4%)
Other	23 (2.9%)	13 (3.3%)	29 (3.7%)	14 (3.6%)
Unknown	1 (0.1%)	0	4 (0.5%)	0

AA=abiraterone acetate; NDA=New Drug Application; 4MSU=4-Month Safety Update

[a] Adverse events reported as unlikely, possibly, or related will be classified as drug-related AEs.

Table taken from applicant's safety update, issue/report date 4/14/2011, table 6, page 13

Table 46 shows the adverse events with an incidence that were increased by 2% in either arm of the 4-month safety update data when compared to the initial NDA submission.

Table 46: Incidence of TEAEs with an Increase of at least 2%

	NDA						4MSU					
	AA (N=791)			Placebo (N=394)			AA (N=791)			Placebo (N=394)		
System Organ Class Preferred Term	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Number of subjects with a treatment-emergent adverse event	782 (98.9%)	347 (43.9%)	84 (10.6%)	390 (99.0%)	186 (47.2%)	44 (11.2%)	784 (99.1%)	382 (48.3%)	96 (12.1%)	390 (99.0%)	194 (49.2%)	46 (11.7%)
Musculoskeletal and connective tissue disorders	576 (72.8%)	148 (18.7%)	7 (0.9%)	291 (73.9%)	89 (22.6%)	7 (1.8%)	599 (75.7%)	170 (21.5%)	8 (1.0%)	297 (75.4%)	94 (23.9%)	7 (1.8%)
Back pain	233 (29.5%)	44 (5.6%)	3 (0.4%)	129 (32.7%)	37 (9.4%)	1 (0.3%)	262 (33.1%)	53 (6.7%)	3 (0.4%)	141 (35.8%)	39 (9.9%)	1 (0.3%)
Bone pain	194 (24.5%)	42 (5.3%)	2 (0.3%)	110 (27.9%)	25 (6.3%)	4 (1.0%)	216 (27.3%)	49 (6.2%)	2 (0.3%)	117 (29.7%)	26 (6.6%)	4 (1.0%)
Arthralgia	215 (27.2%)	33 (4.2%)	0	89 (22.6%)	16 (4.1%)	0	239 (30.2%)	40 (5.1%)	0	95 (24.1%)	17 (4.3%)	0
Pain in extremity	134 (16.9%)	18 (2.3%)	1 (0.1%)	79 (20.1%)	20 (5.1%)	0	156 (19.7%)	23 (2.9%)	1 (0.1%)	82 (20.8%)	20 (5.1%)	0
Musculoskeletal pain	117 (14.8%)	20 (2.5%)	1 (0.1%)	51 (12.9%)	8 (2.0%)	0	134 (16.9%)	22 (2.8%)	1 (0.1%)	56 (14.2%)	8 (2.0%)	0
General disorders and administration site conditions	549 (69.4%)	110 (13.9%)	6 (0.8%)	262 (66.5%)	59 (15.0%)	5 (1.3%)	570 (72.1%)	128 (16.2%)	6 (0.8%)	267 (67.8%)	63 (16.0%)	5 (1.3%)
Fatigue	346 (43.7%)	64 (8.1%)	2 (0.3%)	169 (42.9%)	36 (9.1%)	3 (0.8%)	372 (47.0%)	70 (8.8%)	2 (0.3%)	174 (44.2%)	38 (9.6%)	3 (0.8%)
Asthenia	104 (13.1%)	18 (2.3%)	0	52 (13.2%)	7 (1.8%)	1 (0.3%)	122 (15.4%)	26 (3.3%)	0	54 (13.7%)	7 (1.8%)	1 (0.3%)
Gastrointestinal disorders	531 (67.1%)	59 (7.5%)	5 (0.6%)	264 (67.0%)	30 (7.6%)	2 (0.5%)	558 (70.5%)	73 (9.2%)	8 (1.0%)	267 (67.8%)	33 (8.4%)	2 (0.5%)
Constipation	206 (26.0%)	8 (1.0%)	0	120 (30.5%)	4 (1.0%)	0	223 (28.2%)	10 (1.3%)	0	126 (32.0%)	4 (1.0%)	0
Nausea	233 (29.5%)	12 (1.5%)	1 (0.1%)	124 (31.5%)	10 (2.5%)	0	258 (32.6%)	16 (2.0%)	1 (0.1%)	130 (33.0%)	11 (2.8%)	0
Vomiting	168 (21.2%)	13 (1.6%)	1 (0.1%)	97 (24.6%)	11 (2.8%)	0	191 (24.1%)	20 (2.5%)	1 (0.1%)	101 (25.6%)	12 (3.0%)	0
Diarrhoea	139 (17.6%)	5 (0.6%)	0	53 (13.5%)	5 (1.3%)	0	156 (19.7%)	8 (1.0%)	1 (0.1%)	58 (14.7%)	5 (1.3%)	0
Respiratory, thoracic and mediastinal disorders	267 (33.8%)	18 (2.3%)	7 (0.9%)	116 (29.4%)	11 (2.8%)	10 (2.5%)	299 (37.8%)	24 (3.0%)	10 (1.3%)	121 (30.7%)	13 (3.3%)	11 (2.8%)
Cough	84 (10.6%)	0	0	30 (7.6%)	0	0	101 (12.8%)	0	0	32 (8.1%)	0	0
Blood and lymphatic system disorders	210 (26.5%)	57 (7.2%)	14 (1.8%)	116 (29.4%)	27 (6.9%)	7 (1.8%)	232 (29.3%)	60 (7.6%)	15 (1.9%)	123 (31.2%)	30 (7.6%)	7 (1.8%)
Anaemia	178 (22.5%)	51 (6.4%)	8 (1.0%)	104 (26.4%)	23 (5.8%)	6 (1.5%)	198 (25.0%)	53 (6.7%)	9 (1.1%)	110 (27.9%)	26 (6.6%)	6 (1.5%)

AA=abiraterone acetate; NDA=New Drug Application; 4MSU=4-Month Safety Update

Note: 'Number of subjects with treatment-emergent event' and system organ class rows include all such subjects. Preferred terms rows include events with an increase of at least 2% of subjects in any treatment group.
A subject who had multiple events per system organ class or preferred term is counted twice, once in the column for the worst reported severity among the events and once in the All Grades column.
The All Grades column includes all subjects with worst severities of an event that are less than grade 5, not simply subjects with grades 3 or 4.

Table taken from applicant's safety update, issue/report date 4/14/2011, table 14, page 36.

Reviewer Comment: The 4-month safety update reveals a similar adverse event profile as that of the NDA submission. Notably, there were no deaths reported due to adverse events of interest including hypokalemia, adrenal insufficiency, cardiac failure, hepatotoxicity or hypertension. There were no significant signals to suggest an undiscovered toxicity. The 4-month safety update does not materially change the clinical safety reviewer's impression that abiraterone acetate has a favorable risk:benefit ratio for the treatment of mCRPC patients who have received prior docetaxel based chemotherapy.

7.5 Other Safety Explorations

None

7.5.1 Dose Dependency for Adverse Events

Not Applicable. The safety database included only those patients who took 1000 mg of abiraterone acetate.

7.5.2 Time Dependency for Adverse Events

There is no information to suggest that adverse events have time dependency.

7.5.3 Drug-Demographic Interactions

Demographics and baseline disease characteristics were balanced between groups in the placebo-controlled phase 3 clinical trial. The age groups were evenly distributed when categorized by <65, 65-69, 70-74 and >=75. There was no meaningful difference in the toxicity profiles seen between age groups (Table 47).

Table 47: Overall Safety Profile by Age Subgroups in Study COU-AA-301 Safety Population

	AA			Placebo		
Summary of Adverse Events	Age<65 (N=229)	Age 65-74 (N=344)	Age>=75 (N=218)	Age<65 (N=119)	Age 65-74 (N=166)	Age>=75 (N=109)
Treatment-Emergent Adverse Events	227 (99.1%)	338 (98.3%)	217 (99.5%)	119 (100.0%)	164 (98.8%)	107 (98.2%)
Drug-related[a]	165 (72.1%)	276 (80.2%)	163 (74.8%)	95 (79.8%)	123 (74.1%)	85 (78.0%)
Grade 3-4 Treatment-Emergent Adverse Events	134 (58.5%)	183 (53.2%)	114 (52.3%)	72 (60.5%)	89 (53.6%)	69 (63.3%)
Drug-related[a]	39 (17.0%)	67 (19.5%)	55 (25.2%)	22 (18.5%)	27 (16.3%)	25 (22.9%)
Treatment-Emergent Serious Adverse Events	84 (36.7%)	135 (39.2%)	78 (35.8%)	43 (36.1%)	69 (41.6%)	51 (46.8%)
Drug-related[a]	13 (5.7%)	34 (9.9%)	23 (10.6%)	5 (4.2%)	16 (9.6%)	18 (16.5%)
Grade 3-4	73 (31.9%)	114 (33.1%)	67 (30.7%)	42 (35.3%)	58 (34.9%)	39 (35.8%)
Treatment-Emergent Adverse Events Leading to Treatment Discontinuation	43 (18.8%)	60 (17.4%)	45 (20.6%)	31 (26.1%)	34 (20.5%)	25 (22.9%)
Drug-related[a]	7 (3.1%)	18 (5.2%)	13 (6.0%)	7 (5.9%)	7 (4.2%)	11 (10.1%)
Treatment-Emergent Adverse Events Leading to Death	19 (8.3%)	43 (12.5%)	30 (13.8%)	12 (10.1%)	22 (13.3%)	24 (22.0%)
Drug-related[a]	1 (0.4%)	2 (0.6%)	1 (0.5%)	4 (3.4%)	3 (1.8%)	3 (2.8%)
All deaths within 30 days of last dose	18 (7.9%)	37 (10.8%)	29 (13.3%)	11 (9.2%)	20 (12.0%)	21 (19.3%)
Underlying Disease	15 (9.8%)	27 (11.7%)	18 (11.6%)	7 (10.9%)	15 (15.3%)	17 (28.3%)
Other	3 (2.0%)	10 (4.3%)	10 (6.5%)	4 (6.3%)	5 (5.1%)	4 (6.7%)
Unknown	0	0	1 (0.6%)	0	0	0

(Taken from Applicant's Clinical Study Report COU-AA-301 page 335)

7.5.4 Drug-Drug Interactions

Refer to Clinical Pharmacology review for details.

Effects of Abiraterone Acetate on Drug Metabolizing Enzymes

Abiraterone acetate is an inhibitor of the hepatic drug-metabolizing enzyme Cytochrome P450 (CYP) 2D6. In a CYP2D6 drug-drug interaction trial, the Cmax and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1000 mg daily and prednisone 5 mg twice daily.

Reviewer Comment: Clinical pharmacology labeling recommendation: "Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g, thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug."

Drugs that Inhibit or Induce CYP3A4 Enzymes

Based on in vitro data, abiraterone acetate is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) on the pharmacokinetics of abiraterone have not been evaluated, in vivo.

Reviewer Comment: Clinical pharmacology labeling recommendation: "Avoid or use with caution, strong inhibitors and inducers of CYP3A4 during ZYTIGA treatment."

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There were a small number of secondary malignancies reported in the integrated safety database for the abiraterone arm. There were no malignancies reported in the placebo arm.

Table 48: Second Malignancies Reported in the Integrated Safety Database

AE TERM	Overall AA (N=1070)	Placebo (N=394)
Basal Cell Carcinoma	5	0
Bladder Transitional Cell Carcinoma	1	0
Colon Cancer	2	0
Lung Neoplasm Malignant	1	0
Malignant Melanoma	1	0
Lymphangiosis carcinomatosa	1	0
Squamous cell carcinoma of skin	2	0
Squamous cell carcinoma	3	0

Reviewer Comment: Although the numbers are small, there is an imbalance in the reporting of secondary malignancies in the integrated safety population. This may be due to the 3-fold higher number of patient on the abiraterone arm. The majority of malignancies were non-melanomatous skin cancer, but there were 5 cases of solid tumors in the AA arm and none reported in the placebo arm. The clinical safety reviewer requested that the applicant additional information regarding these patients. The

applicant provided patient narratives and supportive documentation for this finding on 4-19-2011.

Review of these additional information revealed that the majority of cases with secondary malignancies were confounded by the following: 1) patients had prior diagnoses with the same cancer type; 2) lack of pathologic diagnostic evaluation; and 3) secondary malignancies diagnosed soon after commencing abiraterone acetate, suggesting that it was likely that the tumors had been present prior to the initiation of study treatment. Thus, available data do not support the conclusion that abiraterone acetate increases the risk of secondary cancer at this time.

7.6.2 Human Reproduction and Pregnancy Data

Developmental or reproductive toxicology studies were not conducted with abiraterone acetate. Animal toxicology studies were performed and revealed reproductive organ changes consistent with the pharmacological activity of abiraterone. Although very unlikely to be used in women, AA is thus contraindicated in women who are pregnant.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not Applicable

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no reason to believe AA has any potential for drug abuse.

While theoretically, withdrawal of AA may increase testosterone levels, there have been no studies or data provided and thus a rebound effect following AA withdrawal remains unknown.

Prednisone withdrawal: Abiraterone acetate is given concurrently with 10mg of prednisone once daily in order to attenuate mineralocorticoid excess resulting from reduced feedback inhibition of ACTH. After using prednisone for a prolonged period, the withdrawal of prednisone abruptly may precipitate adrenal insufficiency. In the safety database, there were two instances of adrenal insufficiency noted in the phase 3 trial and three cases in the pooled phase 1-2 studies for a total of 5 patients (see section 7.3.5.2) The labeling will include the warnings of the potential for adrenocortical insufficiency both in the setting of corticosteroid withdrawal or taper, or in the setting of increased stress such as infection or other concurrent illness.

8 Postmarket Experience

Not applicable.

9 Appendices

9.1 Literature Review/References

See footnotes on pages where references were made.

9.2 Labeling Recommendations

At the time of this clinical review is written, the labeling revisions are ongoing.

9.3 Advisory Committee Meeting

This NDA was not presented to advisory committee because there were no controversial issues that would necessitate an advisory committee meeting.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YANGMIN NING
04/27/2011

PAUL G KLUETZ
04/27/2011

KE LIU
04/27/2011