CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 202379/ S005

Trade Name: ZYTIGA

Generic Name: Abiraterone acetate

Sponsor: Janssen Biotech

Approval Date: 12/10/2012

Indications: Zytiga is a CYP17 inhibitor indicated in the combination with prednisone for the treatment of metastatic castration-resistant prostate cancer.

CENTER FOR DRUG EVALUATION AND RESEARCH

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202379/S-005

SUPPLEMENT APPROVAL

Janssen Biotech, Inc.
Attention: Kelly Johnson Reid
Associate Director, Regulatory Affairs
800/850 Ridgeview Drive
Horsham, PA 19044

Dear Ms. Johnson Reid:

Please refer to your Supplemental New Drug Application (sNDA) dated June 13, 2012, received June 14, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zytiga® (abiraterone acetate) Tablets 250 mg.

We acknowledge receipt of your amendments dated July 16 and 25; August 8, 9, 17 and 29; September 4, 13, 21, 24, 26 and 27; November 1, 5, 20, 26, and 30, 2012.

This Prior Approval supplemental new drug application provides for a new indication: Zytiga® is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, and patient package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

We acknowledge your June 14, 2012 submission containing final printed carton and container labels.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable because the disease does not exist in children. Metastatic castration-resistant prostate cancer does not affect pediatric patients.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

1973-1 Submit datasets and the final analysis of overall survival for COU-AA-302.

The timetable you submitted on November 20, 2012 states that you will conduct this trial according to the following schedule:

Trial Completion:	June 2014
Final Report Submission:	September 2014

Submit clinical protocols to your IND 071023 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be

prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Amy Tilley, Regulatory Project Manager, at (301) 796-3994.

Sincerely,

{See appended electronic signature page}

Amna Ibrahim, M.D.
Deputy Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURES:
Content of Labeling
Carton and Container Labeling

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

/s/

AMNA IBRAHIM
12/10/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZYTIGA safely and effectively. See full prescribing information for ZYTIGA.

ZYTIGA® (abiraterone acetate) Tablets
For Oral Administration
Initial U.S. Approval – 2011

----------RECENT MAJOR CHANGES----------

Indications and usage (1)	12/2012
Contraindications, Pregnancy (4.1)	12/2012
Warnings and Precautions, Mineralocorticoid excess (5.1)	12/2012
Warnings and Precautions, Adrenocortical Insufficiency (5.2)	12/2012
Warnings and Precautions, Hepatotoxicity (5.3)	12/2012

----------INDICATIONS AND USAGE----------

ZYTIGA is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer. (1)

----------DOSAGE AND ADMINISTRATION----------

Recommended dose: ZYTIGA 1,000 mg (four 250 mg tablets) administered orally once daily in combination with prednisone 5 mg administered orally twice daily. ZYTIGA must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. The tablets should be swallowed whole with water. Do not crush or chew tablets. (2.1)

- For patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the ZYTIGA starting dose to 250 mg once daily. (2.2)
- For patients who develop hepatotoxicity during treatment, hold ZYTIGA until recovery. Retreatment may be initiated at a reduced dose. ZYTIGA should be discontinued if patients develop severe hepatotoxicity. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

Tablet 250 mg (3)

----------CONTRAINDICATIONS----------

- ZYTIGA is contraindicated in women who are or may become pregnant. (4.1, 8.1)

----------WARNINGS AND PRECAUTIONS----------

- Mineralocorticoid excess: 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 in Study 1 or LVEF < 50 % or NYHA Class II to IV heart failure in Study 2 was not established. Control hypertension and correct hypokalemia before treatment. Monitor blood pressure, serum potassium and symptoms of fluid retention at least monthly. (5.1)
- Adrenocortical insufficiency: Monitor for symptoms and signs of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations. (5.2)
- Hepatotoxicity: Increases in liver enzymes have led to drug interruption, dose modification and/or discontinuation. Monitor liver function and modify, interrupt, or discontinue ZYTIGA dosing as recommended. (5.3)
- Food effect: ZYTIGA must be taken on an empty stomach. Exposure (area under the curve) of abiraterone increases up to 10 fold when abiraterone acetate is taken with meals. (5.4)

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥ 10%) are fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion.

The most common laboratory abnormalities (> 20%) are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-526-7736 (1-800-JANSSEN) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

ZYTIGA is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. Avoid co-administration of ZYTIGA with CYP2D6 substrates that have a narrow therapeutic index. If an alternative treatment cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate. (7)

----------USE IN SPECIFIC POPULATIONS----------

- Do not use ZYTIGA in patients with baseline severe hepatic impairment (Child-Pugh Class C). (8.6)

See 17 for Patient Counseling Information and FDA-approved patient labeling.

Revised: [12/2012]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ZYTIGA is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of ZYTIGA is 1,000 mg (four 250 mg tablets) administered orally once daily in combination with prednisone 5 mg administered orally twice daily. ZYTIGA must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken *[see Clinical Pharmacology (12.3)]*. The tablets should be swallowed whole with water. Do not crush or chew tablets.

2.2 Dose Modification Guidelines

Hepatic Impairment

In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of ZYTIGA to 250 mg once daily. A once daily dose of 250 mg in patients with moderate hepatic impairment is predicted to result in an area under the concentration curve (AUC) similar to the AUC seen in patients with normal hepatic function receiving 1,000 mg once daily. However, there are no clinical data at the dose of 250 mg once daily in patients with moderate hepatic impairment and caution is advised. In patients with moderate hepatic impairment monitor ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. If elevations in ALT and/or AST greater than 5X upper limit of normal (ULN) or total bilirubin greater than 3X ULN occur in patients with baseline moderate hepatic impairment, discontinue ZYTIGA and do not re-treat patients with ZYTIGA *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

Avoid ZYTIGA in patients with baseline severe hepatic impairment (Child-Pugh Class C), as ZYTIGA has not been studied in this population, and no dose adjustment can be predicted.

Hepatotoxicity

For patients who develop hepatotoxicity during treatment with ZYTIGA (ALT and/or AST greater than 5X ULN or total bilirubin greater than 3X ULN), interrupt treatment with ZYTIGA *[see Warnings and Precautions (5.3)]*. Treatment may be restarted at a reduced

dose of 750 mg once daily following return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN. For patients who resume treatment, monitor serum transaminases and bilirubin at a minimum of every two weeks for three months and monthly thereafter.

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

If hepatotoxicity recurs at the reduced dose of 500 mg once daily, discontinue treatment with ZYTIGA. The safety of ZYTIGA re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

3 DOSAGE FORMS AND STRENGTHS

ZYTIGA (abiraterone acetate) 250 mg tablets are white to off-white, oval-shaped tablets debossed with AA250 on one side.

4 CONTRAINDICATIONS

4.1 Pregnancy

ZYTIGA can cause fetal harm when administered to a pregnant woman. ZYTIGA is not indicated for use in women. ZYTIGA is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss *[see Use in Specific Populations (8.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess

ZYTIGA may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition *[see Clinical Pharmacology (12.1)]*. In the two randomized clinical trials, grade 3 to 4 hypertension occurred in 2% of patients, grade 3 to 4 hypokalemia in 4% of patients, and grade 3 to 4 edema in 1% of patients treated with ZYTIGA. *[see Adverse Reactions (6)]*.

Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions. Use caution when treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, e.g., those with heart failure,

recent myocardial infarction or ventricular arrhythmia. Use ZYTIGA with caution in patients with a history of cardiovascular disease. The safety of ZYTIGA in patients with left ventricular ejection fraction < 50% or New York Heart Association (NYHA) Class III or IV heart failure (in Study 1) or NYHA Class II to IV heart failure (in Study 2) was not established because these patients were excluded from these randomized clinical trials *[see Clinical Studies (14)]*. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with ZYTIGA.

5.2 Adrenocortical Insufficiency

Adrenal insufficiency occurred in the two randomized clinical studies in 0.5% of patients taking ZYTIGA and in 0.2% of patients taking placebo. Adrenocortical insufficiency was reported in patients receiving ZYTIGA in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. 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 to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations *[see Warnings and Precautions (5.1)]*.

5.3 Hepatotoxicity

In the two randomized clinical trials, grade 3 or 4 ALT or AST increases (at least 5X ULN) were reported in 4% of patients who received ZYTIGA, typically during the first 3 months after starting treatment. Patients whose baseline ALT or AST were elevated were more likely to experience liver test elevation than those beginning with normal values. Treatment discontinuation due to liver enzyme increases occurred in 1% of patients taking ZYTIGA. No deaths clearly related to ZYTIGA were reported due to hepatotoxicity events.

Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with ZYTIGA, every two weeks for the first three months of treatment and monthly thereafter. In patients with baseline moderate hepatic impairment receiving a reduced ZYTIGA dose of 250 mg, measure ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring. If at any time

AST or ALT rise above five times the ULN, or the bilirubin rises above three times the ULN, interrupt ZYTIGA treatment and closely monitor liver function.

Re-treatment with ZYTIGA at a reduced dose level may take place only after return of liver function tests to the patient's baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN *[see Dosage and Administration (2.2)]*.

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

5.4 Increased ZYTIGA Exposures with Food

ZYTIGA must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. Abiraterone C_{max} and $AUC_{0-\infty}$ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasted state. The safety of these increased exposures when multiple doses of abiraterone acetate are taken with food has not been assessed *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

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

- Hypertension, Hypokalemia, and Fluid Retention due to Mineralocorticoid Excess *[see Warnings and Precautions (5.1)]*.
- Adrenocortical Insufficiency *[see Warnings and Precautions (5.2)]*.
- Hepatotoxicity *[see Warnings and Precautions (5.3)]*.
- Increased ZYTIGA Exposures with Food *[see Warnings and Precautions (5.4)]*.

6.1 Clinical Trial Experience

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

Two randomized placebo-controlled, multicenter clinical trials enrolled patients who had metastatic castration-resistant prostate cancer who were using a gonadotropin-releasing hormone (GnRH) agonist or were previously treated with orchiectomy. In both Study 1 and Study 2 ZYTIGA was administered at a dose of 1,000 mg daily in combination with prednisone 5 mg twice daily in the active treatment arms. Placebo plus prednisone 5 mg twice daily was given to control patients.

The most common adverse drug reactions (≥10%) reported in the two randomized clinical trials that occurred more commonly (>2%) in the abiraterone acetate arm were fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion.

The most common laboratory abnormalities (>20%) reported in the two randomized clinical trials that occurred more commonly (≥2%) in the abiraterone acetate arm were anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia.

Study 1: Metastatic CRPC Following Chemotherapy

Study 1 enrolled 1195 patients with metastatic CRPC who had received prior docetaxel chemotherapy. Patients were not eligible if AST and/or ALT ≥ 2.5 XULN in the absence of liver metastases. Patients with liver metastases were excluded if AST and/or ALT > 5X ULN.

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

Table 1: Adverse Reactions due to ZYTIGA in Study 1

System/Organ Class Adverse reaction	ZYTIGA 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
Injury, poisoning and procedural complications				
Fractures[5]	5.9	1.4	2.3	0
Cardiac disorders				
Arrhythmia[6]	7.2	1.1	4.6	1.0
Chest pain or chest discomfort[7]	3.8	0.5	2.8	0
Cardiac failure[8]	2.3	1.9	1.0	0.3

[1] Adverse events graded according to CTCAE version 3.0
[2] Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness
[3] Includes terms Muscle spasms, Musculoskeletal pain, Myalgia, Musculoskeletal discomfort, and Musculoskeletal stiffness
[4] Includes terms Edema, Edema peripheral, Pitting edema, and Generalized edema
[5] Includes all fractures with the exception of pathological fracture
[6] Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradycardia, Atrioventricular block complete, Conduction disorder, and Bradyarrhythmia
[7] Includes terms Angina pectoris, Chest pain, and Angina unstable. Myocardial infarction or ischemia occurred more commonly in the placebo arm than in the ZYTIGA arm (1.3% vs. 1.1% respectively).
[8] Includes terms Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, and Ejection fraction decreased

Table 2 shows laboratory abnormalities of interest from Study 1. Grade 3-4 low serum phosphorus (7%) and low potassium (5%) occurred at a greater than or equal to 5% rate in the ZYTIGA arm.

Table 2: Laboratory Abnormalities of Interest in Study 1

	Abiraterone (N=791)		**Placebo (N=394)**	
Laboratory Abnormality	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Hypertriglyceridemia	62.5	0.4	53.0	0
High AST	30.6	2.1	36.3	1.5
Hypokalemia	28.3	5.3	19.8	1.0
Hypophosphatemia	23.8	7.2	15.7	5.8
High ALT	11.1	1.4	10.4	0.8
High Total Bilirubin	6.6	0.1	4.6	0

Study 2: Metastatic CRPC Prior to Chemotherapy

Study 2 enrolled 1088 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy. Patients were ineligible if AST and/or ALT ≥ 2.5X ULN and patients were excluded if they had liver metastases.

Table 3 shows adverse reactions on the ZYTIGA arm in Study 2 that occurred with a ≥ 2% absolute increase in frequency compared to placebo. The median duration of treatment with ZYTIGA was 13.8 months.

Table 3: Adverse Reactions in ≥5% of Patients on the ZYTIGA Arm in Study 2

	ZYTIGA with Prednisone (N=542)		Placebo with Prednisone (N=540)	
System/Organ Class Adverse reaction	All Grades[1] %	Grade 3-4 %	All Grades %	Grade 3-4 %
General disorders				
Fatigue	39.1	2.2	34.3	1.7
Edema[2]	25.1	0.4	20.7	1.1
Pyrexia	8.7	0.6	5.9	0.2
Musculoskeletal and connective tissue disorders				
Joint swelling/ discomfort[3]	30.3	2.0	25.2	2.0
Groin pain	6.6	0.4	4.1	0.7
Gastrointestinal disorders				
Constipation	23.1	0.4	19.1	0.6
Diarrhea	21.6	0.9	17.8	0.9
Dyspepsia	11.1	0.0	5.0	0.2
Vascular disorders				
Hot flush	22.3	0.2	18.1	0.0
Hypertension	21.6	3.9	13.1	3.0
Respiratory, thoracic and mediastinal disorders				
Cough	17.3	0.0	13.5	0.2
Dyspnea	11.8	2.4	9.6	0.9
Psychiatric disorders				
Insomnia	13.5	0.2	11.3	0.0
Injury, poisoning and procedural complications				
Contusion	13.3	0.0	9.1	0.0
Falls	5.9	0.0	3.3	0.0
Infections and infestations				
Upper respiratory tract infection	12.7	0.0	8.0	0.0
Nasopharyngitis	10.7	0.0	8.1	0.0
Renal and urinary disorders				
Hematuria	10.3	1.3	5.6	0.6
Skin and subcutaneous tissue disorders				
Rash	8.1	0.0	3.7	0.0

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

Table 4 shows laboratory abnormalities that occurred in greater than 15% of patients, and more frequently (>5%) in the ZYTIGA arm compared to placebo in Study 2. Grade 3-4

lymphopenia (9%), hyperglycemia (7%) and high alanine aminotransferase (6%) occurred at a greater than 5% rate in the ZYTIGA arm.

Table 4 : Laboratory Abnormalities in > 15% of Patients in the ZYTIGA Arm of Study 2

Laboratory Abnormality	Abiraterone (N = 542)		Placebo (N = 540)	
	Grade 1-4 %	Grade 3-4 %	Grade 1-4 %	Grade 3-4 %
Hematology				
Lymphopenia	38.2	8.7	31.7	7.4
Chemistry				
Hyperglycemia[1]	56.6	6.5	50.9	5.2
High ALT	41.9	6.1	29.1	0.7
High AST	37.3	3.1	28.7	1.1
Hypernatremia	32.8	0.4	25.0	0.2
Hypokalemia	17.2	2.8	10.2	1.7

[1]Based on non-fasting blood draws

Cardiovascular Adverse Reactions:

In the combined data for studies 1 and 2, cardiac failure occurred more commonly in patients treated with ZYTIGA compared to patients on the placebo arm (2.1% versus 0.7%). Grade 3-4 cardiac failure occurred in 1.6% of patients taking ZYTIGA and led to 5 treatment discontinuations and 2 deaths. Grade 3-4 cardiac failure occurred in 0.2% of patients taking placebo. There were no treatment discontinuations and one death due to cardiac failure in the placebo group.

In Study 1 and 2, the majority of arrhythmias were grade 1 or 2. There was one death associated with arrhythmia and one patient with sudden death in the ZYTIGA arms and no deaths in the placebo arms. There were 7 (0.5 %) deaths due to cardiorespiratory arrest in the ZYTIGA arms and 3 (0.3 %) deaths in the placebo arms. Myocardial ischemia or myocardial infarction led to death in 3 patients in the placebo arms and 2 deaths in the ZYTIGA arms.

7 DRUG INTERACTIONS

7.1 Effects of Abiraterone on Drug Metabolizing Enzymes

ZYTIGA is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. In a CYP2D6 drug-drug interaction trial, the C_{max} and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and

consider a dose reduction of the concomitant CYP2D6 substrate drug *[see Clinical Pharmacology (12.3)]*.

In vitro, ZYTIGA inhibits CYP2C8. There are no clinical data on the use of ZYTIGA with drugs that are substrates of CYP2C8. However, patients should be monitored closely for signs of toxicity related to the CYP2C8 substrate if used concomitantly with abiraterone acetate.

7.2 Drugs that Inhibit or Induce CYP3A4 Enzymes

Based on *in vitro* data, ZYTIGA 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*. Avoid or use with caution, strong inhibitors and inducers of CYP3A4 during ZYTIGA treatment *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X *[see Contraindications (4.1)]*.

ZYTIGA can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. While there are no adequate and well-controlled studies with ZYTIGA in pregnant women and ZYTIGA is not indicated for use in women, it is important to know that maternal use of a CYP17 inhibitor could affect development of the fetus. Abiraterone acetate caused developmental toxicity in pregnant rats at exposures that were lower than in patients receiving the recommended dose. ZYTIGA is contraindicated in women who are or may become pregnant while receiving the drug. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss. Advise females of reproductive potential to avoid becoming pregnant during treatment with ZYTIGA.

In an embryo-fetal developmental toxicity study in rats, abiraterone acetate caused developmental toxicity when administered at oral doses of 10, 30 or 100 mg/kg/day throughout the period of organogenesis (gestational days 6-17). Findings included embryo-fetal lethality (increased post implantation loss and resorptions and decreased number of live fetuses), fetal developmental delay (skeletal effects) and urogenital effects (bilateral ureter

dilation) at doses ≥10 mg/kg/day, decreased fetal ano-genital distance at ≥30 mg/kg/day, and decreased fetal body weight at 100 mg/kg/day. Doses ≥10 mg/kg/day caused maternal toxicity. The doses tested in rats resulted in systemic exposures (AUC) approximately 0.03, 0.1 and 0.3 times, respectively, the AUC in patients.

8.3 Nursing Mothers

ZYTIGA is not indicated for use in women. It is not known if abiraterone acetate is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ZYTIGA, a decision should be made to either discontinue nursing, or discontinue the drug taking into account the importance of the drug to the mother.

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the total number of patients receiving ZYTIGA in phase 3 trials, 73% of patients were 65 years and over and 30% were 75 years and over. No overall differences in safety or effectiveness were observed between these elderly patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Patients with Hepatic Impairment

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

No dosage adjustment is necessary for patients with baseline mild hepatic impairment. In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of ZYTIGA to 250 mg once daily. If elevations in ALT or AST >5X ULN or total bilirubin >3X ULN occur in patients with baseline moderate hepatic impairment, discontinue ZYTIGA treatment *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)]*.

The safety of ZYTIGA in patients with baseline severe hepatic impairment has not been studied. These patients should not receive ZYTIGA.

For patients who develop hepatotoxicity during treatment, interruption of treatment and dosage adjustment may be required *[see Dosage and Administration (2.2), Warnings and Precautions (5.3), and Clinical Pharmacology (12.3)]*.

8.7 Patients with Renal Impairment

In a dedicated renal impairment trial, the mean PK parameters were comparable between healthy subjects with normal renal function (N=8) and those with end stage renal disease (ESRD) on hemodialysis (N=8) after a single oral 1,000 mg dose of ZYTIGA. No dosage adjustment is necessary for patients with renal impairment *[see Dosage and Administration (2.1) and Clinical Pharmacology (12.3)]*.

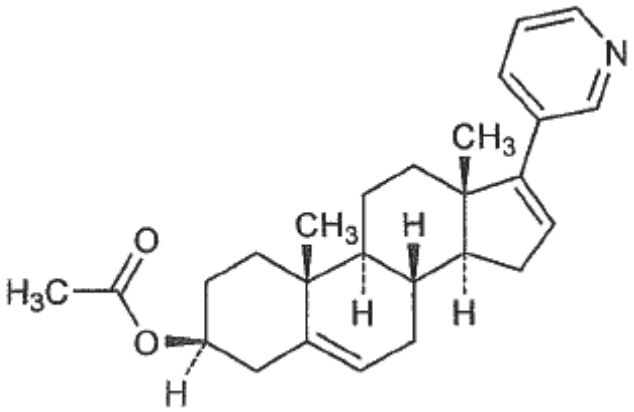
10 OVERDOSAGE

There have been no reports of overdose of ZYTIGA during clinical studies.

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

11 DESCRIPTION

Abiraterone acetate, the active ingredient of ZYTIGA is the acetyl ester of abiraterone. Abiraterone is an inhibitor of CYP17 (17α-hydroxylase/C17,20-lyase). Each ZYTIGA tablet contains 250 mg of abiraterone acetate. Abiraterone acetate is designated chemically as (3β)-17-(3-pyridinyl)androsta-5,16-dien-3-yl acetate and its structure is:



Abiraterone acetate is a white to off-white, non-hygroscopic, crystalline powder. Its molecular formula is $C_{26}H_{33}NO_2$ and it has a molecular weight of 391.55. Abiraterone acetate is a lipophilic compound with an octanol-water partition coefficient of 5.12 (Log P) and is practically insoluble in water. The pKa of the aromatic nitrogen is 5.19.

Inactive ingredients in the tablets are colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

CYP17 catalyzes two sequential reactions: 1) the conversion of pregnenolone and progesterone to their 17α-hydroxy derivatives by 17α-hydroxylase activity and 2) the subsequent formation of dehydroepiandrosterone (DHEA) and androstenedione, respectively, by C17, 20 lyase activity. DHEA and androstenedione are androgens and are precursors of testosterone. Inhibition of CYP17 by abiraterone can also result in increased mineralocorticoid production by the adrenals *[see Warnings and Precautions (5.1)]*.

Androgen sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Androgen deprivation therapies, such as treatment with GnRH agonists or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumor.

ZYTIGA decreased serum testosterone and other androgens in patients in the placebo-controlled phase 3 clinical trial. It is not necessary to monitor the effect of ZYTIGA on serum testosterone levels.

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

12.3 Pharmacokinetics

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

Absorption

Following oral administration of abiraterone acetate to patients with metastatic CRPC, the median time to reach maximum plasma abiraterone concentrations is 2 hours. Abiraterone

accumulation is observed at steady-state, with a 2-fold higher exposure (steady-state AUC) compared to a single 1,000 mg dose of abiraterone acetate.

At the dose of 1,000 mg daily in patients with metastatic CRPC, steady-state values (mean ± SD) of C_{max} were 226 ± 178 ng/mL and of AUC were 1173 ± 690 ng.hr/mL. No major deviation from dose proportionality was observed in the dose range of 250 mg to 1,000 mg.

Systemic exposure of abiraterone is increased when abiraterone acetate is administered with food. Abiraterone C_{max} and $AUC_{0-\infty}$ were approximately 7- and 5-fold higher, respectively, when abiraterone acetate was administered with a low-fat meal (7% fat, 300 calories) and approximately 17- and 10-fold higher, respectively, when abiraterone acetate was administered with a high-fat (57% fat, 825 calories) meal. Given the normal variation in the content and composition of meals, taking ZYTIGA with meals has the potential to result in increased and highly variable exposures. Therefore, no food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. The tablets should be swallowed whole with water *[see Dosage and Administration (2.1)]*.

Distribution and Protein Binding

Abiraterone is highly bound (>99%) to the human plasma proteins, albumin and alpha-1 acid glycoprotein. The apparent steady-state volume of distribution (mean ± SD) is 19,669 ± 13,358 L. *In vitro* studies show that at clinically relevant concentrations, abiraterone acetate and abiraterone are not substrates of P-glycoprotein (P-gp) and that abiraterone acetate is an inhibitor of P-gp. No studies have been conducted with other transporter proteins.

Metabolism

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

Excretion

In patients with metastatic CRPC, the mean terminal half-life of abiraterone in plasma (mean ± SD) is 12 ± 5 hours. Following oral administration of ^{14}C-abiraterone acetate, approximately 88% of the radioactive dose is recovered in feces and approximately 5% in

urine. The major compounds present in feces are unchanged abiraterone acetate and abiraterone (approximately 55% and 22% of the administered dose, respectively).

Patients with Hepatic Impairment

The pharmacokinetics of abiraterone was examined in subjects with baseline mild (n = 8) or moderate (n = 8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 8 healthy control subjects with normal hepatic function. Systemic exposure to abiraterone after a single oral 1,000 mg dose given under fasting conditions increased approximately 1.1-fold and 3.6-fold in subjects with mild and moderate baseline hepatic impairment, respectively. The mean half-life of abiraterone is prolonged to approximately 18 hours in subjects with mild hepatic impairment and to approximately 19 hours in subjects with moderate hepatic impairment. ZYTIGA has not been studied in patients with baseline severe hepatic impairment (Child-Pugh Class C) *[see Dosage and Administration (2.2) and Use in Specific Populations (8.6)]*.

Patients with Renal Impairment

The pharmacokinetics of abiraterone were examined in patients with end-stage renal disease (ESRD) on a stable hemodialysis schedule (N=8) and in matched control subjects with normal renal function (N=8). In the ESRD cohort of the trial, a single 1,000 mg ZYTIGA dose was given under fasting conditions 1 hour after dialysis, and samples for pharmacokinetic analysis were collected up to 96 hours post dose. Systemic exposure to abiraterone after a single oral 1,000 mg dose did not increase in subjects with end-stage renal disease on dialysis, compared to subjects with normal renal function *[see Use in Specific Populations (8.7)]*.

Drug Interactions

In vitro studies with human hepatic microsomes showed that abiraterone is a strong inhibitor of CYP1A2, CYP2D6 and CYP2C8, a moderate inhibitor of CYP2C9, CYP2C19 and CYP3A4/5.

In an *in vivo* drug-drug interaction trial, the C_{max} and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively when dextromethorphan 30 mg was given with abiraterone acetate 1,000 mg daily (plus prednisone 5 mg twice daily). The AUC for dextrorphan, the active metabolite of dextromethorphan, increased approximately 1.3 fold *[see Drug Interactions (7.1)]*.

In a clinical study to determine the effects of abiraterone acetate 1,000 mg daily (plus prednisone 5 mg twice daily) on a single 100 mg dose of the CYP1A2 substrate theophylline, no increase in systemic exposure of theophylline was observed.

Abiraterone is a substrate of CYP3A4, *in vitro*. The effects of strong CYP3A4 inhibitors or inducers on the pharmacokinetics of abiraterone have not been evaluated, *in vivo*. Strong inhibitors and inducers of CYP3A4 should be avoided or used with caution *[see Drug Interactions (7.2)]*.

12.6 QT Prolongation

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of abiraterone acetate.

Abiraterone acetate and abiraterone did not induce mutations in the microbial mutagenesis (Ames) assay and was not clastogenic in both the *in vitro* cytogenetic assay using primary human lymphocytes and in the *in vivo* rat micronucleus assay.

ZYTIGA has the potential to impair reproductive function and fertility in humans based on findings in animals. In repeat-dose toxicity studies in male rats (13- and 26-weeks) and monkeys (39-weeks), atrophy, aspermia/hypospermia, and hyperplasia in the reproductive system were observed at ≥ 50 mg/kg/day in rats and ≥ 250 mg/kg/day in monkeys and were consistent with the antiandrogenic pharmacological activity of abiraterone [*see Nonclinical Toxicology (13.2.)*]. These effects were observed in rats at systemic exposures similar to humans and in monkeys at exposures approximately 0.6 times the AUC in humans.

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

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

13.2 Animal Toxicology and/or Pharmacology

In 13- and 26-week studies in rats and 13- and 39-week studies in monkeys, a reduction in circulating testosterone levels occurred with abiraterone acetate at approximately one half the human clinical exposure based on AUC. As a result, decreases in organ weights and toxicities were observed in the male and female reproductive system, adrenal glands, liver, pituitary (rats only), and male mammary glands. The changes in the reproductive organs are consistent with the antiandrogenic pharmacological activity of abiraterone acetate. A dose-dependent increase in cataracts was observed in rats at 26 weeks starting at $\geq$ 50 mg/kg/day (similar to the human clinical exposure based on AUC). In the 39-week monkey study, no cataracts were observed at higher doses (2 times greater than the clinical exposure based on AUC). All other toxicities associated with abiraterone acetate reversed or were partially resolved after a 4-week recovery period.

14 CLINICAL STUDIES

The efficacy and safety of ZYTIGA in patients with metastatic castration-resistant prostate cancer (CRPC) that has progressed on androgen deprivation therapy was demonstrated in two randomized, placebo-controlled, multicenter phase 3 clinical trials. Patients with prior ketoconazole treatment for prostate cancer and a history of adrenal gland or pituitary disorders were excluded from these trials.

Study 1

Patients with metastatic CRPC who had received prior docetaxel chemotherapy:

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

The following patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 69 years (range 39-95) and the racial distribution was 93.3% Caucasian, 3.6% Black, 1.7% Asian, and 1.6% Other. Eighty-nine

percent of patients enrolled had an ECOG performance status score of 0-1 and 45% had a Brief Pain Inventory-Short Form score of ≥ 4 (patient's reported worst pain over the previous 24 hours). Ninety percent of patients had metastases in bone and 30% had visceral involvement. Seventy percent of patients had radiographic evidence of disease progression and 30% had PSA-only progression. Seventy percent of patients had previously received one cytotoxic chemotherapy regimen and 30% received two regimens.

The protocol pre-specified interim analysis was conducted after 552 deaths and showed a statistically significant improvement in overall survival in patients treated with ZYTIGA compared to patients in the placebo arm (Table 5 and Figure 1). An updated survival analysis was conducted when 775 deaths (97% of the planned number of deaths for final analysis) were observed. Results from this analysis were consistent with those from the interim analysis (Table 5).

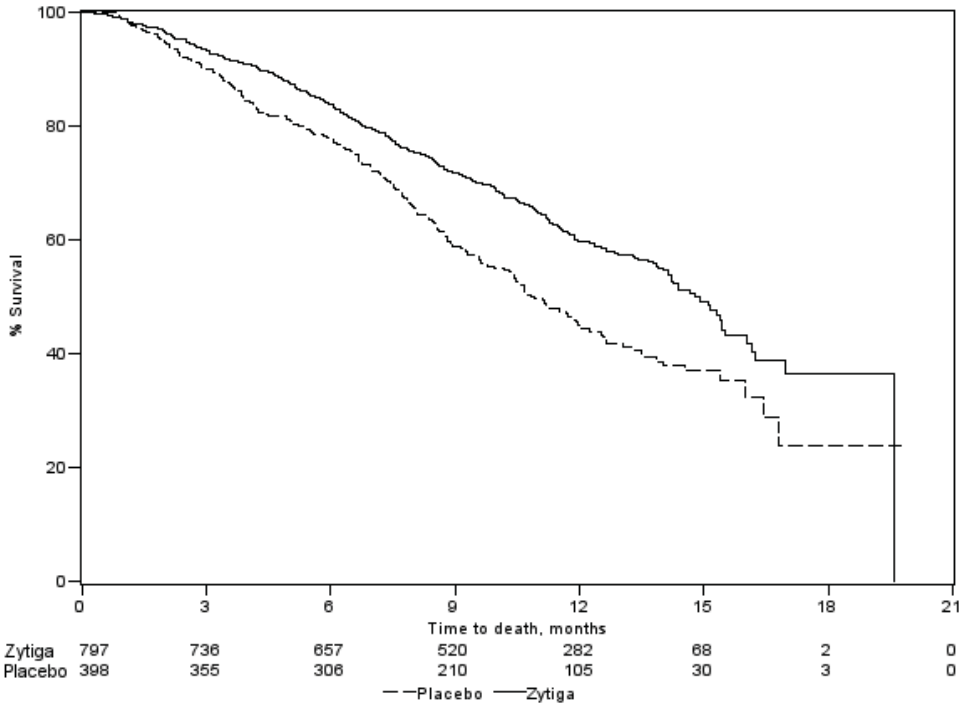
Table 5: Overall Survival of Patients Treated with Either ZYTIGA or Placebo in Combination with Prednisone in Study 1 (Intent-to-Treat Analysis)

	ZYTIGA (N=797)	**Placebo (N=398)**
Primary Survival Analysis		
Deaths (%)	333 (42%)	219 (55%)
Median survival (months) (95% CI)	14.8 (14.1, 15.4)	10.9 (10.2, 12.0)
p-value [a]	< 0.0001	
Hazard ratio (95% CI) [b]	0.646 (0.543, 0.768)	
Updated Survival Analysis		
Deaths (%)	501 (63%)	274 (69%)
Median survival (months) (95% CI)	15.8 (14.8, 17.0)	11.2 (10.4, 13.1)
Hazard ratio (95% CI) [b]	0.740 (0.638, 0.859)	

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

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

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



Study 2

Patients with metastatic CRPC who had not received prior cytotoxic chemotherapy

In Study 2, 1088 patients were randomized 1:1 to receive either ZYTIGA at a dose of 1,000mg once daily (N=546) or Placebo once daily (N=542). Both arms were given concomitant prednisone 5mg twice daily. Patients continued treatment until radiographic or clinical (cytotoxic chemotherapy, radiation or surgical treatment for cancer, pain requiring chronic opioids, or ECOG performance status decline to 3 or more) disease progression, unacceptable toxicity or withdrawal. Patients with moderate or severe pain, opiate use for cancer pain, or visceral organ metastases were excluded.

Patient demographics were balanced between the treatment arms. The median age was 70 years. The racial distribution of patients treated with ZYTIGA was 95.4% Caucasian, 2.8% Black, 0.7% Asian and 1.1% Other. The ECOG performance status was 0 for 76% of patients, and 1 for 24% of patients. Co-primary efficacy endpoints were overall survival and radiographic progression-free survival (rPFS). Baseline pain assessment was 0-1 (asymptomatic) in 66% of patients and 2-3 (mildly symptomatic) in 26% of patients as defined by the Brief Pain Inventory-Short Form (worst pain over the last 24 hours).

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

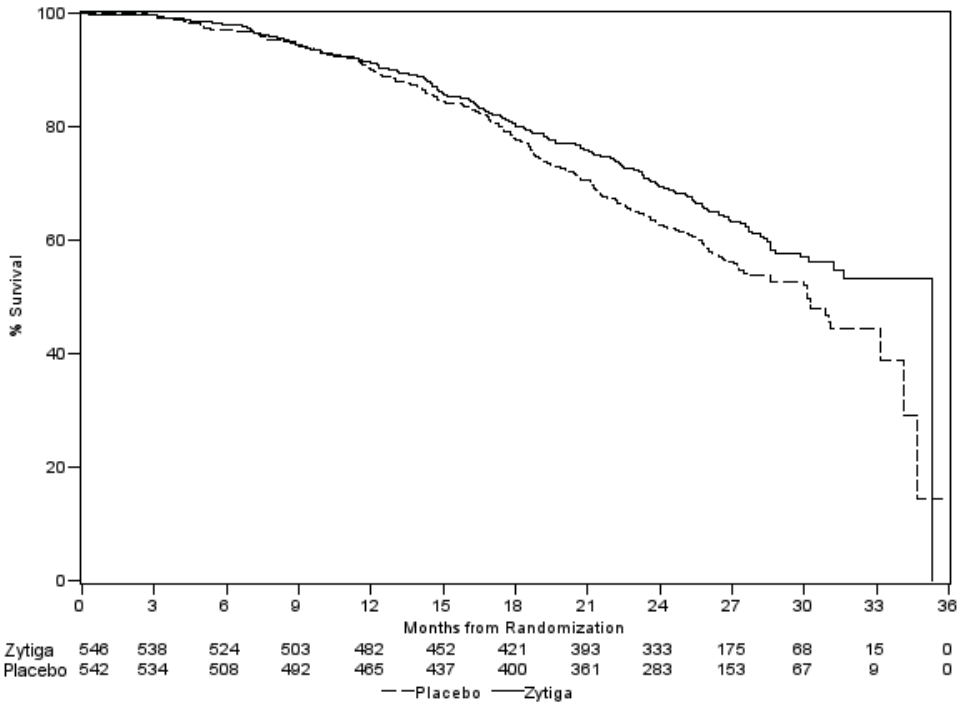
At the protocol pre-specified third interim analysis for overall survival, 37% (200 of 546) of patients treated with ZYTIGA, compared with 43% (234 of 542) of patients treated with placebo, had died. Overall survival was longer for ZYTIGA than placebo with a hazard ratio of 0.792 (95% CI: 0.655 - 0.956). The p value was 0.0151 which did not meet the pre-specified value for statistical significance (Table 6 and Figure 2).

Table 6: Overall Survival of Patients Treated with Either ZYTIGA or Placebo in Combination with Prednisone in Study 2 (Intent-to-Treat Analysis)

Overall Survival	**ZYTIGA (N=546)**	**Placebo (N=542)**
Deaths	200 (37%)	234 (43%)
Median survival (months) (95% CI)	35.3 (31.24, 35.29)	30.1 (27.30, 34.10)
p-value[a]	0.0151	
Hazard ratio[b] (95% CI)	0.792 (0.655, 0.956)	

[a] P-value is derived from a log-rank test stratified by ECOG performance status score (0 vs. 1).
[b] Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors ZYTIGA

Figure 2 – Kaplan Meier Overall Survival Curves in Study 2 (Intent-to-Treat analysis)



At the pre-specified rPFS analysis, 150 (28%) patients treated with ZYTIGA and 251 (46%) patients treated with placebo had radiographic progression. A significant difference in rPFS between treatment groups was observed (Table 7 and Figure 3).

Table 7: Radiographic Progression-free Survival of Patients Treated with Either ZYTIGA or Placebo in Combination with Prednisone in Study 2 (Intent-to-Treat Analysis)

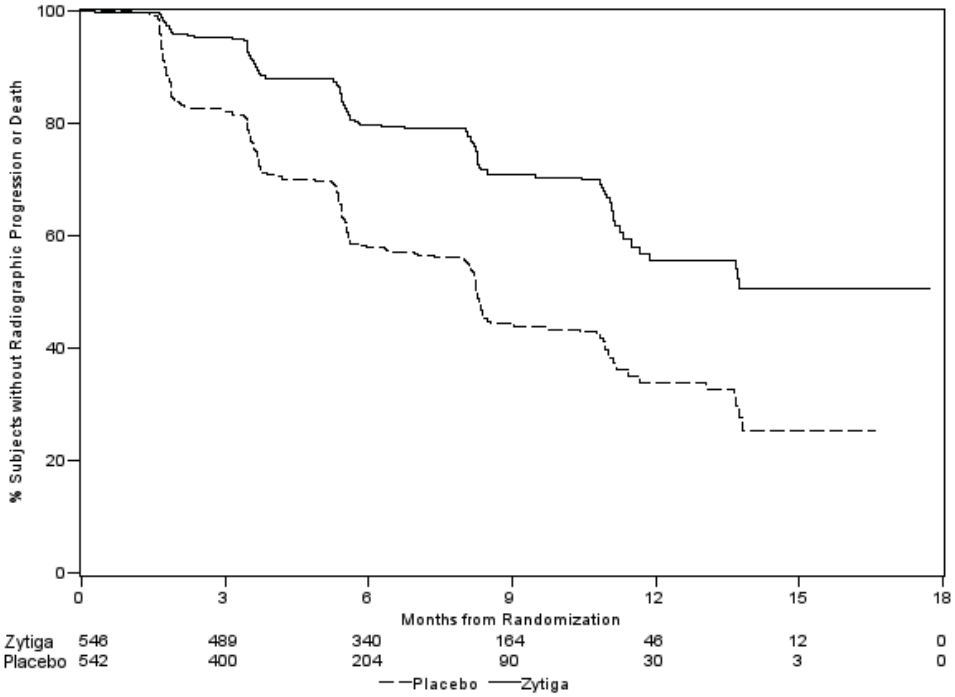
Radiographic Progression-free Survival	ZYTIGA (N=546)	Placebo (N=542)
Progression or death	150 (28%)	251 (46%)
Median rPFS (months) (95% CI)	NR (11.66, NR)	8.28 (8.12, 8.54)
p-value[a]	<0.0001	
Hazard ratio[b] (95% CI)	0.425 (0.347, 0.522)	

NR= Not reached

[a] P-value is derived from a log-rank test stratified by ECOG performance status score (0 vs. 1).

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

Figure 3 – Kaplan Meier Curves of Radiographic Progression-free Survival in Study 2 (Intent-to-Treat Analysis)



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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

ZYTIGA (abiraterone acetate) 250 mg tablets are white to off-white, oval tablets debossed with AA250 on one side. ZYTIGA 250 mg tablets are available in high-density polyethylene bottles of 120 tablets.

NDC Number 57894-150-12

Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted in the range from 15°C to 30°C (59°F to 86°F) *[see USP controlled room temperature]*.

Based on its mechanism of action, ZYTIGA may harm a developing fetus. Therefore, women who are pregnant or women who may be pregnant should not handle ZYTIGA without protection, e.g., gloves *[see Use in Specific Populations (8.1)]*.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

- Patients should be informed that ZYTIGA and prednisone are used together and that they should not interrupt or stop either of these medications without consulting their physician.
- Patients receiving GnRH agonists should be informed that they need to maintain this treatment during the course of treatment with ZYTIGA and prednisone.
- Patients should be informed that ZYTIGA must not be taken with food and that no food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. They should be informed that the tablets should be swallowed whole with water without crushing or chewing. Patients should be informed that taking ZYTIGA with food causes increased exposure and this may result in adverse reactions.
- Patients should be informed that ZYTIGA is taken once daily and prednisone is taken twice daily according to their physician's instructions.
- Patients should be informed that in the event of a missed daily dose of ZYTIGA or prednisone, they should take their normal dose the following day. If more than one daily dose is skipped, patients should be told to inform their physician.
- Patients should be apprised of the common side effects associated with ZYTIGA, including peripheral edema, hypokalemia, hypertension, elevated liver function tests, and urinary tract infection. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Patients should be advised that their liver function will be monitored using blood tests.

- Patients should be informed that ZYTIGA may harm a developing fetus; thus, women who are pregnant or women who may be pregnant should not handle ZYTIGA without protection, e.g., gloves. Patients should also be informed that it is not known whether abiraterone or its metabolites are present in semen and they should use a condom if having sex with a pregnant woman. The patient should use a condom and another effective method of birth control if he is having sex with a woman of child-bearing potential. These measures are required during and for one week after treatment with ZYTIGA.

Manufactured by:

Patheon Inc.

Mississauga, Canada

Manufactured for:

Janssen Biotech, Inc.

Horsham, PA 19044

Revised: December 2012

PATIENT INFORMATION
ZYTIGA® (Zye**-tee-**ga)
(abiraterone acetate)
Tablets

Read this Patient Information that comes with ZYTIGA before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is ZYTIGA?

ZYTIGA is a prescription medicine that is used along with prednisone. ZYTIGA is used to treat men with castration-resistant prostate cancer (prostate cancer that is resistant to medical or surgical treatments that lower testosterone) that has spread to other parts of the body.

ZYTIGA is not for use in women.

It is not known if ZYTIGA is safe or effective in children.

Who should not take ZYTIGA?

Do not take ZYTIGA if you are pregnant or may become pregnant. ZYTIGA may harm your unborn baby.

Women who are pregnant or who may become pregnant should not touch ZYTIGA without protection, such as gloves.

What should I tell my healthcare provider before taking ZYTIGA?

Before you take ZYTIGA, tell your healthcare provider if you:

- have heart problems
- have liver problems
- have a history of adrenal problems
- have a history of pituitary problems
- have any other medical conditions
- plan to become pregnant. See “Who should not take ZYTIGA?”
- are breastfeeding or plan to breastfeed. It is not known if ZYTIGA passes into your breast milk. You and your healthcare provider should decide if you will take ZYTIGA or breastfeed. You should not do both. See “Who should not take ZYTIGA?”

Tell your healthcare provider about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. ZYTIGA can interact with many other medicines.

You should not start or stop any medicine before you talk with the healthcare provider that prescribed ZYTIGA.

Know the medicines you take. Keep a list of them with you to show to your healthcare provider and pharmacist when you get a new medicine.

How should I take ZYTIGA?

- Take ZYTIGA and prednisone exactly as your healthcare provider tells you.
- Take your prescribed dose of ZYTIGA one time a day.
- Your healthcare provider may change your dose if needed.
- Do not stop taking your prescribed dose of ZYTIGA or prednisone without talking with your healthcare provider first.
- Take ZYTIGA on an empty stomach. **Do not take ZYTIGA with food**. Taking ZYTIGA with food may cause more of the medicine to be absorbed by the body than is needed and this may cause side effects.
- No food should be eaten 2 hours before and 1 hour after taking ZYTIGA.
- Swallow ZYTIGA tablets whole. Do not crush or chew tablets.
- Take ZYTIGA tablets with water.
- Men who are sexually active with a pregnant woman must use a condom during and for one week after treatment with ZYTIGA. If their sexual partner may become pregnant, a condom and another form of birth control must be used during and for one week after treatment with ZYTIGA. Talk with your healthcare provider if you have questions about birth control.
- If you miss a dose of ZYTIGA or prednisone, take your prescribed dose the following day. If you miss more than 1 dose, tell your healthcare provider right away.
- Your healthcare provider will do blood tests to check for side effects.

What are the possible side effects of ZYTIGA?

ZYTIGA may cause serious side effects including:

- **High blood pressure (hypertension), low blood potassium levels (hypokalemia) and fluid retention (edema)**. Tell your healthcare provider if you get any of the following symptoms:
  - dizziness
  - fast heartbeats
  - feel faint or lightheaded
  - headache
  - confusion
  - muscle weakness
  - pain in your legs
  - swelling in your legs or feet
- **Adrenal problems** may happen if you stop taking prednisone, get an infection, or are under stress.

- **Liver problems**. You may develop changes in liver function blood test. Your healthcare provider will do blood tests to check your liver before treatment with ZYTIGA and during treatment with ZYTIGA.

The most common side effects of ZYTIGA include:

- weakness
- joint swelling or pain
- swelling in your legs or feet
- hot flushes
- diarrhea
- vomiting
- cough
- high blood pressure
- shortness of breath
- urinary tract infection
- bruising
- low red blood cells (anemia) and low blood potassium levels
- high blood sugar levels, high blood cholesterol and triglycerides
- certain other abnormal blood tests

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ZYTIGA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ZYTIGA?

- Store ZYTIGA at 59°F to 86°F (15°C to 30°C).

Keep ZYTIGA and all medicines out of the reach of children.

General information about ZYTIGA.

Medicines are sometimes prescribed for purposes other than those listed in a patient information leaflet. Do not use ZYTIGA for a condition for which it was not prescribed. Do not give your ZYTIGA to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about ZYTIGA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ZYTIGA that is written for healthcare professionals.

For more information contact Janssen Biotech, Inc. at 1-800-526-7736 (1-800-JANSSEN) or www.Zytiga.com.

What are the ingredients of ZYTIGA?

Active ingredient: abiraterone acetate

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Patheon Inc.
Mississauga, Canada

Manufactured for:
Janssen Biotech, Inc.
Horsham, PA 19044

Revised: December 2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 202379/ S005

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	12/10/2012
From	Amna Ibrahim MD
Subject	Deputy Director Summary Review
NDA/BLA # **Supplement #**	202379 SE-005
Applicant Name	Janssen Biotech Inc
Date of Submission	6/14/2012
PDUFA Goal Date	12/14/2012
Proprietary Name / **Established (USAN) Name**	Zytiga® Abiraterone acetate
Dosage Forms / Strength	Oral tablets/ 250 mg
Proposed Indication(s)	For the treatment of patients with metastatic castration-resistant prostate cancer (b) (4) (b) (4)
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Paul Kleutz
Statistical Review	Zhang, Lijun
CMC	Sharon L Kelly
Pharmacology Toxicology Review	Ringgold, Kimberly R
Clinical Pharmacology Review	Pfuma, Elimika
DDMAC	Safarik, Michelle L
DSI	Lee, Jong Hoon
CDTL Review	Maher, Virginia E
OSE/DMPP	Ford, Latonia
SEALD	Voqui, Jessica

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DSI=Division of Scientific Investigations
DDMP= Division of Medical Policy Programs
CDTL=Cross-Discipline Team Leader

1. Introduction

Zytiga® (NDA 202379) was initially approved on 4/28/2011 for use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel. This approval was based on an improvement in overall survival and an acceptable risk-benefit ratio. With the current submission, the Applicant proposed to expand the indication to metastatic castrate resistant prostate cancer, regardless of whether they had received prior chemotherapy or not. The proposed indication is

(b) (4)

The approved indication will be

Zytiga is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer.

2. Background

Medical Officer Paul Kluetz describes the mechanism of action as, "abiraterone acetate is a prodrug that is converted after adsorption to abiraterone, a 17α-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 already been castrated by medical or surgical means."

As noted by the CDTL, Virginia (Ellen) Maher MD, "agreement was reached on a Special Protocol Assessment for the key trial in this submission on February 6, 2009. The letter containing the agreement stated, "We remind you that although the rPFS definition appears reasonable, the use of rPFS to support approval has not been established." The trial was later modified to add a 3rd interim analysis for OS. This addition was agreed to by the FDA."

The Applicant submitted a single pivotal trial, COU-AA-302 to support the NDA submission for this supplement. The trial was titled "A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Abiraterone Acetate Plus Prednisone in Asymptomatic or Mildly Symptomatic Subjects With Metastatic Castration-Resistant Prostate Cancer." Medically or surgically castrated asymptomatic or mildly symptomatic men with mCRPC who had not received cytotoxic chemotherapy were enrolled. The co-primary efficacy endpoints of this study were radiographic progression-free survival (rPFS) and overall survival (OS).

3. CMC/Device

As also stated by the CDTL, Ellen Maher MD, no new manufacturing information was provided in this supplement. Minor changes to the labeling were made. Sharon Kelly PhD states in her review that the supplement can be approved from the CMC perspective. I concur with her conclusion.

4. Nonclinical Pharmacology/Toxicology

According to the review by Kimberley Ringgold PhD, reports for several nonclinical studies were submitted by the Applicant, that were not requested by the FDA. These included reports for embryo-fetal developmental toxicity studies, nonclinical reproductive and fertility studies and genetic toxicity studies conducted with impurities. Per the review, "in an embryo-fetal developmental toxicity study in rats, developmental toxicity occurred with abiraterone acetate administration during gestation at doses ≥ 10 mg/kg/day as was evident by embryo-fetal lethality and fetal developmental delay. Fetal ano-genital distance was decreased in males at ≥ 30 mg/kg. No NOAEL was established in the fertility or embryofetal development studies. (b) (4) is a potential synthesis impurity that was not previously characterized under the original NDA approval in 2011. Under the conditions tested, (b) (4) (b) (4) does not have mutagenic potential." Dr Ringgold states that "There is nothing in the nonclinical studies submitted to this efficacy supplement that preclude the approval of abiraterone acetate for the proposed indication of treatment of patients with metastatic castration-resistant prostate cancer." Dr Ringgold's review was co-signed by team leader Todd Palmby PhD.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

Elimika Pfuma, PharmD/PhD states in her review that "this submission is acceptable from a clinical pharmacology perspective. Based on recommendations from SEALD, we recommended a change to the title of Section 5.4 of the Warnings and Precautions section of label. We changed the title from (b) (4) to "Increased Zytiga Exposures with Food"." She also stated that population PK analysis was not performed for the current review as no new labeling claims were added based on population PK.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

Per Applicant, "study COU-AA-302 is a Phase 3, multinational, randomized, double-blind, placebo-controlled study conducted at 151 study sites in the US, Europe, and Australia comparing the efficacy and safety of abiraterone acetate plus prednisone with placebo plus prednisone in medically or surgically castrated asymptomatic or mildly symptomatic men with

mCRPC who have not received cytotoxic chemotherapy. Planned enrollment was approximately 1,000 subjects. Subjects were stratified according to Eastern Cooperative Oncology Group (ECOG) performance status Grade (0 versus 1) and were then assigned randomly in a 1:1 ratio to receive either abiraterone acetate plus prednisone or placebo plus prednisone. Eligible subjects received 1,000 mg abiraterone acetate (administered as 4 x 250 mg tablets) or 4 placebo tablets once daily plus prednisone 5 mg twice daily. Food was not to be consumed for at least 2 hours before and for at least 1 hour after the dose of study drug."

The co-primary endpoints were radiographic progression-free survival (rPFS) based on IRC assessment, and overall survival (OS). Treatment with abiraterone acetate improved rPFS. The median rPFS was 8.3 months in the placebo arm and had not yet been reached for those receiving abiraterone acetate [HR 0.43 (95% CI: 0.35, 0.52), $p < 0.0001$]. See figure 1. At the pre-specified third interim analysis, median OS were 35.3 and 30.1 months in the abiraterone acetate and placebo arms, respectively [HR 0.79 (95% CI: 0.66, 0.96)]. See figure 2.These results did not cross the O'Brien-Fleming boundary for statistical significance. The primary endpoints were supported by statistically significant improvements in time-to-opiate use and time-to-cytotoxic chemotherapy.

Figure 1: Kaplan Meier Curves of Radiographic Progression-free Survival (ITT Analysis)

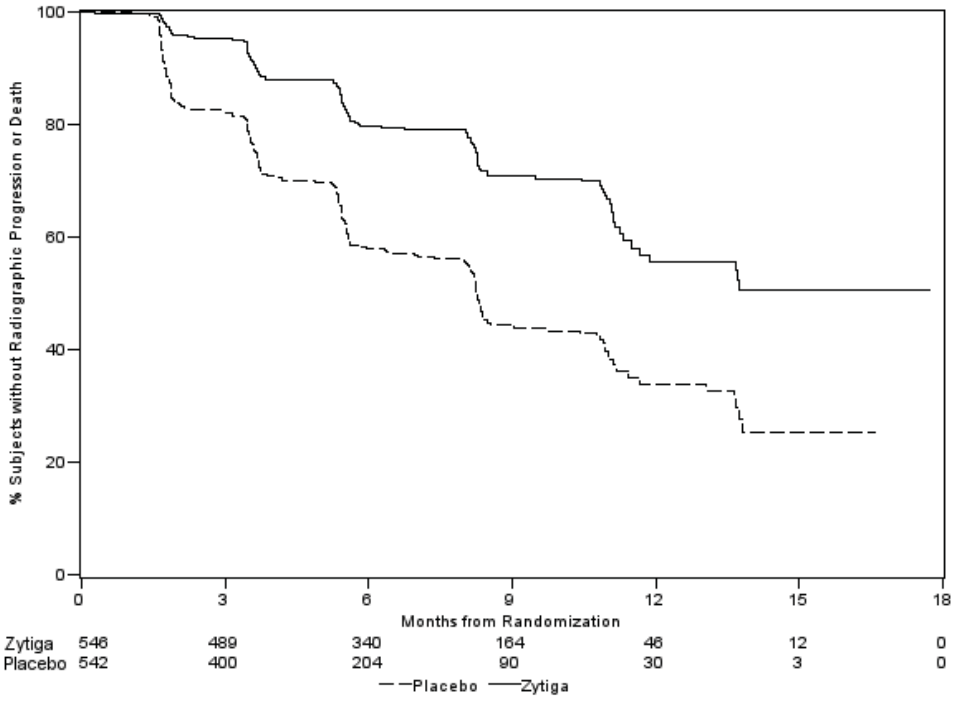
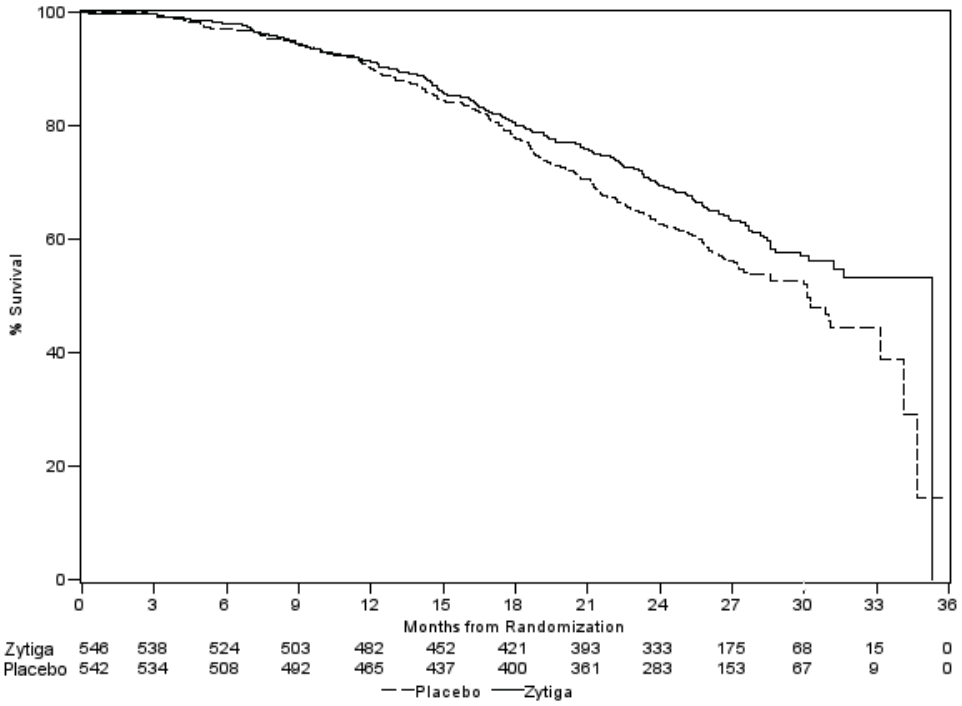


Figure 2: Kaplan Meier Overall Survival Curves (ITT analysis)



In her statistical review, Lijun Zhang, PhD, states that "the abiraterone arm showed a statistically significant improvement over placebo in rPFS as assessed by independent radiographic review. The overall survival results were not mature at this time, with the 3rd interim analysis results numerically but not statistically favoring the abiraterone arm. The abiraterone arm has also demonstrated benefit over the placebo arm in the pre-specified major secondary endpoints, i.e., time to initiation of cytotoxic chemotherapy use, and time to opiate use for cancer pain. In addition, the patient reported data of delaying pain progression supported the time to opiate use for cancer pain. In this disease setting, because rPFS is not an established surrogate endpoint of overall survival, and has not been used to support a marketing approval, the approvability of this supplemental NDA should be considered based on the totality of the data in the pivotal trial (including overall survival, rPFS, other measures representing clinical benefit such as opiate pain use and cytotoxic chemotherapy use, and patient report outcomes) in the context of overall survival benefit of abiraterone acetate demonstrated in a more refractory population. The judgment on the approvability is deferred to the clinical review team."

Medical officer Paul Kluetz MD and CDTL Virginia (Ellen) Maher MD, both recommend approval of this supplemental NDA. Dr Kluetz states in his review that "This recommendation is based on a favorable risk:benefit assessment of data submitted from the randomized clinical trial COU-AA-302 in the chemotherapy-naive mCRPC population. The large improvement seen in the surrogate primary endpoint of radiographic progression free survival (rPFS) is supported by a favorable trend in the co-primary endpoint of overall survival as well as statistically significant improvements in key secondary endpoints. The application is felt to provide substantial evidence that the rPFS result, in this particular application, predicts

meaningful clinical benefit. This determination is made in the context of a known statistically significant overall survival benefit already demonstrated in the initial clinical trial COU-AA- 301 which was conducted in a more refractory prostate cancer setting."

8. Safety

The trial enrolled 1088 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy. Patients were ineligible if AST and/or ALT ≥ 2.5X ULN and patients were excluded if they had liver metastases.

The most common adverse reactions (≥ 10%) are fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion. The most common laboratory abnormalities (> 20%) are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia.

The sections on Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess, Adrenocortical Insufficiency and Hepatotoxicity were updated in WARNINGS AND PRECAUTIONS to include information from the current study.

Per Dr Maher, "As included in the label, in the combined data from 2 studies (study submitted in this NDA and the one that was the basis of the original approval), cardiac failure occurred more commonly in patients treated with Zytiga compared to patients on the placebo arm (2.1% versus 0.7%). Grade 3-4 cardiac failure occurred in 1.6% of patients taking Zytiga and led to 5 treatment discontinuations and 2 deaths. Grade 3-4 cardiac failure occurred in 0.2% of patients taking placebo. There were no treatment discontinuations and one death due to cardiac failure in the placebo group. The majority of arrhythmias were grade 1 or 2. There was one death associated with arrhythmia and one patient with sudden death in the Zytiga arms and no deaths in the placebo arms."

"Death within 30 days due to pulmonary infection was slightly higher in AA than in placebo (5 cases compared with 2). However, the data are insufficient to add death due to pulmonary infections as a significant risk attributed to treatment with abiraterone acetate. Cardiac failure appeared to be a confounder in two cases and is a labeled risk for AA with deaths due to cardiac failure are listed in the label. Increased upper respiratory tract infection is noted to occur more frequently in the COU-AA-302 trial (see Table 53: Adverse Events > 5% in patients taking AA in COU-AA-302), and this adverse reaction will be included as an ADR under that study. The incidence of pneumonia was 2.2% for AA and 1.9% for placebo. There did not appear to be a significant safety signal noted in post-marketing data concerning pneumonia, or pulmonary events."

Per Dr Maher, "no new safety signals were identified and the safety profile of abiraterone was similar to that of placebo. However, there were more deaths in the abiraterone arm." In her review she notes that there were 11 (2%) deaths on the Zytiga arm, and 5 (0.9%) on the placebo arm within 30 days of study drug." In table 9 of her review, she states that none of

these deaths are clearly related to abiraterone. In addition, overall deaths were fewer on the Zytiga arm. Although the submission of the final overall survival analysis and datasets for COU-AA-302 were recommended as a post-marketing requirement by the clinical team, this was added as a PMC in the action letter because of the favorable safety profile of Zytiga as recommended by Dr. Maher in a verbal communication.

9. Advisory Committee Meeting

None conducted for this sNDA.

10. Pediatrics

A waiver was granted because of prostate cancer is not a pediatric disease.

11. Other Relevant Regulatory Issues

- DSI Audits: According to Jong Hoon Lee, at three of four study sites inspected, no significant deficiencies were observed and a Form FDA 483 was not issued. For the fourth site, a Form FDA 483 was issued for minor deficiencies in adhering to the study protocol. He also states that the study data from four inspected sites appear reliable as reported in the NDA supplement.

- Financial Disclosure: Per Dr Kluetz, "There were 10 investigators with financial disclosures to report." "Overall, sites with investigators who may have had a financial conflict enrolled a total of 166 (15%) of study patients randomized to abiraterone acetate (79) or placebo (87). Radiographic PFS and OS appeared similar in this subset The mitigation of potential financial conflicts conducted by the Applicant appeared to be appropriate. It is the determination of the reviewer that there is no evidence that financial conflict materially affected the outcome of the pivotal trial COU-AA-302."

- SEALD Review: Per Jessica Voqui, the SEALD reviewer, (b) (4)

"It is plausible that results from time to opiate use (b) (4) may be used to support labeling statements of treatment benefit in this context."

- Other Consults: For DCDP (Division of Consumer Drug Promotion), Michelle Safarik, PA-C reviewed the label. Latonia Ford, RN, BSN, MBA, reviewed the label for DMPP (Division of Medical Policy Programs). In an email dated 9/11/2012, Frances Fahnbulleh states that in reference to the issue of Zytiga administration with regards to food, DMEPA agrees. Additionally, there are no changes to the insert labeling that require DMEPA comment and no change to the carton and container labeling.

  All comments for labeling were discussed in meetings and there were no remaining issues.

There are no other unresolved relevant regulatory issues

12. Labeling

- Proprietary name: The proprietary name has been previously approved for this sNDA.

- Physician labeling: The proposed indication was expanded to all chemo-naïve mCRPC patients after failure of androgen deprivation therapy (b) (4) The detailed rationale is provided in the MOR. Per Dr Kluetz, "while there is no direct comparison available for docetaxel versus abiraterone in chemotherapy naive metastatic CRPC with moderate to severe pain, there is no compelling biologic rationale for why abiraterone acetate would be less effective in this subgroup. The data from COU-AA-301 provide support that the moderate/severe pain subgroup does not appear to differ with respect to OS, rPFS or antitumor activity endpoints from the overall COU-AA-301 population. While the FDA did not review the methodology or primary data for the pain palliation rate noted in trial 301, it is reassuring to note a near doubling of pain palliation by this measure when compared with placebo. The reviewer believes that treatment of patients with moderate/severe pain with abiraterone should be an option left up to the discretion of the treating physician despite the fact that this specific population was not enrolled on the COU-AA-302 trial". I agree with Dr. Kluetz's rationale.

  As recommended by Dr Zhang, the statistical reviewer, the labeling included results of the third interim OS analysis, the final rPFS analysis, the time to initiation of cytotoxic chemotherapy analysis, and the time to opiate use for cancer pain analysis.

  The labeling was discussed internally and with the Applicant. All issues were resolved.

- Carton and immediate container labels: These we agreed upon by FDA and the Applicant.

- Patient labeling/Medication guide: These we agreed upon by FDA and the Applicant.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action
  Approval

- Risk Benefit Assessment

  Zytiga has demonstrated a relatively large difference in rPFS as well as a trend in improvement in OS. The secondary endpoints and subgroup analyses support the primary endpoints, including clinically meaningful and statistically significant secondary endpoints such as time-to-opiate use and time-to-cytotoxic chemotherapy. The toxicity is generally low in comparison with cytotoxic therapies. A survival benefit has already been demonstrated for mCRPC who have previously received docetaxel. The risk-benefit assessment for Zytiga is favorable for the indicated population.

  All disciplines recommend approval of this sNDA.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

  None

- Recommendation for other Postmarketing Requirements and Commitments

  As a post-marketing commitment, the Applicant will submit the final analysis of OS for study COU-AA-302, the major study submitted to support this sNDA

Amna Ibrahim MD
Deputy Division Director
DOP1, OHOP

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

/s/

AMNA IBRAHIM
12/10/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 202379/ S005

OFFICER/EMPLOYEE LIST

Officer / Employee List
Application: NDA 202379/S-005

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified on this list:

Burke, Laurie
Ford, Latonia
Fuller, Barbara
Ibrahim, Amna
Jenney, Susan
Kacuba, Alice
Kelly, Sharon
Kluetz, Paul
Liu, Qi
Palmby, Todd
Patel, Hasmukh
Pfuma, Elimika
Pohlman, Janice
Ringgold, Kimberly
Safarik, Michelle
Schechter, Genevieve
Sridhara, Rajeshwari
Tang, Shenghui
Tilley, Amy
Toscano, Marybeth
Trentacosti, Ann Marie
Voqui, Jessica
Zhang, Lijun

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 202379/ S005

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	September 4, 2012
From	V. Ellen Maher, M.D.
Subject	Abiraterone acetate
NDA/BLA # **Supplement#**	202379 Supplement 5
Applicant	Janssen Research & Development, LLC
Date of Submission	June 14, 2012
PDUFA Goal Date	December 14, 2012
Proprietary Name / Established (USAN) names	Zytiga/Abiraterone acetate
Dosage forms / Strength	250 mg tablets
Proposed Indication(s)	Zytiga is a CYP17 inhibitor, in combination with prednisone indicated for: the treatment of patients with metastatic castration-resistant prostate cancer (b) (4) (b) (4)
Recommended:	Approval

1. Introduction

The applicant submitted an efficacy supplement for the following proposed indication.

- The treatment of patients with metastatic castration-resistant prostate cancer (b) (4) (b) (4)

2. Background

The key study in this application randomized patients with metastatic castration-resistant prostate cancer (CRPC) who have not received chemotherapy to abiraterone/prednisone (N = 546) or placebo/prednisone (N = 542). Entry was limited to patients with metastases to the bone, soft tissue, or lymph nodes. Patients were followed for the co-primary endpoints radiographic progression-free survival (rPFS) and overall survival (OS). The definition of rPFS was similar to that in the Prostate Cancer Working Group 2 (PCWG2) criteria (JCO 2008 26: 1148). Abiraterone was approved for a similar indication, treatment of patients with metastatic CRPC who have received docetaxel, on April 28, 2011. This approval was based on an improvement in OS with a hazard ratio of 0.65 (95% CI: 0.54, 0.77).

Abiraterone irreversibly inhibits 17α–hydroxylase and C17, 20 lyase, important enzymes in androgen synthesis in the testes, adrenal gland, and in the prostate tumor itself. Gonadotropin releasing hormone (GnRH) analogs inhibit androgen synthesis only in the testes. Disease that has progressed on GnRH analogs is said to be castration-resistant. However, it is thought that these patients have some prostate cancer cells that remain androgen-sensitive and that further inhibition of androgen production by abiraterone will reduce their growth. However, a

consequence of androgen and cortisol inhibition in the adrenal gland by abiraterone is an increase in adrenocorticotropic hormone (ACTH) release and mineralocorticoid excess. Prednisone has been given with abiraterone to suppress ACTH and to provide needed glucocorticoids.

Docetaxel, sipuleucel T, ketoconazole, estrogens, and high dose prednisone are often used in patients with metastatic CRPC. However, few large controlled trials have been conducted with ketoconazole, estrogens and high dose prednisone. Instead, large controlled trials have been conducted, in this population, with the FDA-approved products shown in the table below.

Table 1: Approved Products for Patients with Metastatic Castration-Resistant Prostate Cancer Who Have Not Previously Received Chemotherapy

Approved Agent(s)	Population	Comparator	Basis of Approval
Mitoxantrone Prednisone	Metastatic CRPC	Prednisone	Response: 2-point decrease in pain RR[1] 29% vs. 12%, p = 0.01 Duration of response 7.6 vs. 2.1 mos Median OS 11.3 vs. 10.8 mos
Docetaxel Prednisone	Metastatic CRPC	Mitoxantrone Prednisone	Median OS 18.9 vs. 16.6 mos HR[1] 0.65, p = 0.0094
Sipuleucel-T	Metastatic CRPC	Peripheral Blood Mononuclear Cells	Median OS 25.8 vs. 21.7 mos HR 0.78, p = 0.32 Median OS 25.9 vs. 21.4 mos HR 0.59, p = 0.01

[1]HR-hazard ratio, RR-response rate

Regulatory History

Agreement was reached on a Special Protocol Assessment for the key trial in this submission on February 6, 2009. The letter containing the agreement stated, "We remind you that although the rPFS definition appears reasonable, the use of rPFS to support approval has not been established." The trial was later modified to add a 3rd interim analysis for OS. This addition was agreed to by the FDA.

3. CMC/Device

No new manufacturing information was provided in this supplement.

4. Nonclinical Pharmacology/Toxicology

Fertility and developmental toxicology studies were included in this supplement. Abiraterone resulted in a decrease in fertility in male and female rats with a full recovery in the males after 16 weeks and in the females after 4 weeks. The effect of abiraterone on embryo-fetal development included late resorptions, post-implantation loss, and feminization of the male genitalia. The applicant also submitted a 28-day repeat dose toxicology study of a product impurity. No toxicology findings were attributed to the impurity.

5. Clinical Pharmacology/Biopharmaceutics

During the Phase 3 study, pharmacokinetic assessments were collected on Day 1 of Cycles 1, 2, and 5. The observations were consistent with the model developed during the initial assessment and approval of abiraterone.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

The applicant submitted the following studies in support of this application.

1. Key Study COU-AA-302: A Phase 3, Randomized, Double-blind, Placebo-controlled Study of Abiraterone Acetate Plus Prednisone in Asymptomatic or Mildly Symptomatic Subjects with Metastatic Castration-Resistant Prostate Cancer

2. COU-AA-301: A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Abiraterone Acetate Plus Prednisone in Patients with Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy

The applicant has also conducted 3 Phase 2 and 2 Phase 1-2 studies in prostate cancer.

Design of Key Study

Eligibility

1. Metastatic prostate cancer to the bones, soft tissues, or lymph nodes (LN must be $\geq$ 2 cm in longest diameter); No visceral disease
2. No prior cytotoxic chemotherapy
3. Rising PSA per PCWG2 criteria or radiographic progression (per RECIST) of prostate cancer despite castrate testosterone levels (< 50 ng/dL)
4. Score of 0-3 on Brief Pain Inventory-Short Form Question #3
    a. Question #3: patient's worst pain in the last 24 hours where 0 is no pain and 10 is pain as bad as you can imagine
    b. Patients on opioids were excluded
5. Patients on bicalutamide, flutamide, or nilutamide must have PSA progression after anti-androgen withdrawal. However, the prior use of these agents was not required.
6. No use of ketoconazole (up to 7 d permitted)
7. No viral hepatitis or chronic liver disease; Bilirubin < 1.5xULN, AST/ALT < 2.5xULN
8. No MI or arterial thrombotic event within 6 mos; No severe or unstable angina; No NYHA Class II-IV heart failure; No EF < 50%

Stratification: Performance status (0 vs. 1)

Treatment

1. Abiraterone Acetate 1000 mg po daily + Prednisone 5 mg po bid
2. Placebo + Prednisone 5 mg po bid

- Gonadotropin releasing hormone analog should be continued
- Discontinue study drug for clinical progression defined as:
    i. Cancer pain requiring chronic use of opioids
    ii. Decline in performance status to ECOG PS 3-4

iii. Need for cytotoxic chemotherapy, radiation or surgical intervention

- May remain on study drug with radiographic/PSA progression if there is no clinical progression

Monitoring:

- Liver Function Tests: Cycle 1-3 Days 1, 15, then Day 1 q cycle and EOT
- Echo: Baseline
- Patient Reported Outcomes:
  - BPI-SF/Analgesic Use: Day 1 q cycle and EOT
  - FACT-P: Day 1 every other cycle and EOT
- Con Meds: Every cycle during treatment w/study drug then q 3 mos
- PSA: Day 1 Cycles 1, 3, 5, 7, and 10 then every 3 cycles, EOT
- Tumor Imaging by CT/MR and Bone Scan: Day 1 Cycles 1, 3, 5, 7, and 10 then every 3 cycles, EOT

Statistical Analysis

Primary Endpoints

Overall survival and rPFS were the co-primary endpoints. The primary analysis of rPFS used the results of an independent review of CT/MR imaging and bone scan and was defined as:

- Bone Scan Progression
  - < 12 weeks from randomization: If $\geq$ 2 new lesions are seen compared to baseline, progression must be confirmed by a 2nd bone scan $\geq$ 6 weeks later showing $\geq$ 2 additional new lesions ($\geq$ 4 lesions compared to baseline).
  - $\geq$ 12 weeks from randomization: If $\geq$ 2 new lesions are seen compared to baseline, progression must be confirmed by a 2nd bone scan $\geq$ 6 weeks later showing at least the same 2 new lesions ($\geq$ 2 lesions compared to baseline).
- CT/MRI Progression
  - RECIST criteria were used to evaluate soft tissue or nodal progression or the appearance of new lesions (other than bone).
- Death from any cause in the absence of progression

Censoring rules for rPFS: Please see primary review for complete censoring rules. Note that patients who missed $\geq$ 2 or had $\geq$ 2 consecutive uninterpretable scans or discontinued study drug without progression were censored at their last interpretable scan prior to additional therapy. Further, patients who discontinued study drug with new, but unconfirmed bone scan lesions were censored at their last interpretable scan prior to additional therapy.

The primary analysis for both rPFS and OS used a Cox proportional hazard model to estimate the hazard ratio, a stratified (randomization strata) logrank test to estimate the p-value, and the Kaplan-Meier method to estimate the median progression-free or overall survival.

The statistical analysis plan was amended on June 22, 2011 to include the following interim analyses. Overall alpha for OS was 0.04 and for rPFS 0.01. Note that the IDMC unblinded the trial after review of the data at the 2nd interim analysis of OS (December 20, 2011) and that patient crossover did not begin until May 7, 2012.

Table 2: Planned Interim Analyses of the Primary Endpoints				
Planned Timing	Actual Data Cutoff	Actual Events	rPFS	OS
~15% OS Events ~378 rPFS Events	12-20-2010	98 Deaths (13%) 410 rPFS Events	Primary Analysis	Interim Analysis 1
~40% OS Events	12-20-2011[1]	333 Deaths (43%)	None	Interim Analysis 2
~55% OS Events	5-22-2012	434 Deaths (56%)	None	Interim Analysis 3
~ 773 OS Events			None	Final Analysis

[1]Study unblinded by IDMC after review of this data; Crossover from placebo to abiraterone began on 5-7-2012

Secondary Endpoints

Secondary endpoints were to be tested in the order below using the Hochberg procedure with an alpha of 0.05. Please see primary review for additional information.

1. Time to opiate use for cancer pain
2. Time to initiation of cytotoxic chemotherapy
3. Time to deterioration in ECOG performance status (PS) by $\geq$ 1 point
4. Time to PSA progression

Patient Disposition

Patient disposition is typically presented as of the date of the primary analysis. Here, patient disposition is shown at the time of the primary analysis of rPFS and at the time of the 2nd interim analysis of OS (time of IDMC unblinding). Note that this table provides the number of patients with investigator (INV)-determined radiographic progression. This differs from the number of patients with independent radiology committee (IRC)-determined progression in the analysis of rPFS.

While the percentage of patients who discontinued due to unequivocal clinical progression was similar in each arm at the December 20, 2011 time point, a substantial number of patients discontinued due to clinical rather than radiographic progression. That is, the radiographic criteria used in this study did not capture progression in ~ 20% of patients. Further, the majority of patients whose discontinuation was categorized as "Other", discontinued due to radiographic or clinical progression which did not meet the pre-defined study criteria for these events. Interestingly, the patients with Clinical Progression Only were more likely to have > 20 bone scan lesions (75/247, 30%) than the population as a whole (220/1086, 20%). This may have lead to the difficulty in determining radiographic progression in these patients. Finally, in the disposition dataset, using the December 20, 2011 cutoff, 40 patients in the abiraterone arm discontinued due to an adverse event (1 discontinuation due to patient death). In the adverse event dataset using the same cutoff date, 53 patients discontinued due to an adverse event. The adverse events leading to discontinuation will be discussed in Section 8, Safety.

Table 3: Patient Disposition				
	Primary Analysis of rPFS Data Cutoff 12-20-10		Time of Unblinding Data Cutoff 12-20-11	
	Abiraterone	Placebo	Abiraterone	Placebo
Randomized	546	542	546	542
Treated	542	540	542	540
Ongoing	330 (60%)	204 (38%)	166 (30%)	86 (16%)
Discontinued	216 (40%)	338 (62%)	376 (69%)	454 (84%)
Progression	142 (26%)	248 (46%)	283 (52%)	351 (62%)
Radiographic Progression per Investigator[1]	89 (16%)	143 (26%)	172 (32%)	215 (40%)
Clinical Progression Only	53 (10%)	105 (19%)	111 (20%)	136 (25%)
Additional Therapy Only	34	74	79	93
Opiate Use Only	6	18	10	22
ECOG PS $\geq$ 3 Only	5	1	7	4
Multiple Categories	8	12	15	17
Adverse Event/Death	36	28	41	29
Withdrawal/Lost to Follow Up	26	40	33	46
Other	12	22	19	28

[1]Includes pts with radiographic progression only and with both radiographic and clinical progression

Demographics and Baseline Disease Characteristics

Patients were recruited at 151 sites with 43% of patients from the US. Patient demographics were well balanced between arms with a median age of 71 years (range 44-96). Ninety-five percent of patients were White. In both arms, 76% of patients had a performance status of 0.

This table provides information on baseline disease characteristics. The median time since diagnosis and median PSA were similar between arms. At entry, patients were required to have evidence of disease progression (rising PSA or radiographic progression per RECIST). However, this information was not captured. While patients with visceral disease were excluded from entry, IRC review of baseline scans found that 4-6% of patients had visceral disease.

Table 4: Baseline Disease Characteristics		
	Abiraterone N = 546	Placebo N = 542
Median Time from Diagnosis (range)	5.5 years (0-28)	5.1 years (0-28)
Median PSA at Entry (range)[1]	42 ng/mL (0-3927)	38 ng/mL (0.7-6606)
Extent of Disease at Entry by IRC[1]		
Bone	525 (96%)	522 (96%)
Soft Tissue, Lymph Node/Spleen, Pleura/Omentum	275 (50%)	274 (51%)
Visceral Disease[2]	22 (4%)	31 (6%)
Liver	13 (2%)	12 (2%)
Target Lesions	N = 225	N = 228
Median Sum of the Longest Diameter (range)	5.3 cm (1.5-45.4)	5.6 cm (1.1-77.4)

[1]Based on fewer than 546 pts in the abiraterone and 542 pts in the placebo arm
[2]Adrenal, liver, lung, pancreas

Primary Endpoint

Overall Survival

The table and figure below provide information on overall survival at the last available analysis of OS (3rd interim analysis, 56% of events) and has a cutoff date of May 22, 2012. The p-value of this analysis, 0.015, did not cross the O'Brien-Fleming boundary (required ≤ 0.0035). This study was unblinded after the 2nd interim analysis of OS, but patient crossover did not begin until May 7, 2012. Thus, information from the 3rd interim analysis was minimally affected by crossover. All of the pre-planned subgroup analyses are consistent with the primary analysis of OS. The hazard ratio (HR) for OS in US patients was 0.69. An additional subgroup analysis (unplanned) in patients with visceral disease per IRC found a HR of 0.83.

Table 5: Third Interim Analysis of Overall Survival

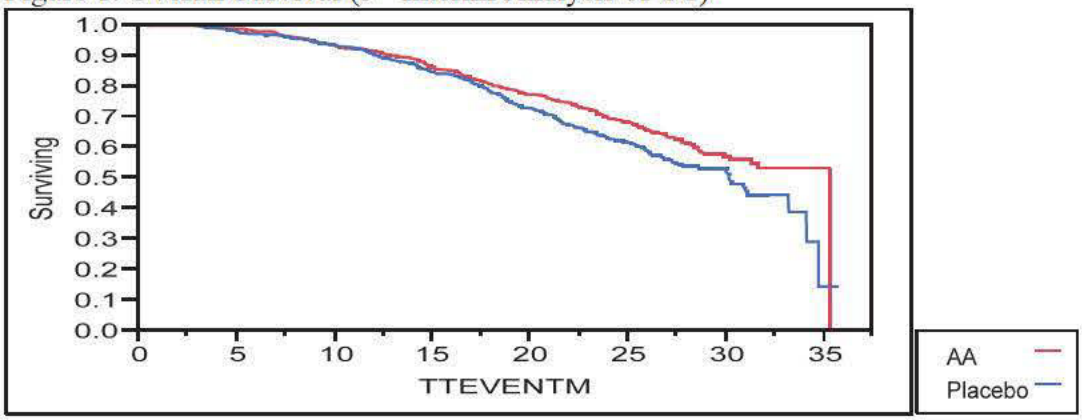
	Abiraterone N = 546	Placebo N = 542
Events	200 (37%)	234 (43%)
Median OS	35 months	30 months
Hazard Ratio[1] (95% CI)	0.79 (0.66, 0.96)	
p-value[1]	0.015	

[1]NR = not reached

Data Cutoff 5-22-12

[2]HR: proportional hazards model; p-value: stratified logrank test

Figure 1: Overall Survival (3rd Interim Analysis of OS)



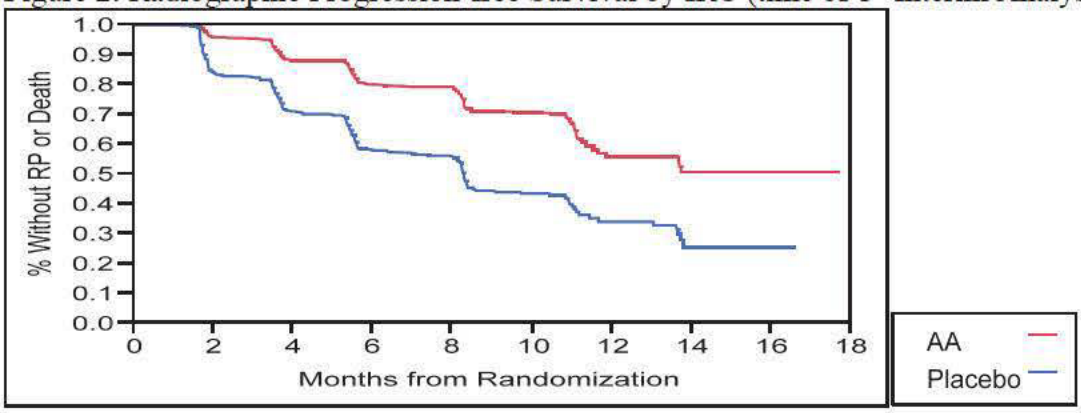
Radiographic Progression-free Survival

This table provides information on the primary analysis of rPFS (at the time of the 1st interim analysis of OS) using IRC-determined progression. The primary analysis of IRC-determined progression was supported by an analysis using INV-determined progression (HR = 0.49). All of the pre-planned subgroup analyses and sensitivity analyses were consistent with the primary endpoint. The HR for US patients was 0.32. An exploratory subgroup analysis of patients with visceral disease found a HR of 0.35. A 2nd exploratory subgroup analysis found a HR of 0.45 for patients who received bicalutamide, nilutamide, or flutamide within 1 year of study entry. Please see primary review for additional information on sensitivity and subgroup analyses. Note that 327 patients continued on study drug after INV-determined progression.

Table 6: Primary Analysis of Radiographic Progression-free Survival by IRC		
	Abiraterone	Placebo
rPFS Events	150 (28%)	251 (46%)
Progression by Bone Scan Only	57	79
Progression by CT/MRI Only	66	115
Progression by Both	18	46
Death	9	11
Median rPFS	Not Evaluable	8.3 months
Hazard Ratio[1] (95% CI) p-value[1]	0.43 (0.35, 0.52) p < 0.0001	

[1]HR: stratified proportional hazards model; p-value: stratified logrank Data Cutoff 12-20-2010

Figure 2: Radiographic Progression-free Survival by IRC (time of 1st Interim Analysis of OS)



This review examines the use of the PCWG2 criteria and the discordance between IRC and INV assessment of progression. The PCWG2 criteria require confirmation of a CT-based assessment of progression at the 1st evaluation. Among the patients with PD at Week 8 who had a subsequent scan ≥ 6 weeks later, all had confirmation of PD. This suggests that confirmation may not be necessary for an assessment of PD on the initial CT.

The PCWG2 assessment of bone scan progression when the initial bone scan is obtained < 12 weeks after entry requires that 2 new lesions on the 1st assessment be confirmed by 2 additional lesions on a subsequent assessment (2+2). The IRC found 260 Week 8 bone scans with ≥ 2 new lesions. Among patients with a subsequent scan ≥ 6 weeks later, 28% had confirmation of disease progression. This suggests that confirmation is essential to the assessment of PD on initial bone scan.

Discordance between the INV and IRC assessment of progression (both CT and bone scan) was found in 36% of patients receiving abiraterone (21% type and 15% timing) and in 44% of patients receiving placebo (24% type and 20% timing). This included discordance in CT assessment of PD in 15% of abiraterone and 18% of placebo patients and discordance in bone scan assessment in 13% of abiraterone and 18% of placebo patients.

Secondary Endpoints

Median time to opiate use for cancer pain was not reached (at least 28 months) and 23.7 months in the abiraterone and placebo arms, respectively (HR 0.69, p = 0.0001). These findings are limited by concerns regarding the completeness of data collection. After

discontinuation of study drug, concomitant medications were collected, in follow up, every 3 months. Further, 41% of patients on the abiraterone and 32% of patients on the placebo arm had no documented opiate use prior to death. An exploratory examination of patient-reported pain (BPI-SF) was consistent with this improvement in the time to opiate use. Median time to initiation of cytotoxic chemotherapy was 25.2 months in the abiraterone and 16.8 months in the placebo arm (HR 0.58, $p < 0.0001$). The order of analysis for the secondary endpoints in the statistical plan allowed for an assessment of the time to deterioration in ECOG performance status by ≥ 1 level. While this analysis was statistically significant (HR 0.82, $p = 0.005$), the difference between arms (1.4 months difference in medians) was not clinically relevant and an analysis of the next endpoint, time to PSA progression, will not be included in this review.

Response rate was an additional endpoint in the statistical plan. The applicant's response rate was limited to patients with measurable disease by CT (pre-specified modification of the RECIST criteria). It did not consider the persistence of bone scan lesions (for an assessment of CR) or the development of 1 new bone scan lesion (for an assessment of PR).

Additional Studies

COU-AA-301 was a Phase 3 trial that randomized patients with metastatic CRPC who had received docetaxel to abiraterone + prednisone or placebo + prednisone. Analysis of the primary endpoint, OS, found that median OS was 15.8 months in the abiraterone and 11.2 months in the placebo arm (HR 0.74, $p < 0.0001$). This demonstration of an improvement in overall survival in a similar patient population strongly supported the primary analysis of the current study (302). Further, examination of the small number of patients with visceral disease in the current study (302) was supported by examination of patients with visceral disease in Study 301. In study 301 (post-docetaxel), the HR for OS in patients with visceral disease (N = 353) was 0.68. Finally, the current study (302) was limited to patients without pain or with mild pain at baseline. Study 301 (post-docetaxel) included patients with moderate to severe pain at baseline (N = 536). Here, the HR for OS in patients with moderate to severe pain was 0.67. This suggests that abiraterone is effective in patients with or without visceral metastases and in patients with severe pain as well as patients with no pain at baseline.

8. Safety

The abiraterone safety database includes 1,680 patients who have received abiraterone 1000 mg/d. This review focuses on the patients (542 abiraterone, 540 placebo) in the key study who received abiraterone or placebo prior to docetaxel. It also focuses on patients (1333 abiraterone, 934 placebo) in the 2 randomized Phase 3 studies in patients with metastatic CRPC (prior to or after docetaxel). Note that the duration of exposure differed markedly in these 2 Phase 3 studies. In the key study, median exposure to abiraterone was 13.8 months and median exposure to placebo 8.3 months. In Study 301 (post-docetaxel), median exposure to abiraterone was 7.4 months and median exposure to placebo was 3.6 months.

Safety Summary

The table below provides a summary of safety in the key study in this application. No new safety signals were identified and the safety profile of abiraterone was similar to that of placebo. However, there were more deaths in the abiraterone arm. In addition to the 11 deaths due to an adverse event listed below, 2 other deaths (cause of death listed as prostate cancer) are of concern. Patient 130-2006 was found unconscious and paramedics were summoned. He was found to be bradycardic with agonal respirations. He was unable to be resuscitated. Patient 812-2009 died due to multi-organ failure after presenting with heart failure and pneumonia. The 11 deaths listed below include 3 patients who died due to pneumonia, 1 whose death was due to aspiration pneumonia, and an additional patient with respiratory failure and cord compression. Two patients in the placebo arm died due to respiratory infection. Review of these narratives did not reveal a clear safety signal. The incidence of infection was 7% in the abiraterone and 6% in the placebo arm. The incidence of death due to pneumonia was also examined in the applicant's other Phase 3 study of patients with CRPC (Study 301, post-docetaxel). In Study 301, 1 patient in the abiraterone arm died to a respiratory disorder (productive cough, no antibiotics) and 2 patients in the placebo arm died due to pneumonia.

Table 7: Safety Summary

Category	Abiraterone N = 542	Placebo N = 540	Adverse Events on the Abiraterone Arm
Deaths Due to Adverse Event Within 30 Days of Study Drug	11 (2%)	5 (0.9%)	Pneumonia (3), GI ischemia (2), Deaths NOS (2), Aspiration pneumonia (1), MI/CHF (1), Respiratory failure/cord compression (1), Suicide (1)
Discontinuation Due to Adverse Event	53 (10%)	42 (8%)	Hepatic (12), General (10), Cardiovascular (9), Pain (7), Infection (5), Neoplasms (3), GI(2), Other (12)
Serious Adverse Events	178 (33%)	142 (26%)	SAEs > 1%: Hematuria, PE, UTI, Atrial fibrillation, Pneumonia
Grade 3-4 Adverse Events	258 (48%)	225 (42%)	AEs > 2%: ALT increased, HTN, AST increased, Dyspnea, Hyperglycemia, Hypokalemia, Fatigue, Anemia
Grade 1-4 Adverse Events	537 (99%)	524 (97%)	AEs > 20%: Fatigue, Back pain, Arthralgia, Peripheral edema, Constipation, Hot flush, Nausea, Diarrhea, Hypertension

Data Cutoff: 12-20-11

Adverse Events of Concern

Hepatotoxicity: Grade 3-4 elevations in ALT occurred in 6% of patients on the abiraterone and 0.7% of patients on the placebo arm. There were no cases that fulfilled the criteria for Hy's Law. Hepatotoxicity was reported as an adverse event (excluding laboratory reported as an AE) in 3 patients in the abiraterone arm (jaundice (2), liver toxicity) and in 3 patients in the placebo arm (jaundice/palpable liver edge (1), jaundice (1), hepatomegaly (1)). AERS reports were also examined. No deaths due to hepatic failure which were clearly attributable to abiraterone have been reported.

Cardiotoxicity: Grade 3-4 cardiac failure was reported in 7 patients in the abiraterone and no patients in the placebo arm. Grade 3-4 chest pain was reported more commonly in the placebo arm while grade 3-4 arrhythmia was reported in 11 patients in the abiraterone and in 6 patients in the placebo arm. This is consistent with the analysis of Study 301 (patients with CRPC who have received docetaxel).

Mineralocorticoid Excess and Adrenal Insufficiency: Grade 1-4 edema (25% vs. 21%), grade 3-4 hypokalemia (3% vs. 2%), and grade 3-4 hypertension (3.9% vs. 3%) occurred more commonly in the abiraterone arm when compared to placebo. Two patients on the abiraterone arm were reported to have adrenal insufficiency. One experienced syncope and was found to have low cortisol levels on an ACTH stimulation test. The 2nd patient was reported to have grade 1 adrenal insufficiency and lethargy.

Grade 1-4 Adverse Events

The table below provides information on Grade 1-4 and grade 3-4 adverse events which occurred on the key study in this application. The adverse event profile in this study is similar to that in the applicant's previous Phase 3 study in a similar population.

Table 8: Grade 1-4 Adverse Reactions in > 10% of Patients in the Abiraterone Arm with a ≥ 2% Increase in Incidence Compared to Placebo

	Abiraterone N = 542		Placebo N = 540	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
General Disorders				
Fatigue	212 (39%)	12 (2%)	185 (34%)	9 (2%)
Edema[1]	136 (25%)	2 (0.4%)	112 (21%)	6 (1%)
Musculoskeletal Disorders				
Joint Swelling/Discomfort[2]	164 (30%)	11 (2%)	136 (25%)	11 (2%)
Gastrointestinal Disorders				
Constipation	125 (23%)	2 (0.4%)	103 (19%)	3 (0.6%)
Diarrhea	117 (22%)	5 (0.9%)	96 (18%)	5 (0.9%)
Dyspepsia	60 (11%)	0	27 (5%)	1 (0.2%)
Vascular Disorders				
Hot Flush	121 (22%)	1 (0.2%)	98 (18%)	0
Hypertension	117 (22%)	21 (4%)	71 (13%)	16 (3%)
Respiratory Disorders				
Cough	94 (17%)	0	73 (14%)	1 (0.2%)
Dyspnea	64 (12%)	13 (2%)	52 (10%)	5 (0.9%)
Psychiatric Disorders				
Insomnia	73 (13%)	1 (0.2%)	61 (11%)	0
Injuries and Procedural Complications				
Contusion	72 (13%)	0	49 (9%)	0
Infections				
Upper Respiratory Infection	69 (13%)	0	43 (8%)	0
Nasopharyngitis	58 (11%)	0	44 (8%)	0
Renal Disorders				
Hematuria	56 (10%)	7 (1%)	30 (6%)	3 (0.6%)

[1]Includes edema peripheral, pitting edema, and generalized edema
[2]Includes arthritis, arthralgia, joint swelling, and joint stiffness
CTCAE v 3.0
Data Cutoff 12-20-11

The incidence of grade 1-4 adverse reactions was also examined in both of the randomized Phase 3 trials conducted in patients with CRPC. Grade 1-4 adverse events in > 10% of patients in the abiraterone arm of both Phase 3 trials and which occurred with a ≥ 2% increase in incidence compared to placebo included fatigue, joint swelling/discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection, and contusion. Grade 1-4 laboratory abnormalities that occurred in > 20% of patients in the abiraterone arm of both

Phase 3 trials and which occurred with a > 5% increase in incidence compared to placebo included anemia, elevated alkaline phosphatase (AKP), hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT, and hypokalemia. These analyses are used in the package insert.

9. Advisory Committee Meeting

Based on the strength of evidence (see Section 13), an advisory committee meeting was not held.

10. Pediatrics

A pediatric waiver was granted.

11. Other Relevant Regulatory Issues

See primary clinical review

12. Labeling

The indication statement submitted by the applicant was changed

From:

ZYTIGA is a CYP 17 inhibitor, in combination with prednisone indicated for:

(b) (4)

To:

ZYTIGA is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer.

Since abiraterone demonstrated efficacy in patients who were asymptomatic or had mild pain (Study 302-key study in this supplement) as well as in patients with moderate to severe pain (Study 301-patients with CRPC post-docetaxel) it was decided to remove this limitation. A second concern was that the key study in this application excluded patients with visceral disease. However, abiraterone demonstrated efficacy in the small number of patients with visceral disease who entered the key study and in the larger number of patients with visceral disease who entered Study 301. It was, therefore, decided that this limitation was not needed.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Approval
- Risk Benefit Assessment

Table 9: Abiraterone Benefit-Risk Assessment Framework		
Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Approximately 28,170 men will died from prostate cancer in the US in 2012. Median survival in the placebo arm of the current study was 30 months.	Castration-resistant prostate cancer is a serious and life-threatening condition.
Medical Need	Current standards of care for the treatment of patients with metastatic CRPC prior to docetaxel include Sipuleucel-T (asymptomatic patients), docetaxel, and anti-androgens/secondary hormonal therapy.	• None of these is a curative therapy. • Docetaxel has substantial toxicity. Elderly patients or those with co-morbid conditions are often unable to tolerate docetaxel. • Anti-androgens/secondary hormonal therapy has limited activity.
Clinical Benefit	The key trial randomized patients with metastatic CRPC whose disease was limited to the bones, lymph nodes, and soft tissue to abiraterone + prednisone or placebo + prednisone. The co-primary endpoints were OS and rPFS. • The HR for the interim analysis of OS was 0.79 (95% CI: 0.66, 0.96), p = 0.015. This did not cross the interim boundary for statistical significance. • The HR for the primary analysis of rPFS was 0.43 (95% CI: 0.35, 0 52), p < 0.0001.	These findings were considered in light of : • Abiraterone's approval was based on a substantial difference in OS in a similar patient population. • The effect of abiraterone on rPFS was large. Small differences in the determination of progression would not affect the result of this analysis. • The secondary endpoints and subgroup analyses support the primary endpoints.
Risk	• The number of deaths was higher in the abiraterone arm (2%) than in the placebo group (0.9%). • Grade 3-4 AEs were increased in the abiraterone arm (48% vs. 42%). Non-laboratory, grade 3-4 AEs in > 2% of patients included hypertension, dyspnea, and fatigue. • Adverse event of concern include hepatotoxicity, heart failure, mineralocorticoid excess, and adrenal insufficiency. • Grade 1-4 adverse events in > 10% of patients include fatigue, joint swelling/discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary infection, and contusion. • Grade 1-4 laboratories in > 20% of patients include decreased hemoglobin, lymphocytes, phosphate, and phosphorous and elevated AKP, triglycerides, cholesterol, glucose, AST, and ALT. • Abiraterone must be taken on an empty stomach. • Drug-drug interactions exist with CYP2D6. Abiraterone should not be used in patients with severe hepatic impairment. • A reproductive risk exists in females.	• None of these deaths are clearly related to abiraterone. • While AEs in the abiraterone arm are increased compared to placebo, the safety profile of abiraterone is acceptable in this patient population in light of the clinical benefit demonstrated by this product.
Risk Management	• Routine laboratory monitoring for elevations in ALT and bilirubin and decreases in potassium are recommended. • No food should be taken with abiraterone. • Dose adjustment is recommended for hepatotoxicity.	Given the overall favorable benefit-risk assessment these risk management activities are adequate.

- Recommendation for Postmarketing Risk Management Activities: None

- Recommendation for other Postmarketing Study Requirements/Commitments

The applicant will submit the final analysis of OS for the key study in this application.

- Recommended Comments to Applicant: None

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/s/

VIRGINIA E MAHER
11/29/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 202379/ S005

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	**NDA Efficacy Supplement**
Application Number(s)	**202379-005**
Priority or Standard	**Priority**
Submit Date(s)	**6-13-2012**
Received Date(s)	**6-14-2012**
PDUFA Goal Date	**12-14-2012**
Division / Office	**CDER / OHOP**
Reviewer Name(s)	**Paul G. Kluetz, M.D.**
Lead Clinical Reviewer	**V. Ellen Maher, M.D.**
Review Completion Date	**11/20/2012**
Established Name	**abiraterone acetate**
(Proposed) Trade Name	**ZYTIGA®**
Therapeutic Class	**CYP17 inhibitor**
Applicant	**Janssen / Johnson and Johnson**
Formulation(s)	**250mg tablets**
Dosing Regimen	**Four 250mg tablets (1000mg) by mouth once daily**
Proposed Indication(s)	**Treatment of patients with metastatic castration-resistant prostate cancer** (b) (4) (b) (4) (b) (4)
Intended Population(s)	**metastatic castration resistant prostate cancer patients**

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical reviewer recommends regular approval of NDA 202379, supplement 005 which provides an indication for abiraterone acetate (AA) for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC). Abiraterone acetate (ZYTIGA®) was initially approved in April of 2011 for the treatment of mCRPC patients after the failure of docetaxel chemotherapy based on a statistically significant overall survival advantage.

This recommendation is based on a favorable risk:benefit assessment of data submitted from the randomized clinical trial COU-AA-302 in the chemotherapy-naive mCRPC population. The large improvement seen in the surrogate primary endpoint of radiographic progression free survival (rPFS) is supported by a favorable trend in the co-primary endpoint of overall survival as well as statistically significant improvements in key secondary endpoints. The application is felt to provide substantial evidence that the rPFS result, in this particular application, predicts meaningful clinical benefit. This determination is made in the context of a known statistically significant overall survival benefit already demonstrated in the initial clinical trial COU-AA-301 which was conducted in a more refractory prostate cancer setting.

The indication for abiraterone acetate has been altered to include patients with metastatic castration resistant prostate cancer regardless of (b) (4) prior chemotherapy use. The rationale behind this decision is provided in the clinical efficacy section of the review.

1.2 Risk Benefit Assessment

Efficacy supplement 005 provides data from trial COU-AA-302: A phase 3 randomized, double-blind, placebo-controlled international trial of abiraterone acetate in asymptomatic or mildly symptomatic metastatic castration resistant prostate cancer. The co-primary endpoints were radiographic progression free survival (rPFS) and overall survival (OS). Patients must have demonstrated confirmed metastatic disease and have a pain score of 3 or less on the Brief Pain Index - Short Form item #3. Patients were excluded who had prior chemotherapy or known liver, brain, or visceral organ metastasis. Treatment was continued until protocol-defined unequivocal clinical progression. The trial appeared to be well designed and well conducted. The study was un-blinded at the second interim analysis for overall survival based on a unanimous recommendation from an independent data monitoring committee.

Efficacy:
A total of 1,088 patients were randomized in a 1:1 fashion to receive abiraterone acetate at a dose of 1000mg once daily in combination with prednisone 5mg orally twice daily (N=546) or placebo orally once daily plus prednisone 5mg orally twice daily (N=542). Important baseline characteristics at enrollment were balanced between the arms. The median age was 70 years. The racial distribution of patients treated with ZYTIGA was 95.4% Caucasian, 2.8% Black, 0.7%

Asian and 1.1% Other. The ECOG performance status was 0 for 76% of patients, and 1 for 24% of patients. Baseline pain assessment was 0-1 (asymptomatic) in 66% of patients and 2-3 (mildly symptomatic) in 26% of patients as defined by the Brief Pain Inventory- Short Form (worst pain over the last 24 hours). The co-primary endpoint of radiographic progression free survival (rPFS) met statistical significance at the pre-planned primary rPFS analysis (12/20/2010 cutoff) by independent radiographic review. Abiraterone acetate (AA) demonstrated a statistically persuasive and large magnitude of reduction in the risk of radiographic progression or death (HR 0.43, 95% CI: 0.35 - 0.52, p<0.0001). Median rPFS was 8.3 months in the placebo group and had not been reached in the AA group. The rPFS result was supported by symmetric timing of radiographic assessments between the treatment groups, a high level of scan compliance (>90% for all cycles) and high concordance between investigator and independent rPFS review.

For the co-primary endpoint of overall survival, the second interim analysis with data cutoff 12/20/2011 did not meet its O'Brien-Fleming efficacy boundary for statistical significance. However; there was a strong trend favoring abiraterone acetate (HR=0.75; p=0.01). The overall survival results were consistent across pre-specified subgroups. Results from the third interim analysis for overall survival with data cutoff 5/22/2012 were submitted during the NDA review period and while also not meeting statistical significance (HR 0.79; [CI: 0.66, 0.96]; p=0.015), there was persistence of the OS trend favoring abiraterone.

The surrogate rPFS findings were further supported by statistically significant improvements in all four pre-specified secondary endpoints. Two of these endpoints were felt to be more closely related to clinical benefit. The median time to first opiate use was 720 days (23.7 months) for placebo and had not been reached with AA (HR=0.69 [95%CI: 0.57-0.84], P=0.0002). This finding was further supported by time to pain progression data from patient reported outcomes. The median time to initiation of cytotoxic chemotherapy was 25.2 months in the abiraterone acetate arm and 16.8 months in the placebo arm (HR 0.58, 95% CI 0.49-0.69; P<0.0001). Finally, exploratory patient reported outcome data from the Brief Pain Index Short Form (BPI-SF) and Functional Assessment of Cancer Therapy - Prostate Scale (FACT-P) were supportive. Taken together, the findings of key secondary endpoints and patient reported outcomes data increased the reviewer's confidence that the delay in asymptomatic radiographic progression is predictive of meaningful clinical benefit in the COU-AA-302 trial.

Safety:

The safety review was based on submitted safety datasets from 2 large randomized, placebo-controlled clinical trials (COU-AA-301 and -302) and phase 1 and 2 trials from patients receiving 1,000mg of AA once daily totaling 1,680 safety-evaluable patients receiving AA and 934 patients receiving placebo. In addition, post-marketing data was requested from the applicant and the FDA adverse event reporting system was queried with Office of Surveillance and Epidemiology consultation. In general, the adverse event and laboratory data submitted for COU-AA-302 appeared to be consistent with its known toxicity profile.

The most common adverse reactions (>10%) seen in the COU-AA-302 trial included fatigue, joint swelling/discomfort, edema, constipation, hot flush and diarrhea, hypertension, cough,

insomnia, contusion, upper respiratory tract infection, dyspnea, dyspepsia, nasopharyngitis and hematuria. Grade 3 to 4 adverse reactions occurred in 48% and 42% of patients taking AA and placebo respectively. The most frequently reported adverse reactions leading to drug discontinuation were related to hepatic toxicity in 2.2% of patients receiving AA compared to 0.2% receiving placebo. There were no hepatic deaths noted in the submitted integrated safety database. In a review of the available post-marketing data by both the FDA and the applicant, there was insufficient data to support an association between abiraterone acetate and fatal outcomes from drug-induced hepatotoxicity or hepatic failure. The review demonstrated a continued increase compared with placebo in the incidence of adverse events related to mineralocorticoid excess which is consistent with AA's mechanism of action. The incidence of grade 3-4 mineralocorticoid-related events for AA compared with placebo were hypertension (3.9% vs 3.0%), hypokalemia (2.8% vs. 1.7%), and edema (0.4% vs. 1.1%). In addition, there remains a higher incidence of adverse events consistent with cardiac failure (1.8% vs 0.4%) seen in the abiraterone acetate arm. The incidence of adrenal insufficiency was reported in only 2 patients on both arms in the COU-AA-302 trial.

Risk:Benefit Analysis:
While the improvement in asymptomatic radiographic progression free survival alone may not have been sufficient evidence for meaningful clinical benefit, the overall risk:benefit assessment of this efficacy supplement is felt to be favorable. There were several key components of this application that increased the reviewer's confidence that the improvement in the surrogate endpoint of rPFS predicts a meaningful clinical benefit for patients with chemotherapy-naive metastatic CRPC in trial COU-AA-302:

1. Existing Trial with Overall Survival Benefit. (Approved Drug)
   AA is already approved in a more refractory population of the same disease with a statistically significant overall survival benefit when compared to placebo (COU-AA-301 study).

2. Overall Survival Results COU-AA-302:
   While not meeting pre-specified statistical significance, the overall survival results from COU-AA-302 revealed a strong improvement favoring the AA arm.

3. Large Magnitude of Effect on Primary Endpoint rPFS:
   The application demonstrated a statistically persuasive and large improvement in both the relative and absolute magnitude of delay in radiographic progression or death.

4. Internal Consistency of Secondary Endpoints
   All prespecified secondary endpoints demonstrated a statistically significant benefit favoring AA. In particular, improvements in both time to cytotoxic chemotherapy and time to opiate use supported by patient reported pain results were thought to provide supportive evidence of clinical benefit.

5. Quantity of Safety Data and Favorable Toxicity Profile
   There is a large randomized trial and post-marketing safety database available. The safety review reveals a favorable safety profile for abiraterone in these minimally symptomatic patients which strengthens the finding that treatment with abiraterone in this earlier population prolongs the time before a patient will need to be treated with a more toxic and less convenient chemotherapy such as docetaxel.

6. Patient Reported Outcomes
   Patient reported outcomes data from both the Functional Assessment of Cancer Treatment- Prostate (FACT-P) and Brief Pain Index - Short Form (BPI-SF) were supportive of the clinical benefit of abiraterone acetate in this application.

In summary, the reviewer concludes the benefit:risk profile of AA is highly favorable for (b) (4) chemotherapy-naive patients with mCRPC who have progressed on androgen deprivation therapy. Furthermore, (b) (4) the indication is supported by abiraterone acetate's efficacy in patients with moderate or higher pain and/or visceral metastatic disease demonstrated in the COU-AA-301 trial.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No safety signals were identified that would warrant a REMS.

1.4 Recommendations for Postmarket Requirements and Commitments

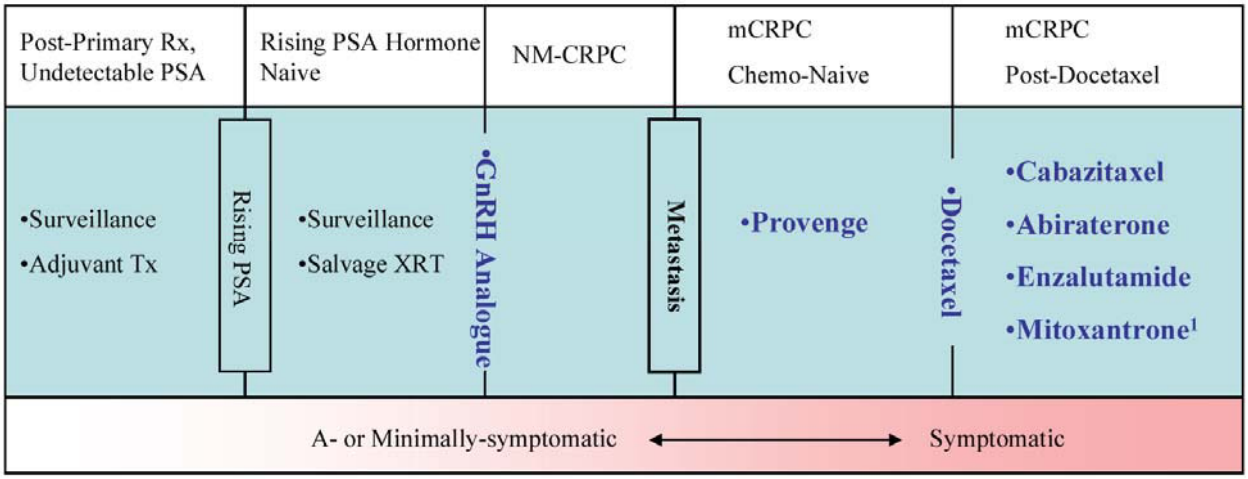
The submission of the final overall survival analysis and datasets for COU-AA-302 will be added as a post-marketing requirement. No other clinical requirements or commitments are identified by the primary clinical reviewer for the proposed indication.

2 Introduction and Regulatory Background

Over 240,000 men in the United States are predicted to be diagnosed with prostate cancer in 2012.[1] It is the leading non-cutaneous malignancy in U.S. men and the second leading cause of death. While most patients are diagnosed at an early localized stage, approximately 15-30% of patients will recur following curative surgical or radiation therapy. Androgen deprivation therapy (ADT) with either surgical castration or gonadotropin releasing hormone (GnRH) analogs is indicated for the palliative treatment of advanced prostate cancer. In the PSA era, the initiation of GnRH analogues prior to the development of symptomatic metastatic disease (PSA relapse only) is commonplace despite the lack of strong evidence for its benefit. When patients recur on ADT in the setting of "castrate" levels of testosterone, patients are termed "castration resistant". The

FDA approved therapies for the treatment of metastatic castration resistant prostate cancer (mCRPC) are illustrated in Figure 1 below:

Figure 1: Prostate Cancer Treatment Landscape



[1] Mitoxantrone approved in 1996 for treatment of pain related to advanced hormone refractory prostate cancer.

Since 2004, there have been 5 products approved for metastatic castration resistant prostate cancer (mCRPC):

- Docetaxel (2004): androgen independent (hormone refractory) metastatic prostate cancer
- Provenge (2010): asymptomatic or minimally symptomatic mCPRC
- Cabazitaxel (2010): mCRPC previously treated with docetaxel
- Abiraterone (2011): mCRPC previously treated with docetaxel
- Enzalutamide (2012): mCRPC previously treated with docetaxel

As you can see from Figure 1 above, following the approval of docetaxel (TAXOTERE®) indications for metastatic castration resistant prostate cancer (mCRPC) have been defined based on a patient's symptoms or whether or not they have received docetaxel cytotoxic chemotherapy. All five drugs approved in the last 10 years have been approved based on overall survival, a direct measure of clinical benefit. As therapies have been studied earlier in the disease history, the size and length of trials associated with utilization of an overall survival primary endpoint have led to an interest in alternative primary endpoints measuring disease progression. Importantly, endpoints such as radiographic progression free survival are considered unestablished surrogate endpoints for direct clinical benefit in prostate cancer. Other endpoints used in prostate cancer approvals that have been considered measures of direct clinical benefit include reduction in skeletal related events (denosumab, zometa) and improvements in composite pain endpoints (mitoxantrone).

Prostate cancer can have an indolent natural history. For most patients, the time from metastatic disease to death from prostate cancer takes years and some patients may die of a cause other than their malignancy. Because of the potentially longer time to more direct measures of clinical benefit such as overall survival, there has been interest in the prostate cancer research

community to development surrogate endpoints which can be measured earlier and can predict clinical benefit. One such endpoint is radiographic progression-free survival (rPFS).

Radiographic progression free survival has not been used for the approval of a prostate cancer indication in the United States. rPFS in the setting of prostate cancer is challenging when compared to the use of PFS in other solid tumor malignancies. This is in large part because prostate cancer metastases are predominately located in bone and the interpretation of bone scans can be challenging[1]. Bone scan lesions are non-measurable and even with improved imaging technology, changes in intensity or size of lesions on bone scan is not considered interpretable. As such, bone scan progression relies on the appearance of new lesions. Furthermore, isolated low volume bone metastatic disease in prostate cancer can be asymptomatic and a delay in an asymptomatic radiographic endpoint, in and of itself, is not considered a direct clinical benefit.

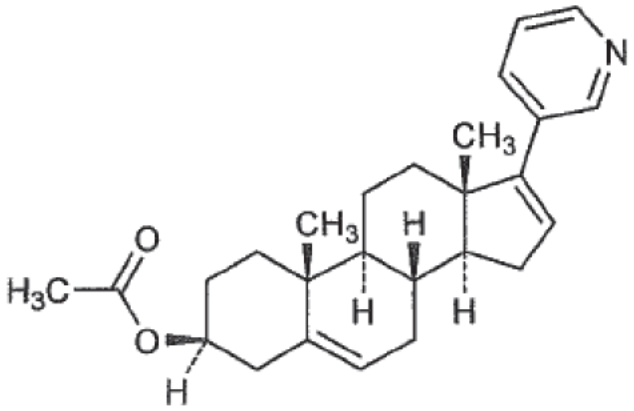
Standardization of the definition for progression in prostate cancer has been an important goal in the research community. The first attempt at standardizing definitions for progression was published in 1999 by Bubley and colleagues and is known as the prostate cancer working group 1 (PCWG-1) criteria or Bubley criteria[2]. Efforts to validate the ability of rPFS to predict direct clinical benefit in prostate cancer have been made. In a pooled analysis of 1,296 men with CRPC treated on nine CALGB clinical trials from 1991-2004, Halabi and colleagues noted that using the PCWG-1 criteria for bone scan progression, PFS at 3 months and 6 months predicted overall survival.[3] The most recent attempt at standardizing progression criteria in prostate cancer was published in the Journal of Clinical Oncology by Scher and colleagues and is known as the Prostate Cancer Working Group 2 criteria (PCWG-2).[4] While the standardization of progression measures in prostate cancer has advanced, radiographic progression free survival as an asymptomatic imaging endpoint has not yet been accepted as a regulatory endpoint for clinical benefit to date.

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 2 below:

[1] Dawson et al., *Eur J Cancer* 1997; (33), 560-565.
[2] Bubley et al., *JCO* 1999; (17), 3461-3467.
[3] Halabi et al., *JCO* 2009; (17), 2766-2771.
[4] Scher et al., *JCO* 2008; (26), 1148-1159.

Figure 2: 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 Chemotherapy-Naive Metastatic Castration-Resistant Prostate Cancer:

Table 1: FDA Approved Anti-Tumor Therapy for chemotherapy-naive mCRPC

Drug and Approval Year	Indication	Approval Endpoint and Magnitude
Mitoxantrone (Novantrone®) 1996	Treatment of pain related to Hormone-Resistant Prostate Cancer	Composite Pain Response 29% vs 12% (P=0.011)
Docetaxel (TAXOTERE®) 2004	Androgen Independent Metastatic Prostate Cancer	Overall Survival (P=0.009) Median 2.4 month improvement
Sipuleucel-T (PROVENGE®) 2010	Asymptomatic or minimally symptomatic Metastatic Castrate Resistant Prostate Cancer.	Overall Survival (P=0.032 and 0.01) Median 4.1 - 4.5 month improvement

(b) (4)

[redacted] (b) (4) [redacted], sipuleucel-T is typically reserved for patients who do not have moderate or severe symptoms or evidence of rapid disease progression. The use of mitoxantrone, while potentially having a labeled indicated in this population, is very uncommon in this setting as it was approved for treatment of pain and is less effective than docetaxel in head to head trials.[6] Patients with metastatic castration resistant prostate cancer who are mildly symptomatic may also be treated with docetaxel chemotherapy, which was approved in 2004 for the treatment of metastatic prostate cancer based on an approximately 2.4 month improvement in overall survival. While effective, docetaxel chemotherapy requires every 3 week intravenous administration and has an adverse event profile significant for neutropenia, fluid retention, mucositis and hypersensitivity. Because of the toxicity profile of docetaxel, it is typically reserved for patients with rapidly progressive disease, significant symptoms or visceral disease (metastases to the liver, lung, brain, etc.). In the absence of these features, oncologists typically utilize secondary hormonal therapies such as anti-androgens (bicalutamide, flutamide, nilutamide), the adrenal androgen synthesis inhibitor ketoconazole or less commonly steroids, DES or other estrogens. There is limited high quality data on the clinical benefit of these secondary hormonal therapies in this setting however they are frequently used in an effort to delay the initiation of cytotoxic chemotherapy or in an attempt to delay the onset of significant cancer-related symptoms in patients who cannot tolerate cytotoxic chemotherapy.

2.3 Availability of Proposed Active Ingredient in the United States

Abiraterone acetate (ZYTIGA®) is marketed in the United States for treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel.

2.4 Important Safety Issues With Consideration to Related Drugs

Due to its mechanism of action as a CYP17 inhibitor, AA can produce mineralocorticoid excess leading to hypertension, hypokalemia and edema. In addition, both AA and the adrenal androgen synthesis inhibitor ketoconazole are known to increase aspartate and alanine aminotransferase serum levels. Mineralocorticoid and hepatic adverse drug reactions are labeled safety issues for AA and will be highlighted in this review.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The applicant notes in their submission the following historical context for the design of the pivotal trial COU-AA-302:

> Enrollment in Study COU-AA-302 began in April 2009. Thus, it was designed before CYP17α inhibition had been shown to improve survival in patients with mCRPC who had previously received docetaxel (Study COUAA-301) and at a time when no therapy had

[5] Kantoff, NEJM 2010; (5) 411-422.
[6] Tannock, NEJM 2004; (351) 1502-1512.

demonstrated a survival benefit in asymptomatic or mildly symptomatic patients who had not received chemotherapy.

Advice on the Study COU-AA-302 design was obtained from the US FDA in May 2008. The protocol for this study was also submitted to the FDA for Special Protocol Assessment (SPA). In February 2009, agreement was reached that the design with co-primary endpoints and planned analyses "adequately addresses the objectives necessary to support a regulatory submission." However, the FDA indicated that regulatory approval based on radiographic progression free survival (rPFS) had not been established. The study should have sufficient power to use OS as an endpoint.

Table 2: Key Regulatory Interactions and Milestones

May 2008	Type C Meeting - Clinical Development Plan for Chemotherapy naive patients.
Nov 2008	COU-AA-302 SPA Non-Agreement Letter
Dec 2008	Type A Meeting to Discuss SPA
Feb 2009	COU-AA-302 SPA Agreement Letter
Apr 2009	Enrollment in COU-AA-302 Begins
Apr 2010	Sipuleucel-T (PROVENGE®) Receives Regular Approval in Asymptomatic or Minimally Symptomatic mCRPC
Dec 2010	NDA 202379 Submitted for Post-Docetaxel mCRPC
Apr 2011	NDA 202379 Receives Regular Approval in Post-Docetaxel mCRPC
Feb 2012	IDMC recommends unblinding of COU-AA-302 based on 2nd Interim Analysis

Summary of the IDMC Evaluation of Interim Analyses:
Pre-submission regulatory meeting minutes noted early on that rPFS would be an unestablished surrogate endpoint and would rely on overall survival results. The IDMC meeting minutes were reviewed for both the 7/22/2011 and the 2/27/2012 meetings. The meeting minutes corroborate that it was the IDMCs determination to continue the study on 7/22/2011 and to unblind treatment at the 2/27/2012 meeting. The applicant scheduled an emergency teleconference with the agency to disclose the plan to unblind COU-AA-302 based on the IDMC recommendation. The agency noted that while it is the applicant's decision whether to unblind the trial, that rPFS remains an unestablished surrogate endpoint for efficacy and overall survival had not met its statistical significance making the determination of meaningful clinical benefit problematic. The review for this application has focused on evaluating all key secondary and exploratory endpoints to attempt to increase the certainty that the magnitude of rPFS benefit seen is likely predictive of true clinical benefit.

Primary rPFS / 1st Interim OS Analysis: IDMC Meeting 7/22/2011:

- Reviewed the blinded primary rPFS analysis and overall survival results with data cutoff 20 December 2010. At that time there were 401 rPFS events and 98 deaths were observed.
- The IDMC recommended continuing the study.

2nd Interim OS Analysis: IDMC Meeting 2/27/2012:

- Reviewed the blinded results with data cutoff 20 December 2011, at which time 333 deaths (43% of the total OS events) were observed.
- The IDMC concluded that all of the efficacy data demonstrate a "highly significant advantage" for subjects in Arm X. The data were then unmasked and revealed to the IDMC that Arm X was the abiraterone acetate group. The IDMC unanimously recommended unblinding the treatment and allowing subjects in the placebo group to receive abiraterone acetate. As a result, the sponsor made the decision to adhere to the IDMC recommendations to unblind the treatment assignments, and provide abiraterone acetate for subjects assigned to the placebo group.

3 Ethics and Good Clinical Practices

Clinical trial AA-302 appears to have been conducted in adherence to Good Clinical Practice. An independent audit certificate is included in the application by Global Research and Development Quality Assurance.

3.1 Submission Quality and Integrity

The submission is complete and well organized. A debarment certification is submitted with the application. A table of study sites and investigators is included which reported the accrual, number of severe adverse events and major protocol violations per site. This information was reviewed in consultation with the Office of Scientific Investigations and several domestic and international clinical sites were selected for inspection.

3.2 Compliance with Good Clinical Practices

The applicant submitted an analysis of their internal audit observations. Nine site audits were conducted by Cougar/Johnson and Johnson. Critical and major protocol violations were reviewed and do not appear to materially affect the validity of the data. Most of the issues identified were addressed through corrective and preventative action plans and increased monitoring.

3.2.1 Sites Placed on Screening Hold

It was noted in the clinical study report that 4 sites were put on screening hold (Sites 103, 113, 122 and 919). An information request was sent by the FDA on July 12, 2012 requesting additional information which was reviewed with key information presented below:

Site 103: Enrolled a total of 6 patients. (103-2004, 103-2005, 103-2006, 103-2007, 103-2008, 103-2009)

Reason for Screening Hold:
Deficiencies in timeliness of data entry into the CRF due to limited data entry staff.

Despite the site's effort's delays continued and 2/3/2010 site agreed to temporarily hold screening. Following increasing resources and study tools, the site became current with reporting by June 2010 but global accrual was complete.

Throughout the screening hold, patients continued to be followed and the site monitored every 4 weeks with timely reporting of SAEs. No major protocol deviations were reported.

Site 113: Enrolled a total of 12 patients. (113-2001, 113-2002, 113-2004, 113-2005, 113-2008, 113-2009, 113-2012, 113-2015, 113-2017, 113-2019, 113-2023, 113-2024)

Reason for Screening Hold:
Problems with organization of source documentation in EMR leading to delay/difficulty with data entry and source verification.

- On Nov 24 2009 a corrective action plan (CAP) was initiated with reorganization of source documentation and improved processes / training.
- On March 2, 2010 screening was halted at the site until all actions in the CAP were completed. There was no further screening between 3/2/2010 and the close of global enrollment in 6/2010.

Throughout the screening hold, patients continued to be followed and the site monitored every 4 weeks with timely reporting of SAEs. No major protocol deviations were reported.

Site 122: Enrolled a total of 5 patients. (122-2001, 122-2003, 122-2007, 122-2008, 122-2009)

Reasons for Screening Hold:
Eligibility issues and early patient discontinuation.

- May 29, 2009: The site mistakenly enrolled a patient meant for study AA-301 to the AA-302 resulting in multiple eligibility violations (prior chemotherapy, opiate use, BPI score of 7). A CAP and additional training were initiated. The site was reopened to screening on July 27, 2009
- In October 2009, concerns arose regarding early discontinuations and a screening hold was placed on October 14, 2009. Additional training was initiated. The site reopened to screening on November 19, 2009.
- On January 19, 2010, the site was put on hold for the entry of a potentially ineligible patient. The patient was verified to be eligible and screening reopened on January 27, 2010.

Throughout the screening hold, patients continued to be followed and the site monitored every 4 weeks. This site had 6 major protocol violations.

Site 919: Enrolled a total of 7 patients. (919-2001, 919-2002, 919-2003, 919-2005, 919-2006, 919-2007, 919-2008)

Reasons for Screening Hold:
Significant delays in data entry and source notes were not adequate.

- In December 2009, the study coordinator resigned and the monitor trained a new coordinator.
- Improvement was noted, but monitoring identified issues with eligibility with 3/7 patients:

Throughout the screening hold, patients continued to be followed and the site monitored every 4 weeks. This site had 5 major protocol violations.

Evaluation by the medical monitor determined that there was not a safety concern with allowing the ineligible patients to remain on the trial and the patients were not unblinded. The sponsor submitted a summary of the above site issues to the FDA Division of Scientific Investigations on July 30, 2010.

Reviewer Comment: The issues prompting screening hold for these four sites appear to be relatively minor. Of the 30 patients enrolled to these sites, 12 were randomized to AA and 18 to placebo. The sponsor appeared to act appropriately and with due diligence in attempting to address the issues at these sites. It the reviewer's determination that the relatively small number of patients (30 of 1,088) coupled with randomization and blinding mitigate any potential bias introduced by protocol violations and deviations from these sites.

3.2.2 Potential Subject Unblinding:
In the study report it was noted that an error resulted in the wrong abiraterone acetate study drug tablets being distributed by the sponsor. From 15 December 2011 through 29 March 2012, these tablets were dispensed to 62 subjects assigned to the abiraterone acetate group at 24 sites in the US and Canada. The affected tablets contained the proper dosage and formulation of abiraterone acetate, but were debossed with the text “AA250.” The correct study tablets are not marked. An information request from the FDA was sent for further clarification.

At the time of the 12/20/2011 data cutoff, only 2 patients had been given the de-bossed tablets.
Patient 157-2037 dispensed on 12/19/2011 (at risk for 2 days)
Patient 160-2028 dispensed on 12/15/2011 (at risk for 6 days)

Reviewer Comment: It appears that inadvertent unblinding from the de-bossed tablets would not affect rPFS analyses conducted at the 12/20/2011 cutoff. A sensitivity analysis was conducted by the sponsor on data submitted for the 3rd interim analysis of OS (55% OS events). However it is acknowledged that OS results would be unlikely to be affected by inadvertent unblinding.

Applicant sensitivity analysis: Patients who received the debossed tablets were censored at the earliest date the debossed tablets were dispensed or the date of study unblinding (27 March 2012); the data for the remaining patients were censored at the date of study unblinding if they had an event after 27 March 2012. The resulting hazard ratio for OS is 0.805 (95% CI: 0.662-0.979; p=0.0295)..."

The sensitivity analysis unequally censors patients in the abiraterone arm, but affects only 62 of 1,088 patients. Even given the biased sensitivity analysis, the results continue to favor the AA arm. The reviewer concludes that any inadvertent unblinding resulting from the debossed tablets did not materially affect the results of the trial.

3.2.3 Protocol Deviations:

The dataset [PVIO] was reviewed. There were 5,289 protocol deviations in total, 498 in the AA arm and 490 for placebo. Minor protocol deviations were primarily based on missing or delayed follow up evaluations. Missing or delayed CT/MRI scans and bone scans will be discussed below. Major protocol deviations were relatively rare and were well-balanced between the arms. The definition of major protocol deviations was provided by the sponsor and includes:

Major deviations will be defined as: any protocol deviation that has the potential to impact or impacts subject's rights, safety, or well-being, or the integrity and/or results of the trial. Patients meeting the following criteria will be flagged as potential major deviations:

- Subjects who entered the trial, but did not satisfy entry criteria
- Subjects who developed withdrawal criteria during the study, but were not withdrawn
- Subjects who received the wrong treatment or incorrect dose
- Subjects who received a disallowed concomitant treatment.
- Enrollment of subject without proper informed consent, IRB/EC approval or IRB/EC renewal
- Any other issues that may significantly impact subject safety or data integrity

The major protocol deviations from COU-AA-302 are listed in Table 3 below.

Table 3: Protocol Deviations

		AA	**546**	**Placebo**	**542**
Any Deviations		498	91.2%	490	90.4%
Major Deviations		68	12.5%	55	10.1%
P1100	Eligibility	30	5.5%	24	4.4%
P1600	Prohibited ConMed	20	3.7%	13	2.4%
P1504	Dose Administration	6	1.1%	3	<1%
P1501	**Discontinuation Criteria**	**5**	**<1%**	**13**	**2.4%**
P9999	No Continuous LHRH	3	<1%	1	<1%
P1200	Scans	2	<1%	2	<1%
P1502	Drug Dispensing Error	2	<1%	4	<1%
P1500	Dose Mod/Tox Mgmt	1	<1%	0	<1%
PNULL	Late SAE reporting	1	<1%	0	<1%
P1202	PK samples lost	0	<1%	1	<1%

Source: dataset [PVIO]

Reviewer Comment: The protocol deviations based on discontinuation criteria (P1501) were largely based on patients staying on study (on either arm) past the discontinuation criteria of prolonged opiate use, palliative radiation therapy for pain or decreased ECOG performance status to 3. Overall, protocol deviations appear to be well-balanced and not likely to affect the validity of the study data.

3.3 Financial Disclosures

For the following 8 investigators (Table 4), complete financial disclosure information was not obtainable "because no response was received or no forwarding address was available". None were principal investigators of their site, and their respective sites enrolled a total of 28 patients (10 AA, 18 Placebo):

Table 4: Investigators with incomplete financial disclosure information

Site No.	Investigator Name
(b) (6)	

There were 10 investigators with financial disclosures to report (Table 5).

Table 5: Investigators with Financial Disclosures

Site	Investigator	Amount	Patients Enrolled	Company Conflict Mitigation Strategy
(b) (6)		20,000 Cougar shares	5	Sold Stock Prior to Study Participation
		Stock in J&J >$50k	8	Study blinding/CRF collection
		Payments >$25k Veridex Speaker Bureau	7	Did not use the Veridex test.
		Cougar Stock >$50k	5	Sold prior to 7/16/2008
		Payments > $25k	13	Study blinding/CRF collection
		Payments >$25k	7	Study blinding/CRF collection
		J&J Stock > $50k	41	Stock Sold 3/2011, representing only 0.25% of Dr. Portfolio

(b) (6)	[redacted]	Payments > $25k	15	Study blinding/CRF collection
	[redacted]	Cougar Stock >$50k , Payments > $25k, Chair of Scientific Advisory Board	40	"Stock has been 100% paid out and he now owns no remaining stock"
	[redacted]	Payments > $25k	2	Study blinding/CRF collection

The remainder of the investigators reported no financial disclosures.

*Reviewer Comment: Overall, sites with investigators who may have had a financial conflict enrolled a total of 166 (15%) of study patients randomized to abiraterone acetate (79) or placebo (87). Radiographic PFS and OS appeared similar in this subset (see section **6.1.10 Additional Efficacy Analyses**). The mitigation of potential financial conflicts conducted by the sponsor appeared to be appropriate. It is the determination of the reviewer that there is no evidence that financial conflict materially affected the outcome of the pivotal trial COU-AA-302.*

3.4 FDA Site Inspections:

Four study sites (157, 160, 812 and 814) enrolling a total of 114 subjects were inspected by the Division of Scientific Investigations (DSI). As illustrated in Table 6, at the time of the completion of this clinical review, the report from Site 160 was completed with no action indicated (NAI). Of the remaining 3 sites, one had a preliminary designation of NAI and two had a preliminary voluntary action indicated (VAI) designation.

Table 6: Clinical Site Inspections

	Clinical Investigator	Site & Subjects	Inspection Dates	Outcome Classification
1	Charles Ryan, MD UCSF Medical Center 1600 Divisadero Street, Box 1711 San Francisco, California 94115	Site 157 40 subjects	Aug 9 - 21, 2012	Pending Preliminary NAI
2	Dana E. Rathkopf, MD Memorial Sloan Kettering Hospital 1275 York Avenue New York, NY 10065	Site 160 41 subjects	Aug 21 - 24, 2012	NAI
3	Joan Carles, M.D. Hospital Universitari Vall d´Hebron Servicio Oncologia Passeig Vall d'Hebron, 119-129 Barcelona, 08035 Spain	Site 812 15 subjects	Sep 17 - 24, 2012	Pending Preliminary NAI
4	Jose P. Rodriguez, M.D. Institut Catala d'Oncologia L'Hospitalet Servicio Oncologia Avda Gran Via de l'Hospitalet, 199-203 Barcelona, 08907 Spain	Site 814 18 subjects	Sep 25 - 28, 2012	Pending Preliminary VAI

NAI = no action indicated, no deviation from regulations; VAI = voluntary action indicated, deviation from regulations; OAI = official action indicated, significant deviation from regulations and/or data unreliable

Pending: This preliminary classification is based on information on Form FDA 483 and communication with the field investigator; final inspection report has not been received from the field office and OSI's complete review of the report remains pending as of this clinical inspection summary.

Source: DSI consultation.

The overall assessment by DSI was that the study data from the four inspected sites appear reliable as reported in the NDA supplement.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See CMC Review

4.2 Clinical Microbiology

N/A

4.3 Preclinical Pharmacology/Toxicology

See Pharmacology/Toxicology Review

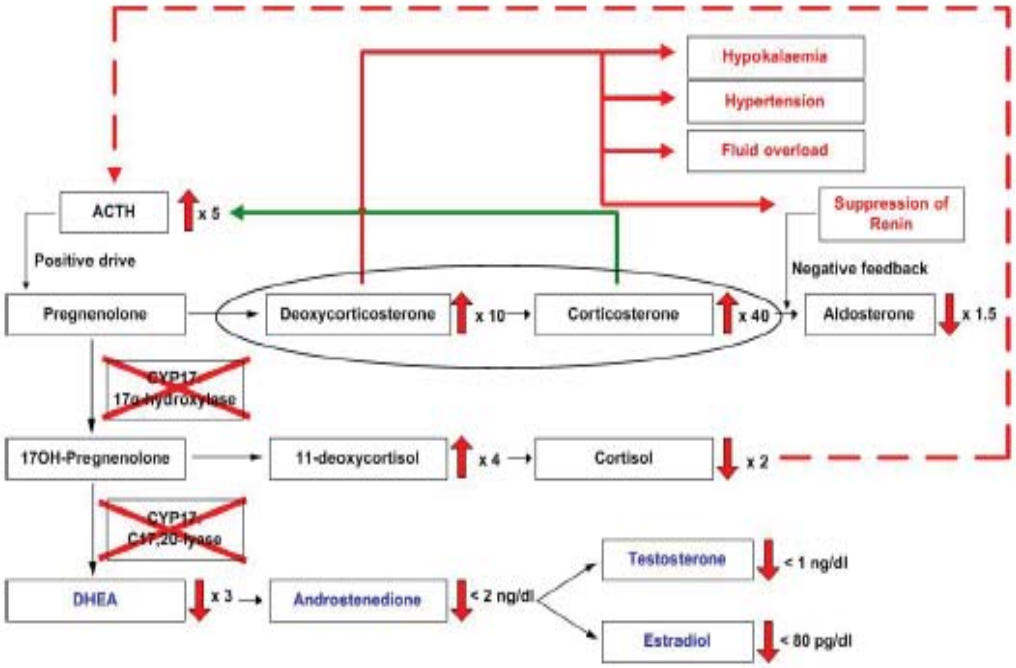
4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

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 already been castrated by medical or surgical means. Figure 3 below shows a schematic diagram illustrating the mechanism of abiraterone action.

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

Figure 3: Abiraterone acetate Mechanism of Action: CYP17 Inhibition[7]



[7] 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

4.4.2 Pharmacodynamics

See clinical pharmacology review.

4.4.3 Pharmacokinetics

See clinical pharmacology review.

5 Sources of Clinical Data

Multiple clinical trials are submitted to support this efficacy supplement. The pivotal clinical trial (b) (4) is the COU-AA-302 trial in asymptomatic or mildly symptomatic mCRPC who have not received prior chemotherapy.

5.1 Tables of Studies/Clinical Trials

The table of clinical trials with submitted data is presented in Table 7 below:

Table 7: Table of Clinical Trials

Trial Name	Title	# Subjects	Population
COU-AA-301	Phase 3, randomized, double-blind, placebo controlled, trial of abiraterone acetate and prednisone compared with placebo and prednisone	1195 797 AA 398 Placebo	mCRPC following docetaxel based chemotherapy
COU-AA-302	**Phase 3, randomized, double-blind, placebo controlled trial of abiraterone acetate and prednisone compared with placebo and prednisone**	**1088 546 AA 542 Placebo**	**Chemotherapy naive asymptomatic or mildly symptomatic mCRPC**
COU-AA-001/001EXT	Phase 1/2, open-label, single arm dose-escalation study investigating abiraterone acetate	54	Chemotherapy naive CRPC
COU-AA-002	Phase 1/2, open-label, single arm, dose-escalation study	33	Chemotherapy naive CRPC
COU-AA-BE	Phase 1, open-label, 2–arm study with a 4-stage design comparing the PK of abiraterone acetate capsule vs. tablet formulations under fed and fasted conditions	33	Chemotherapy-naive or chemotherapy-refractory advanced prostate cancer
COU-AA-015	Phase 1b, open–label, abiraterone acetate plus prednisone drug-drug interaction study with dextromethorphan (Group A) and theophylline (Group B)	34	mCRPC who had received no more than 1 chemotherapy regimen
COU-AA-006	Phase 1, open-label, single arm study to evaluate effects of abiraterone acetate plus prednisone on cardiac QT/QTc interval by using pharmacokinetic and time-matched ECGs	33	mCRPC with PSA ≥2 who had received no more than 1 chemotherapy regimen
COU-AA-004	Phase 2, open-label, single arm study investigating antitumor effects and safety of abiraterone acetate	58	Advanced CRPC following docetaxel based chemotherapy

COU-AA-003 / EXT	Phase 2, open-label, single arm study investigating antitumor effects of abiraterone acetate	47	Advanced CRPC following docetaxel based chemotherapy
COU-AA-BMA	Phase 2, open-label, single arm observational study designed to evaluate the effect of abiraterone acetate and prednisone on androgens and steroid metabolites in bone marrow plasma	56	mCRPC

5.2 Review Strategy

The clinical study reports, supportive analyses and risk:benefit assessment submitted by the applicant were reviewed. Key safety and efficacy datasets were re-analyzed by the clinical and statistical reviewers. The reliability of the data were assessed based on information obtained from OSI site visits, conflict of interest data, protocol deviations and via random cross-validation of some datasets with CRF forms. Sensitivity analyses and subgroup analyses were performed as necessary.

5.3 Discussion of Trial COU-AA-302

COU-AA-302 was a phase 3, randomized, double-blind, placebo-controlled study of abiraterone acetate plus prednisone in asymptomatic or mildly symptomatic subjects with metastatic castration-resistant prostate cancer. The key difference in the COU-AA-302 population compared to the currently labeled indication (based on the COU-AA-301 trial) is the inclusion of patients who have not received docetaxel based chemotherapy (chemotherapy naive) and the requirement that the patients have no- or mild symptoms. Other important eligibility differences were that patients were excluded for visceral metastatic disease and were required to have baseline AST/ALT $\leq$ 2.5 times ULN. Patients were also ineligible if they had New York Heart Association (NYHA) II or higher heart disease. By contrast, in the COU-AA-301 trial, liver and visceral metastases were allowed as were those with AST/ALT < 5 times ULN in patients with liver metastases and patients with NYHA class II heart disease.

5.3.1 COU-AA-302 Protocol Amendments:

There were 3 amendments to the clinical protocol which are presented in Table 8: COU-AA-302 Protocol Amendments below.

Table 8: COU-AA-302 Protocol Amendments

Date	Milestone	Major Changes
2/11/2009	Original Protocol	As agreed upon under 2/6/2009 SPA
4/14/2010	Amendment 1	Genetic Analyses expanded to include biomarkers other than TMPRESS2-ERG
6/7/2011	Amendment 2	Additional interim analysis (IA) for OS added Timing of IA was adjusted Strategy for adjusting for cross-over added
4/2/2012	Amendment 3	Updated eligibility criteria and modified schedule of

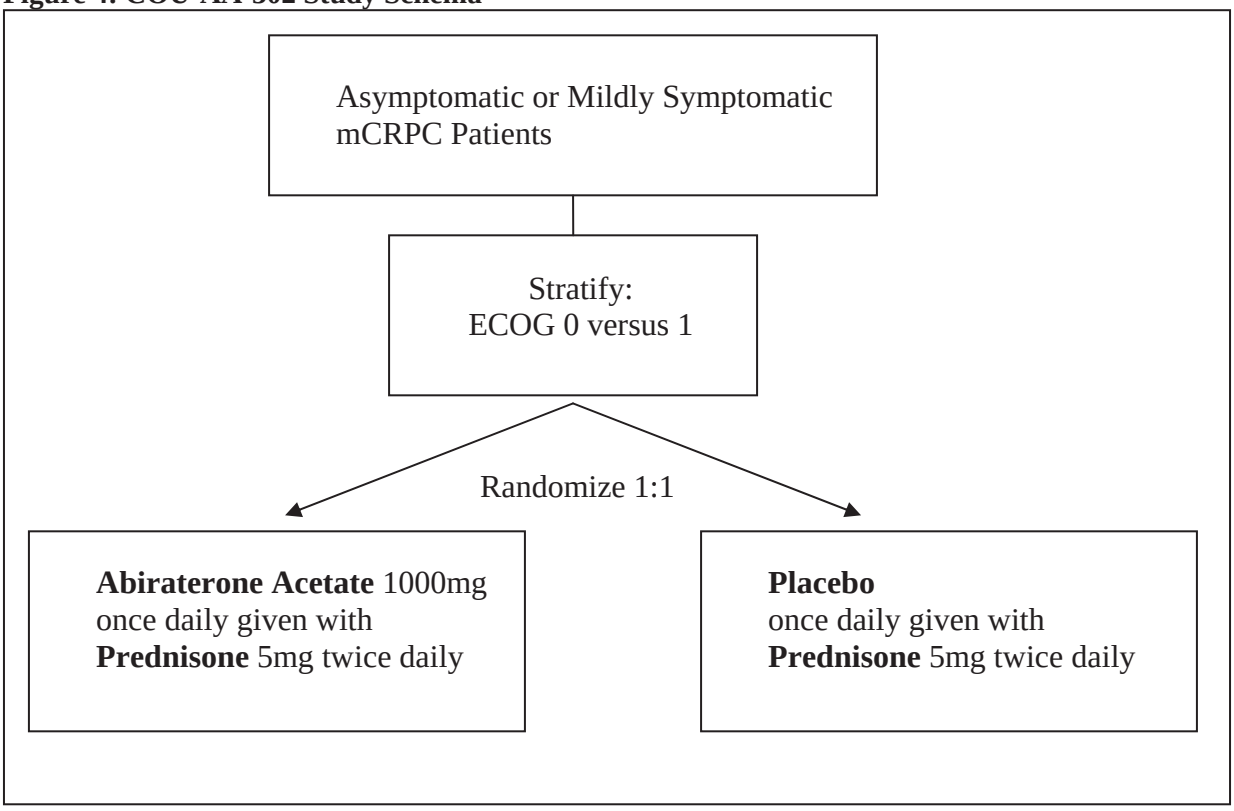
		events for those crossing over from placebo to AA after unblinding Provided information on the IDMC recommendation to unblind Company sponsorship language updated

Reviewer Comment: There were 3 protocol amendments. The reviewer found the rationale for each amendment acceptable.

5.3.2 COU-AA-302 Trial Design Synopsis

COU-AA-302 is a phase 3, randomized, double-blind, placebo-controlled study of abiraterone acetate plus prednisone in asymptomatic or mildly symptomatic subjects with metastatic castration-resistant prostate cancer. The study schema is presented in Figure 4 below:

Figure 4: COU-AA-302 Study Schema



Co-Primary efficacy endpoints:

- Overall survival (OS)
- Radiographic progression-free survival (rPFS)

Secondary efficacy endpoints:

- Time to opiate use for cancer pain
- Time to initiation of cytotoxic chemotherapy
- Time to deterioration in ECOG performance score by ≥1 points
- Time-to-PSA progression based on PCWG2 criteria

Other endpoints:

- PSA response rate [Proportion of patients achieving a PSA decline ≥ 50% according to PCWG2 criteria]
- Objective response rate in patients with measurable disease (RECIST)
- Duration of response in patients with measurable disease
- QoL total score and each subscale score as assessed by FACT-P
- Time to pain progression
- Time to analgesic progression

Key Inclusion Criteria:

- Adult male patients with adenocarcinoma of the prostate
- Metastatic disease documented by positive bone scan or metastatic lesions, other than liver or visceral metastasis, on computed tomography (CT) or magnetic resonance imaging (MRI). If lymph node metastasis was the only evidence of metastasis, it must have been ≥2 cm in diameter.
- Documented prostate cancer progression by prostate-specific antigen (PSA), according to adapted Prostate Cancer Clinical Trials Working Group-2 (PCWG2), or radiographic progression according to modified Response Evaluation in Solid Tumors (RECIST) criteria
- Asymptomatic or mildly symptomatic from prostate cancer, as defined by a score of 0 or 1 (asymptomatic) or 2-3 (mildly symptomatic) on the Brief Pain Inventory-Short Form (BPI-SF) Question No. 3
- Surgical or medical castration, as demonstrated by serum testosterone levels of <50 ng/dL (<2.0 nM). Luteinizing hormone-releasing hormone (LHRH) agonist therapy must have been initiated at least 4 weeks prior to Cycle 1 Day 1 and must have continued throughout the study.
- Previous antiandrogen therapy followed by documented PSA progression after discontinuing the antiandrogen (≥4 weeks since last flutamide, ≥6 weeks since last bicalutamide or nilutamide) prior to enrollment
- ECOG performance status Grade 0 or 1
- Hemoglobin ≥10.0 g/dL, independent of transfusion
- Platelet count ≥100,000/μL
- Serum albumin ≥3.5 g/dL
- Serum creatinine <1.5 x upper limit of normal (ULN) or a calculated creatinine clearance ≥60 mL/min
- Serum potassium ≥3.5 mmol/L
- Adequate liver function as defined by:

- Serum bilirubin <1.5 x ULN (except for subjects with documented Gilbert's disease)
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) <2.5 x ULN

Key Exclusion Criteria

- Any chronic medical condition that required a higher dose of corticosteroid than 5 mg prednisone/prednisolone twice a day
- Pathological finding of small cell carcinoma of the prostate
- Known liver, brain, or visceral organ metastasis
- Use of opiate analgesics for cancer-related pain, including codeine and dextropropoxyphene,within 4 weeks of Cycle 1 Day 1
- Prior cytotoxic chemotherapy or biologic therapy for the treatment of CRPC
- Radiation therapy for treatment of the primary tumor within 6 weeks of Cycle 1 Day 1
- Radiation or radionuclide therapy for treatment of mCRPC
- Prior therapy with ketoconazole for prostate cancer lasting more than 7 days
- Prior systemic therapy with an azole drug (eg, fluconazole, itraconazole) within 4 weeks of cycle 1 Day 1
- Prior flutamide treatment within 4 weeks of Cycle 1 Day 1 (subjects whose PSA did not decline for 3 or more months in response to antiandrogen given as a second-line or later intervention required only a 2-week washout prior to Cycle 1 Day 1).
- Prior bicalutamide or nilutamide within 6 weeks of Cycle 1 Day 1 (subjects whose PSA did not decline for 3 or more months in response to antiandrogen given as a second-line or later intervention required only a 2-week washout prior to Cycle 1 Day 1).
- Uncontrolled hypertension (systolic blood pressure [BP] ≥160 mmHg or diastolic BP ≥95 mmHg). Subjects with a history of hypertension were allowed, provided BP was controlled by antihypertensive therapy.
- Active or symptomatic viral hepatitis or chronic liver disease
- History of pituitary or adrenal dysfunction
- Clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the 6 months prior to screening, severe or unstable angina, or New York Heart Association (NYHA) Class II through IV heart disease or cardiac ejection fraction measurement of <50% at baseline
- Atrial fibrillation, or other cardiac arrhythmia requiring medical therapy
- Other malignancy, except non-melanoma skin cancer, with a ≥30% probability of recurrence within 24 months

*Reviewer Comment: Patients were chemotherapy naive with baseline pain defined as mild or less by the patient-reported outcome measurement Brief Pain Index - Short Form (**Figure 32**). Patients had no evidence of visceral metastatic disease. As with most pivotal clinical trials, the eligibility criteria define a more narrow population than that of the proposed labeled indication. Key subpopulations of patients with asymptomatic or mildly symptomatic mCRPC for which the safety and efficacy of AA cannot be determined based on the results of the COU-AA-302 clinical trial include those patients with symptomatic heart failure, liver dysfunction, pituitary or adrenal*

disease and those metastatic CRPC patients with liver, brain or visceral metastases or with moderate or severe pain.

Patient monitoring and assessments:
The timing of assessments for COU-AA-302 was based on 28 day treatment cycles with safety and efficacy assessments conducted as depicted in Figure 5 and Figure 6 below:

Figure 5: Schedule of Assessments for COU-AA-302

Table of Scheduled Events

		Treatment Phase						Follow-Up Phase
Evaluation	Screening Day -14 to 1	[1]Day 1 of Cycle 1	Day 15 of Cycle 1	[2]Day 1 of Cycles 2, 4, 6, 8, 9, 11, 12…	Day 15 of Cycles 2 and 3	[2]Day 1 of Cycles 3, 5, 7, 10…, and at Treatment Discontinuation[3]	End of Study Treatment Visit[4]	Q3 Months up to Month 60
Procedures								
Signed consent form	X[17]							
Medical history, demographics, prior prostate therapies	X							
QOL - FACT-P		X				X	X	
BPI-SF, analgesic usage	X	X		X		X	X	
Physical exam and Weight[5]	X		X	X		X	X	
Vital signs[6]	X	X	X	X		X	X	
ECOG	X	X	X	X		X	X	
12 Lead ECG[7]	X					X	X	
MUGA Scan or Cardiac ECHO[8]	X							
Dosing compliance			X	X		X	X	
Concomitant medications	X	X	X	X		X	X	
Adverse events	X[9]	X	X	X		X	X[10]	
Laboratory Assessments								
Hematology	X	X		X		X	X	
Coagulation Factors- PT/PTT (INR)	X		X					
Serum chemistry, electrolytes	X	X	X	X		X	X	
Fasting Glucose	X					X	X	
Serum Lipids	X					X	X	

		Treatment Phase						Follow-Up Phase
Evaluation	Screening Day -14 to 1	[1]Day 1 of Cycle 1	Day 15 of Cycle 1	[2]Day 1 of Cycles 2, 4, 6, 8, 9, 11, 12…	Day 15 of Cycles 2 and 3	[2]Day 1 of Cycles 3, 5, 7, 10…, and at Treatment Discontinuation[3]	End of Study Treatment Visit[4]	Q3 Months up to Month 60
Liver function tests[16]					X[16]			
PSA[11]	X	X				X	X	
Serum testosterone	X							
Urinalysis (dipstick)	X							
Tumor Assessments								
CT / MRI /other imaging procedure	X[12]					X		
Bone Scan	X[12]					X[13]		
Disease progression assessment						X		
TMPRSS2-ERG and other biomarkers (at selected study centers)	X[18]							
PK[14] Sampling at Select Study Centers								
Pre-dose PK		X[14]		X[14]		X[14]		
In Clinic Dosing of Study Treatment for PK		X[14]		X[14]		X[14]		
Post-dose 12-Lead ECG		X[14]		X[14]		X[14]		
Post–dose PK		X[14]		X[14]		X[14]		
Follow-Up Period Assessments								
Follow-Up Assessments[15]								X[15]

1 The Cycle 1 Day 1 visit may occur on the same day as the Screening Visit provided that all screening assessments have been completed and results reviewed prior to the commencement of Cycle 1 Day1 assessments.

2 If patients continue on study without disease progression or discontinuation of treatment beyond Cycle 12, they should receive visit assessments as follows:

- At Cycle 13 and every third cycle thereafter (i.e. Cycles 13, 16, 19, 22…), patients should receive the same assessments as indicated for Cycles 3, 5, 7, and 10.
- At all other cycles (i.e. Cycles 14, 15, 17, 18, 20, 21…) they should receive the same assessments as indicated for Cycles 2, 4, 6, 8, 9, 11, and 12.

3 Treatment Discontinuation Visit can occur at any scheduled or unscheduled visit when applicable. At this visit, documentation to confirm progressive disease is required.

4 End of Study Treatment Visit should be scheduled to collect safety assessments between 15 to 28 days after the patient stops treatment. Patients will enter Follow up Phase at that time.

5 Weight will be recorded at every indicated visit. Height will be measured at Screening visit only.

6 Vitals include upright blood pressure, heart rate, respiratory rate, and oral or aural body temperature.

7 ECGs should not be obtained when serum potassium is < 3.5mg/mL. Hypokalemia should be corrected prior to ECG collection.

8 A MUGA scan should be obtained at baseline (up to 28 days prior to Cycle 1 Day 1). A cardiac ECHO can be used if MUGA is not available or when ECHO is standard of care at the study site.

9 Pre-Treatment SAEs should be reported from time patient signs a consent form up to Cycle 1 Day 1 treatment administration.

10 Adverse event follow-up is 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 exists. Follow-up could be conducted by sites via telephone attempts and must be documented in source notes.

11 If patient undergoes a digital rectal exam (DRE), PSA must be sampled prior to the DRE

12 Scans (CT, MRI, and Bone) performed up to 28 days prior to Cycle 1 Day 1 can be used for baseline assessments.

13 If disease progression is observed on the bone scan, confirmatory bone scan is required at least 6 weeks later. Study treatment should be continued in the interim unless there is unequivocal clinical progression as defined in Section 6.6. If the confirmatory scan is negative (does not confirm PD), then the patient should be seen again at the next scheduled study visit as specified in the protocol.

14 Selected Study Centers Only: PK blood samples collected pre and post dose at the following visits: Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 5 Day 1. Patients will be asked to withhold their daily dose and take study treatment following pre-dose PK collection.

15 Follow-up assessments may be collected by telephone interview or chart review. Information will be collected on overall survival, opiate use, ECOG performance status, next therapy for prostate cancer (including dose and treatment duration of cytotoxic chemotherapy), and study treatment related SAEs.

16 Liver function tests include: ALK-P, ALT (SGPT), AST (SGOT), LDH, and direct and total bilirubin

17 Informed consent may be obtained prior to Day -14, as long as it is obtained before any study-specific procedures are completed.

18 Shipment of samples to the central laboratory for biomarker analysis can be completed at any point after Screening.

Source: Sponsor Protocol version 4.0, April 2, 2012.

5.3.3 Definition and Censoring Rules for Primary Endpoints:

CO-PRIMARY:

Overall Survival (OS)

- Time from randomization to death from any cause

Censoring Rules for OS:

Living subjects were censored at the last date a subject was known to be alive or lost to follow-up as of the cutoff date for the interim analysis database lock.

Radiographic Progression Free Survival (rPFS):

- Radiographic progression-free survival is based on parameters suggested by prostate cancer working group 2 criteria (PCWG2)[8] and modified RECIST as the time from randomization to the occurrence of one of the following:

  1. A patient is considered to have progressed by bone scan if:
     a. The first bone scan with ≥2 new lesions compared to baseline is observed <12 weeks from randomization and is confirmed by a second bone scan taken ≥6 weeks later showing ≥2 additional new lesions (a total of ≥4 new lesions compared to baseline);
     b. The first bone scan with ≥2 new lesions compared to baseline is observed ≥12 weeks from randomization and the new lesions are verified on the next bone scan ≥6 weeks later (a total of ≥2 new lesions compared to baseline).

  2. Progression of soft tissue lesions measured by CT or MRI as defined in modified RECIST criteria.

  3. Death from any cause

  Censoring Rules for rPFS were provided in the Statistical Analysis Plan:

  1. If the patient does not a have baseline scan or on-study scans, the patient will be censored on the date of randomization;
  2. If the patient does not show progression according to modified RECIST or bone scan, the patient will be censored on the date of the last scheduled scan;
  3. If the patient remains on study treatment and prior scans do not show radiographic progression, the patient will be censored on the date of the last scan showing no disease progression;
  4. If the patient discontinues study treatment for any reason and progression was not observed in the scans prior to the discontinuation, the patient will be censored on the last scan showing no disease progression;
  5. If the patient discontinues study treatment for any reason and additional new lesions were observed in the scan prior to the discontinuation, and there was no confirmatory scan, the patient will be censored on the date of the last scan that showed no disease progression;
  6. Patients will also be censored on the date of the last scan that shows no disease progression if:
     a. the patient receives another therapy (ie, cytotoxic chemotherapy) known or intended for treatment of metastatic CRPC during the study;

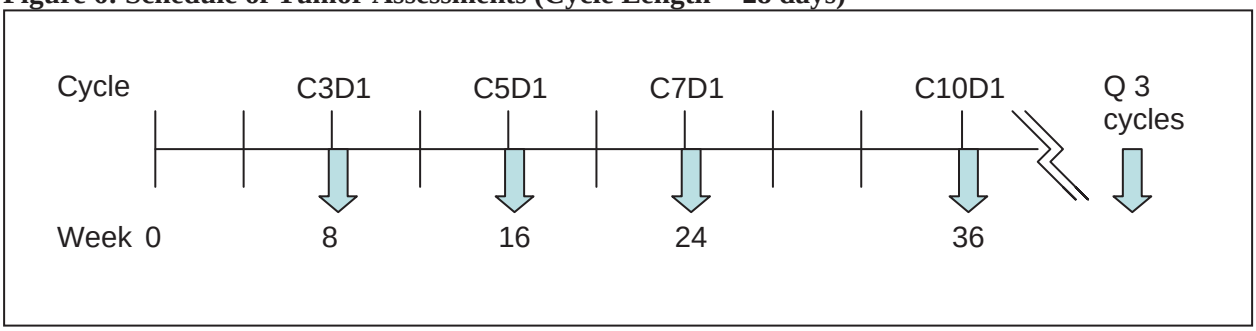
[8] Scher et al., JCO 2008; (26), 1148-1159.

b. the patient misses ≥2 planned radiographic scans or has ≥2 consecutive unreadable scans;
*[c. the patient has unequivocal progression of non-bone non-target lesions (e.g., appearance of nonmeasurable visceral metastases or pathologically confirmed malignant effusions)]. * See Reviewer Comment Below*

Reviewer Comment: The censoring rules from the clinical study report (page 41) differ from those of the SAP (dated 6/7/2011). In the CSR, censoring rule 6c is not included. An information request was sent to the sponsor regarding this discrepancy. The sponsor replied that 6c was removed and should have been described in the CSR. These cases were considered as events. The reviewer agrees with removing this rule as unequivocal progression of non-bone, non-target lesions should be considered a radiographic progression event.

*In order to mitigate premature study discontinuation for disease not detected on pretreatment scan and / or adjust for bone scan "flare" phenomena, the PCWG-2 criteria require scans with 2 new lesions at the first assessment (< 16 weeks) to be confirmed by two additional lesions in a subsequent scan. Thus, given the schedule of tumor assessments for COU-AA-302 (*Figure 6 *below), if a patient has ≥ 2 new bone scan lesions at C3D1, they must be confirmed by 2 additional lesions at the next (C5D1 / 16 week) or later assessment.*

Figure 6: Schedule of Tumor Assessments (Cycle Length = 28 days)



5.3.4 Treatment:

- Treatment cycles defined as 28 day cycles
- Patients were treated until radiographic progression of disease **and/or unequivocal clinical progression.** If the patient had radiographic progression but no unequivocal clinical progression and alternate treatment was not initiated, the patient may have continued on study treatment, at the investigator's discretion.

For this study, **unequivocal clinical progression** was characterized as:

Figure 7: Rules for Unequivocal Progression

1) Cancer pain requiring initiation of chronic administration of opiate analgesia (oral opiate use for ≥3 weeks; parenteral opiate use for ≥7 days. Patients with cancer pain requiring opiate analgesia for relief should also be assessed by the investigator for the need for initiating systemic chemotherapy.

Or

2) Immediate need to initiate cytotoxic chemotherapy or the immediate need to have either radiation therapy or surgical intervention for complications due to tumor progression, even in the absence of radiographic evidence of disease progression.

Or

3) Deterioration in ECOG performance status to grade 3 or higher. Patients whose ECOG performance status decreases to grade 2 during the study should be assessed carefully for their need for docetaxel therapy.

5.3.5 Randomization / Blinding:

- The randomization schedule was generated by an independent statistician
- Subjects were assigned randomly in a 1:1 ratio to receive either abiraterone acetate plus prednisone or placebo plus prednisone.
- Subject eligibility was verified by the investigators, who then entered the stratification factor (i.e., baseline ECOG performance status Grade [0 versus 1]) into the Almac Interactive Web Response System (IWRS)/ Interactive Voice Response System (IVRS) system.
- All subjects, family members, study personnel (at the study site, the sponsor, or participating Clinical Research Organization) and the IDMC were to remain blinded to treatment assignment until completion of the study with the following exceptions:
    - The Independent Biostatistician and Independent Statistical Programmer (employed by Novella) responsible for preparing interim tables, listings, and graphs for IDMC review who had no other responsibilities associated with the study.
    - The IDMC, in order to evaluate whether the study should be stopped early for efficacy/futility or safety.
    - Laboratory personnel performing plasma concentration assays for pharmacokinetic analysis.

5.3.6 COU-AA-302 Statistical Analysis Plan:

The primary study objective was to compare the clinical benefit of AA with that of Placebo and was assessed using rPFS and OS as the co-primary endpoints. The general hypotheses used to address this objective were as follows:

Ho: The survival distributions of the AA group, SA(t), and the PBO group, SP(t), are equal at all time points t:
SA(t) = SP(t), for all t > 0

versus

H1: The survival distributions are not equal for at least one time point t:
SA(t) ≠ SP(t), for some t > 0

- Hypotheses will be tested using a stratified log rank test
- Overall alpha of 0.05 was split between the co-primary endpoints (rPFS 0.01, OS 0.04)
- Analysis of rPFS will be performed only once (no adjustment necessary)
- Analysis of OS was performed within the context of a group sequential testing design.
    - The O'Brien-Fleming boundaries as implemented by Lan-DeMets alpha spending function were used for the efficacy boundary. Operating characteristics for these boundaries are presented in Figure 8 below.

Figure 8: Statistical Operating Characteristics for OS

Variable	Analyses			
	Interim 1* (~15% of Total Events)	**Interim 2 (40% of Total Events)**	**Interim 3 (55% of Total Events)**	**Final**
Projected Observed OS Events	**116**	**311**	**425**	**773**
Efficacy Boundary (HR)	**0.336**	**0.672**	**0.751**	**0.861**
Cumulative Stop Prob. Under (H_o)	**<0.0001**	**0.0005**	**0.0034**	**0.0400**
HR=Hazard ratio; H_o = 0% improvement; H_1 = 25% improvement ***At the time of final rPFS analysis**				

Source: Statistical Analysis Plan for COU-AA-302 Date June 7, 2011

Key secondary endpoints were compared between treatment groups according to Hochberg's test procedure at an overall 2-sided 0.05 level of significance (Figure 9):

Figure 9: Key secondary endpoints for COU-AA-302

Variable	Description
TT_OPUSE	Time to opiate use for cancer pain The time interval from the date of randomization to the date of opiate use. Patients who have no opiate use at the time of analysis will be censored at the last known **on-study** date of no opiate use. Patients with no on-study assessment or no baseline assessment will be censored at date of randomization.~~.~~
TT_CHEMO	Time to initiation of cytotoxic chemotherapy The time interval from the date of randomization to the date of initiation of cytotoxic chemotherapy for prostate cancer. Patients who have no cytotoxic chemotherapy administration at the time of analysis will be censored at the last known **on-study** date of no cytotoxic chemotherapy administered. Patients with no on-study assessment or no baseline assessment will be censored at date of randomization.
TT_ECOG	Time to deterioration in ECOG performance score by ≥1 point~~s~~ The time interval from the date of randomization to the first date in which at least one point change (worsening) in the ECOG PS. Patients who have no deterioration in ECOG PS at the time of analysis will be censored at the ~~earlier of~~ last known date of no deterioration. Patients with no on-study assessment or no baseline assessment will be censored at date of randomization.
TT_PSA	Time to PSA progression The time interval from the date of randomization to the date of the PSA progression as defined in the PCWG2 criteria (Appendix ~~4~~ **3** of protocol). Patients who have no PSA progression at the time of analysis will be censored at the ~~earlier of~~ last known date of no progression. Patients with no on-study assessment or no baseline assessment will be censored at date of randomization.

Source: Statistical Analysis Plan for COU-AA-302 Date June 7, 2011

Preplanned subgroups for the co-primary endpoints rPFS and OS were to be analyzed separately:

- Age (<65, ≥65, ≥75)
- Baseline ECOG performance status grade (IWRS) (0 versus 1)
- Baseline BPI (0-1 versus 2-3)
- Baseline PSA was greater than the median baseline value (Yes versus No)
- Subjects who entered the study with metastasis to bone only (Yes versus No)
- LDH value was greater than the median baseline value (Yes versus No); the additional LDH subgroup analysis (LDH is ≤ULN versus >ULN [Yes versus No]) may have been performed, if a sufficient number of subjects was available
- Baseline ALP value was greater than the median baseline value (Yes versus No)
- Region (North America [US and Canada] versus non-North America [Europe and Australia])

Patient Reported Outcomes Assessments:

Measures of patient reported pain were obtained using the Brief Pain Index - Short Form (BPI-SF) instrument (Figure 32). Measures of patient reported functional status and quality of life

were obtained using the Functional Assessment of Cancer Therapy - Prostate (FACT-P) instrument (Figure 33). The collection schedule for PRO instruments is presented below.

Figure 10: PRO Collection Schedule

Treatment Visit	BPI-SF	FACT-P
Screening	X	
Cycle 1	X	X
Cycle 2	X	
Cycle 3	X	X
Cycle 4	X	
Cycle 5	X	X
Cycle 6	X	
Cycle 7	X	X
Cycle 8	X	
Cycle 9	X	
Cycle 10	X	X
Additional Cycles	X	
Every 3rd cycle beyond Cycle 10		X
End of Study Treatment Visit	X	X

Source: Applicant statistical methods [stat-methods-couaa302.pdf]

6 Review of Efficacy

Efficacy Summary

From April 28, 2009 until June 23, 2010 1,088 subjects were randomized at 151 sites in the U.S., Europe, Australia and Canada. This comprised the intent-to-treat population. Patients were stratified based on ECOG performance status 0 or 1 and 546 patients were randomized to abiraterone acetate (AA) and 542 to placebo. Baseline demographics and disease characteristics were well-balanced.

The co-primary endpoint of rPFS by independent radiographic review met statistical significance at the predefined final rPFS analysis (1st interim OS analysis) dated 12/20/2010. Based on independent radiographic review, 401 (37%) patients had radiographic progression or died, 150 (28%) in the AA group and 251 (46%) in the placebo arm. Radiographic progression or death was significantly delayed in the AA group compared with placebo with a hazard ratio (HR) of 0.43 (95% CI: 0.35, 0.52; p <0.0001). The median rPFS was not reached in the AA group and was 8.3 months in the placebo group. An unplanned update of investigator-defined rPFS was performed at the second interim analysis for OS (12/20/2011). This analysis was based on 607

rPFS events and demonstrated a median rPFS of 16.5 months in the abiraterone acetate arm. The rPFS benefit appeared consistent across all pre-specified subgroups analyzed.

While radiographic progression alone may not have been sufficient for regular approval, this result was supported by an improvement in overall survival which did not meet the pre-specified boundary for statistical significance. At the third interim analysis for overall survival 37% (200 of 546) of patients treated with AA, compared with 43% (234 of 542) of patients treated with placebo, had died. While not meeting the threshold for statistical significance, overall survival was longer for AA than placebo with a hazard ratio of 0.79 (95 % CI: 0.66, 0.96). The application is further supported by the prior approval of AA based on an overall survival benefit in a similar population. Additional supportive evidence of efficacy was demonstrated by statistically significant improvements in time to opiate use for cancer pain and time to cytotoxic chemotherapy. The time to opiate use result was consistent with an improvement seen in patient reported outcomes for pain via every 28 day assessments with the Brief Pain Inventory - Short Form. Finally there was an improvement in time to worsening of functional status and patient reported quality of life scores using the FACT-P instrument.

Taken together, there is substantial evidence that the rPFS result predicts a meaningful clinical benefit for the use of abiraterone acetate in patients with metastatic castration resistant prostate cancer prior to the use of cytotoxic chemotherapy.

6.1 Indication

The initial proposed indication for NDA 202379 supplement 005 is:

" ZYTIGA® (abiraterone acetate) 250 mg tablets, in combination with prednisone, for the treatment of patients with metastatic castration-resistant prostate cancer (b) (4) (b) (4)

6.1.1 Methods

The FDA analysis of efficacy for this supplemental NDA is focused primarily on the clinical trial COU-AA-302. Data from the randomized trial COU-AA-301 was also used as supportive data. (Table 7) The efficacy analyses were performed on the intent to treat population. The statistical analysis plan dated 6/9/2011 defined the ITT population as "all patients randomized into the study and who will be classified according to their assigned treatment group, regardless of the actual treatment received. This population will be used for all efficacy analyses, and all analyses of disposition, demographic, and baseline disease characteristics."

The clinical FDA review focused on a detailed analysis of the design and conduct of the pivotal clinical trial. The conduct of the pivotal clinical trial was examined including assessment of protocol violations, conflict of interest and results from FDA clinical site visits. Verification of the reliability of the datasets was conducted via random cross validation of CRF and datasets. An analysis of the definition and clinical relevance of selected secondary endpoints was

undertaken with the assistance of the FDA study endpoints and labeling (SEALD) group. Recalculation of the primary and secondary efficacy endpoints was performed in conjunction with the statistical reviewer from the submitted datasets with attention to missing data and other potential confounders. Sensitivity analyses were performed as appropriate. Finally, the results of primary and secondary efficacy endpoints as well as quality of life and other data were interpreted in the context of the specific disease indication to form an integrated determination of overall clinical efficacy.

6.1.2 Demographics

From April 2009 through June 2010 1,088 subjects were randomized at 151 sites in the U.S., Europe, Australia and Canada. The geographic distribution of trial participants is presented below:

Table 9: Geographic Distribution of Patients in COU-AA-302

		AA N=546		Placebo N=542	
North America		**297**	**54.4%**	**275**	**50.7%**
	United States	234	42.9%	238	43.9%
	Canada	63	11.5%	37	6.8%
Non-North America		**249**	**45.6%**	**267**	**49.3%**
	Australia	60	11.0%	72	13.3%
	Germany	46	8.4%	32	5.9%
	United Kingdom	42	7.7%	56	10.3%
	Belgium	25	4.6%	17	3.1%
	Spain	25	4.6%	20	3.7%
	France	24	4.4%	29	5.4%
	Netherlands	15	2.7%	15	2.8%
	Greece	7	1.3%	7	1.3%
	Sweden	4	0.7%	13	2.4%
	Italy	1	0.2%	6	1.1%

Source: dataset [POPULATN]

The baseline characteristics of patients enrolled in the COU-AA-302 trial were analyzed and are presented in **Table 10** below. The sole stratification factor of ECOG 0 or 1 was equally distributed between the arms. A large portion of the population was White (95%) with approximately 2.6% of patients identified as Black. Baseline characteristics appeared to be relatively well balanced between the groups. Of note, time from diagnosis to first dose of study therapy being >9 years slightly favored the abiraterone arm 161 (29.5%) to 139 (25.6%). There was a minor imbalance favoring the placebo arm in the number of current smokers (10% vs. 6.8%) and slightly more never smokers in the abiraterone arm (48.2% vs. 44.6%).

Table 10: Baseline Patient Characteristics COU-AA-302

		AA (N=546)		**Placebo (N=542)**	
AGE	< 65	135	24.7%	155	28.6%
	65-69	112	20.5%	103	19.0%
	70-74	114	20.9%	119	22.0%
	>=75	185	33.9%	165	30.4%
RACE	White	520	95.2%	510	94.1%
	Black	15	2.7%	13	2.4%
	Other	6	1.1%	6	1.1%
	Asian	4	0.7%	9	1.7%
	Native Hawaiian/Other Pacific Islander	0	0.0%	2	0.4%
	Missing	1	0.2%	2	0.4%
ETHNICITY	Not Hispanic or Latino	520	95.2%	515	95.0%
	Hispanic or Latino	25	4.6%	24	4.4%
	Missing	1	0.2%	3	0.6%
ALCOHOL	Current	281	51.5%	286	52.8%
	Non-drinker	192	35.2%	196	36.2%
	Former	55	10.1%	45	8.3%
	Missing	18	3.3%	15	2.8%
SMOKING	**Never**	**263**	**48.2%**	**242**	**44.6%**
	Former	231	42.3%	231	42.6%
	Current	**37**	**6.8%**	**54**	**10.0%**
	Missing	15	2.7%	15	2.8%
ECOG	0	413	75.6%	409	75.5%
	1	133	24.4%	133	24.5%

Source: dataset [DEMO] and [ECOG]

The baseline disease characteristics were well balanced are presented below in Table 11 and Table 12:

Table 11: Baseline Disease Characteristics for COU-AA-302

		AA	**546**	**Placebo**	**542**
SITE OF MET	Bone	452	82.8%	432	79.7%
	Lymph Node	267	48.9%	271	50.0%
	Other	4	0.7%	7	1.3%
TIME from DIAGNOSIS to On-Study TREATMENT	< 1 Year	22	4.0%	25	4.6%
	1-3 Years	131	24.0%	125	23.1%
	3-6 Years	135	24.7%	153	28.2%
	6-9 Years	93	17.0%	98	18.1%
	> 9 Years	**161**	**29.5%**	**139**	**25.6%**
GLEASON	≥ 8	263	48.2%	254	46.9%
	4+3	78	14.3%	98	18.1%
	3+4	81	14.8%	90	16.6%
	<7	65	11.9%	64	11.8%
	Missing	59	10.8%	36	6.6%
STAGE at Diagnosis	II	87	15.9%	72	13.3%
	III	52	9.5%	63	11.6%
	IV	190	34.8%	187	34.5%
	Missing	217	39.7%	220	40.6%
T Stage	T1	65	11.9%	71	13.1%
	T2	151	27.7%	149	27.5%
	T3	173	31.7%	162	29.9%
	T4	31	5.7%	39	7.2%
	Missing	126	23.1%	119	22.0%
N Stage	N0	218	39.9%	220	40.6%
	N1	61	11.2%	58	10.7%
	N2	16	2.9%	10	1.8%
	N3	8	1.5%	8	1.5%
	Missing	243	44.5%	246	45.4%
PSA at Diagnosis	Median	22.3		21.0	

Source: dataset [DEMO] and [ECOG]

Table 12: Baseline On-Study Laboratory Values

		AA	546	**Placebo**	542
Baseline PSA	<10	92	16.8%	88	16.2%
	10-19	73	13.4%	83	15.3%
	20-125	258	47.3%	261	48.2%
	126-499	98	17.9%	82	15.1%
	>=500	25	4.6%	24	4.4%
Alk Phos	<250	498	91.2%	488	90.0%
	>=250	48	8.8%	51	9.4%
LDH	<300	515	94.3%	509	93.9%
	>=300	19	3.5%	27	5.0%
Hemoglobin	<12	101	18.5%	101	18.6%

Source: dataset [DEMO]

Table 13: Sites of Baseline Lesions at Study Entry (Independent Review)

	N = 543	N = 541
Bone	525	522
Soft Tissue, Lymph Node, Pleura/Omentum/Spleen	275	274
Bladder or Prostate Mass	34	27
Visceral Disease[1]	22	31
Liver	13	12
Target Lesions	225	228

[1] Includes Adrenal, Liver, Lung and Pancreas Lesions
Source: dataset [XD]

Reviewer Comment: Patients with visceral metastatic disease were excluded from the 302 trial, however several patients were enrolled who had visceral disease. This small subset was evaluated carefully to determine their response to therapy given that the proposed indication includes patients regardless of site of metastases.

Comparison of the Demographics between Trial -301 and -302:
The sponsor provided a comparison of the demographic information from the pre- (COU-AA-302) and post-docetaxel (COU-AA-301) patient populations and this data is presented in **Table 14** below. The population enrolled in COU-AA-302 (chemotherapy-naive) differed from COU-AA-301 (post-docetaxel) mainly due to its exclusion of prior chemotherapy, visceral metastatic disease (-302 had approximately 50% of patients metastatic to bone-only versus 37-42% in the -301 population) and ECOG status >1. The chemotherapy-naive patients in AA-302 also had lower baseline PSA and slightly shorter time since diagnosis reflective of these patients being enrolled earlier in the natural history of their disease. The characteristics of the patients' tumors upon initial diagnosis (TNM staging and Gleason score) were generally similar between the groups. The post-docetaxel AA-301 study patients had slightly more patients T3/T4 at diagnosis (approximately 44% vs. 38%) and metastatic at diagnosis (approximately 30% vs. 25%). Also, 75% of patients enrolled on the COU-AA-302 study had an ECOG performance status of 0 compared with only 34% of COU-AA-301 patients, again reflective of both inclusion of ECOG 2 patients in the -302 trial and the post-chemotherapy nature of the -302 population.

Table 14: Baseline Characteristics of Patients on COU-AA-301 vs. AA-302

	COU-AA-301		COU-AA-302		Combined	
	AA (N=791)	Placebo (N=394)	AA (N=542)	Placebo (N=540)	AA (N=1333)	Placebo (N=934)
Years since initial diagnosis to 1st dose						
n	791	394	542	540	1333	934
Mean ± SD	7.1 ± 4.46	6.9 ± 4.69	6.7 ± 4.85	6.5 ± 4.77	7.0 ± 4.63	6.6 ± 4.74
Median	6.3	5.3	5.5	5.1	6.0	5.2
Range	(0, 25)	(0, 25)	(0, 28)	(0, 28)	(0, 28)	(0, 28)
Tumor (T) Stage at Diagnosis						
n	759	387	539	539	1298	926
T0	1 (0.1%)	0	0	2 (0.4%)	1 (0.1%)	2 (0.2%)
T1, T1a, T1b, T1c	89 (11.7%)	39 (10.1%)	64 (11.9%)	70 (13.0%)	153 (11.8%)	109 (11.8%)
T2, T2a, T2b, T2c	201 (26.5%)	99 (25.6%)	151 (28.0%)	149 (27.6%)	352 (27.1%)	248 (26.8%)
T3, T3a, T3b, T3c	278 (36.6%)	135 (34.9%)	172 (31.9%)	161 (29.9%)	450 (34.7%)	296 (32.0%)
T4, T4a, T4b	56 (7.4%)	31 (8.0%)	31 (5.8%)	39 (7.2%)	87 (6.7%)	70 (7.6%)
TX	102 (13.4%)	55 (14.2%)	42 (7.8%)	35 (6.5%)	144 (11.1%)	90 (9.7%)
Unknown	NA	NA	77 (14.3%)	79 (14.7%)	77 (5.9%)	79 (8.5%)
Not Applicable	32 (4.2%)	28 (7.2%)	2 (0.4%)	4 (0.7%)	34 (2.6%)	32 (3.5%)
Lymph Node (N) Stage at Diagnosis						
n	751	384	540	538	1291	922
N0	340 (45.3%)	153 (39.8%)	217 (40.2%)	218 (40.5%)	557 (43.1%)	371 (40.2%)
N1	84 (11.2%)	46 (12.0%)	61 (11.3%)	58 (10.8%)	145 (11.2%)	104 (11.3%)
N2	26 (3.5%)	11 (2.9%)	16 (3.0%)	10 (1.9%)	42 (3.3%)	21 (2.3%)
N3	5 (0.7%)	7 (1.8%)	8 (1.5%)	8 (1.5%)	13 (1.0%)	15 (1.6%)
NX	241 (32.1%)	131 (34.1%)	118 (21.9%)	114 (21.2%)	359 (27.8%)	245 (26.6%)
Unknown	NA	NA	116 (21.5%)	121 (22.5%)	116 (9.0%)	121 (13.1%)
Not Applicable	55 (7.3%)	36 (9.4%)	4 (0.7%)	9 (1.7%)	59 (4.6%)	45 (4.9%)
Metastasis (M) Stage at Diagnosis						
n	759	386	540	539	1299	925
M0	344 (45.3%)	170 (44.0%)	238 (44.1%)	228 (42.3%)	582 (44.8%)	398 (43.0%)
M1, M1a, M1b, M1c	227 (29.9%)	120 (31.1%)	135 (25.0%)	142 (26.3%)	362 (27.9%)	262 (28.3%)
MX	154 (20.3%)	75 (19.4%)	75 (13.9%)	88 (16.3%)	229 (17.6%)	163 (17.6%)
Unknown	NA	NA	90 (16.7%)	75 (13.9%)	90 (6.9%)	75 (8.1%)
Not Applicable	34 (4.5%)	21 (5.4%)	2 (0.4%)	6 (1.1%)	36 (2.8%)	27 (2.9%)
Gleason score at initial diagnosis						
n	694	347	486	506	1180	853
<7	103 (14.8%)	37 (10.7%)	65 (13.4%)	64 (12.6%)	168 (14.2%)	101 (11.8%)
7	235 (33.9%)	123 (35.4%)	158 (32.5%)	189 (37.4%)	393 (33.3%)	312 (36.6%)
2+5=7	1 (0.1%)	0	0	1 (0.2%)	1 (0.1%)	1 (0.1%)
3+4=7	139 (20.0%)	61 (17.6%)	80 (16.5%)	90 (17.8%)	219 (18.6%)	151 (17.7%)
4+3=7	95 (13.7%)	62 (17.9%)	77 (15.8%)	98 (19.4%)	172 (14.6%)	160 (18.8%)
>=8	356 (51.3%)	187 (53.9%)	263 (54.1%)	253 (50.0%)	619 (52.5%)	440 (51.6%)

	COU-AA-301		COU-AA-302		Combined	
	AA (N=791)	Placebo (N=394)	AA (N=542)	Placebo (N=540)	AA (N=1333)	Placebo (N=934)
Baseline Extent of Disease						
n	790	392	542	540	1332	932
Bone	705 (89.2%)	355 (90.6%)	450 (83.0%)	430 (79.6%)	1155 (86.7%)	785 (84.2%)
Bone only	289 (36.6%)	166 (42.3%)	272 (50.2%)	266 (49.3%)	561 (42.1%)	432 (46.4%)
Soft Tissue/Node[a]	485 (61.4%)	218 (55.6%)	267 (49.3%)	270 (50.0%)	752 (56.5%)	488 (52.4%)
Other	39 (4.9%)	18 (4.6%)	4 (0.7%)	7 (1.3%)	43 (3.2%)	25 (2.7%)
Baseline ECOG Performance Status						
n	791	394	542	540	1333	934
0	271 (34.3%)	134 (34.0%)	409 (75.5%)	408 (75.6%)	680 (51.0%)	542 (58.0%)
1	439 (55.5%)	217 (55.1%)	133 (24.5%)	132 (24.4%)	572 (42.9%)	349 (37.4%)
2	81 (10.2%)	43 (10.9%)	0	0	81 (6.1%)	43 (4.6%)
Baseline PSA (ng/mL)						
n	789	394	542	538	1331	932
Mean ± SD	438.62 ± 888.049	399.56 ± 809.769	133.87 ± 324.778	127.75 ± 388.228	314.52 ± 729.788	242.66 ± 617.887
Median	127.30	136.50	41.45	37.50	84.00	62.51
Range	(0.1, 9253.0)	(0.1, 10114.0)	(0.0, 3927.4)	(0.7, 6606.4)	(0.0, 9253.0)	(0.1, 10114.0)

Source: [Applicant Summary of Clinical Safety] AA-302 Data verified by dataset [DEMO]

Prior Prostate Cancer Therapies:
Approximately half of the patients received surgery and half radiation for their primary curative treatment.

Table 15: Prior Prostate Cancer Treatment in COU-AA-302

	AA (N=546)			Placebo (N=542)	
Hormonal Therapy	544	99.6%		542	100%
Radiation Therapy	283	51.8%		303	55.9%
Surgery	256	46.9%		244	45.0%
Other	82	15.0%		63	11.6%

A total of 44 patients (4%) had prior orchiectomy, 20 in the AA arm and 24 in the placebo arm.

2 patients in the AA group did not receive prior hormonal therapy and both were captured as protocol deviations. Patient 211-2004 withdrew consent "to travel" and was not treated. Patient 520-2023 was prematurely randomized, was found to be ineligible, and was not treated. The sponsor notes that the time period from the initial use of hormonal therapy (LHRH agonist) to first dose of study drug was equal between the arms at approximately 40 months and this analysis was confirmed by the review team.

Review of the category "other" for prior prostate cancer therapies was performed. There was no significant imbalance in the use of prior therapies known to prolong the survival of men with prostate cancer such as docetaxel or sipuleucel-T. (Table 16)

Table 16: Other Prior Prostate Cancer Directed Therapies Noted at Baseline

		AA	544	Placebo	542
OTHER Prostate Cancer Therapy		**82**		**63**	
Bisphosphonate/Denosumab		22	4.0%	20	3.7%
Prednisone/Dexamethasone		11	2.0%	6	1.1%
Other Investigational Rx		10	1.8%	12	2.2%
Casodex		9	1.6%	3	0.6%
Endothelin receptor antagonist		8	1.5%	2	0.4%
5-alpha-Reductase		7	1.3%	11	2.0%
Salvage local (HIFU/Photodynamic/XRT)		6	1.1%	4	0.7%
Taxotere/Taxol		3	0.5%	1	0.2%
DES		2	0.4%	0	0.0%
Ketoconazole		1	0.2%	0	0.0%
Herbal		1	0.2%	4	0.7%
Immunotherapy	Provenge	1	0.2%	2	0.4%
	Other	3	0.5%	3	0.6%
Cyproterone or estramustine		0	0.0%	3	0.6%

Source: Datalisting [LSUB12]. In addition, there were no significant imbalances noted by reviewing the dataset [CONMED].

Reviewer Comment: Review of the applicant's submitted demographic tables and analysis coupled with the FDA analysis of the [DEMO] and [CONMED] datasets and [LSUB12] datalisting reveal no significant imbalances in baseline patient demographics that would materially bias the efficacy or safety results of study 302.

6.1.3 Subject Disposition

Patients were to continue treatment until radiographic progression, unequivocal clinical progression or death. For those patients who had radiographic progression without unequivocal clinical progression, patients were allowed to continue to receive study therapy at the investigator's discretion if alternative treatment was not initiated. The reviewer analyzed dataset [DISP] which was included in the primary submission and is based on the 2nd interim analysis of OS with data cutoff 12/2011. The analysis was performed based on the primary submission given the compressed timeline of this priority review. Patient disposition characteristics are shown in Table 17 and Table 18 below.

Table 17: Patient Disposition

	AA N=546	Placebo N=542
Treatment Ongoing	166 (30.4%)	86 (15.9%)
Progression	283 (51.8%)	351 (65.0%)
Radiographic Progression Only	115 (21.1%)	162 (29.9%)
Unequivocal Clinical Progression Only	111 (20.3%)	136 (25.1%)
Radiographic and Clinical Progression	57 (10.4%)	53 (9.8%)
Adverse Event	40 (7.3%)	29 (5.4%)
Withdrew Consent	33 (6.0%)	46 (8.5%)
Other	24 (4.4%)	30 (5.6%)

12/2011 Data Cutoff: Dataset [DISP]. 4 patients in AA and 2 patients in Placebo did not receive study drug and are included in "Other".

Thirty percent of those taking AA compared with 16% of placebo patients had treatment ongoing at the data cutoff. More patients in the placebo arm progressed both by radiographic progression only and unequivocal clinical progression only. The patients discontinuing due to "other" were reviewed. Most were discontinued for progression not meeting section 6.6 criteria (unequivocal progression). Patients were discontinued by investigator discretion in 8 patients in the placebo arm and 7 in the abiraterone arm. The reasons for discontinuation due to protocol defined unequivocal clinical progression are presented below:

Table 18: Patients with Unequivocal Clinical Progression

	AA N=546	Placebo N=542
Unequivocal Clinical Progression	168	189
Opiate Use	38 (22.6%)	50 (26.5%)
Opiate Use ONLY	18 (10.7%)	27 (14.3%)
ECOG>=3	7 (4.2%)	8 (4.2%)
ECOG >=3 ONLY	7 (4.2%)	4 (2.1%)
Cytotoxic Chemo	81 (48.2%)	100 (52.9%)
Cytotoxic Chemo ONLY	68 (40.5%)	85 (45.0%)
Radiation Rx	64 (38.1%)	53 (28.0%)
Radiation Rx ONLY	45 (26.8%)	36 (19%)
Surgical Intervention	6 (3.6%)	10 (5.3%)
Surgical Intervention ONLY	2 (1.2%)	8 (4.2%)

Source: Dataset [DISP].

More patients in the AA arm received radiation therapy compared with placebo. All other categories of unequivocal clinical progression occurred more commonly in the placebo arm. For further analysis of AEs leading to discontinuation see Table 50.

Reviewer Comment:

More patients in the AA arm had unequivocal clinical progression based on radiation treatment than the placebo arm. This may be due to that fact that patients were on treatment longer on the AA arm and may have needed radiation to existing lesions more commonly. Otherwise, there were no large imbalances in the criteria for patients to come off study treatment.

6.1.4 Analysis of Primary Endpoint(s)

6.1.4.1 Radiographic Progression Free Survival (rPFS)
For complete definition of rPFS and censoring rules see section 5.3 Discussion of Trial COU-AA-302. Briefly, rPFS was based on confirmed appearance of 2 new bone lesions defined by prostate cancer working group 2 criteria (PCWG2) and progression of non-bone lesions by modified RECIST. Radiographic progression free survival is defined as the time from randomization to the occurrence of one or more of the following: Bone Scan Progression, Soft Tissue Progression by CT/MRI or death from any cause.

The FDA analysis of the co-primary endpoint of radiographic progression free survival (rPFS) is presented in Table 19 below. There was a large improvement in the number of patients free from radiographic progression or death favoring the Abiraterone Acetate arm with a hazard ratio of 0.43. The median time to radiographic progression or death was 8.3 months in the placebo arm and had not been reached in the AA arm.

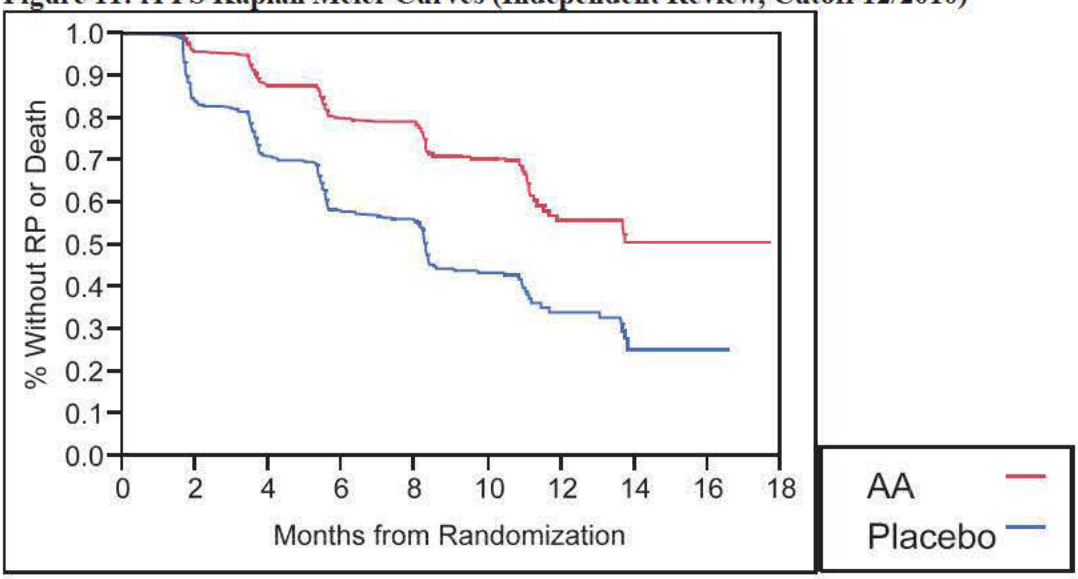
Table 19: FDA rPFS analysis (independent radiographic review 12/20/2010)

	AA N= 546	**Placebo N=542**
	N (%)	**N (%)**
No. of PFS Events	150 (28%)	251 (46%)
No. Censored	396 (72%)	291 (54%)
Median PFS in months (95% CI)	NE (11.66, NE)	8.28 (8.12, 8.54)
Hazard ratio (95% CI), p-value	**0.43 (0.35, 0.52), p < 0.0001**	

Stratified by ECOG 0 or 1. Source dataset [RECIST10]

The Kaplan Meier curve for rPFS separates at the first radiographic assessment and continues to show an improvement throughout the study period (Figure 11).

Figure 11: rPFS Kaplan Meier Curves (Independent Review, Cutoff 12/2010)



RP=Radiographic Progression. Source [ATRISK10]

There were few deaths at the prespecified rPFS analysis. The progression events were distributed evenly between progression by bone scan only and progression by CT/MRI only. Table 20 below lists the rPFS event types for both arms based on the independent reviewer primary rPFS analysis conducted in December of 2010.

Table 20: RPFS Events (Independent Review, Cutoff 12/2010)

RPFS EVENT	Abiraterone 150	Placebo 251
Death	9 (6%)	11 (4%)
Progression by bone scan only	57 (38%)	79 (32%)
Progression by both bone and CT/MRI	18 (12%)	46 (18%)
Progression by CT/MRI only	66 (44%)	115 (46%)

Source: dataset [PPFSREAS]

Censoring:
At the data cutoff of 12/20/2010 (independent review), a total of 396 (72.5%) patients on AA and 291 (53.7%) patients on placebo had been censored. The reasons for censoring are listed in Table 21 below:

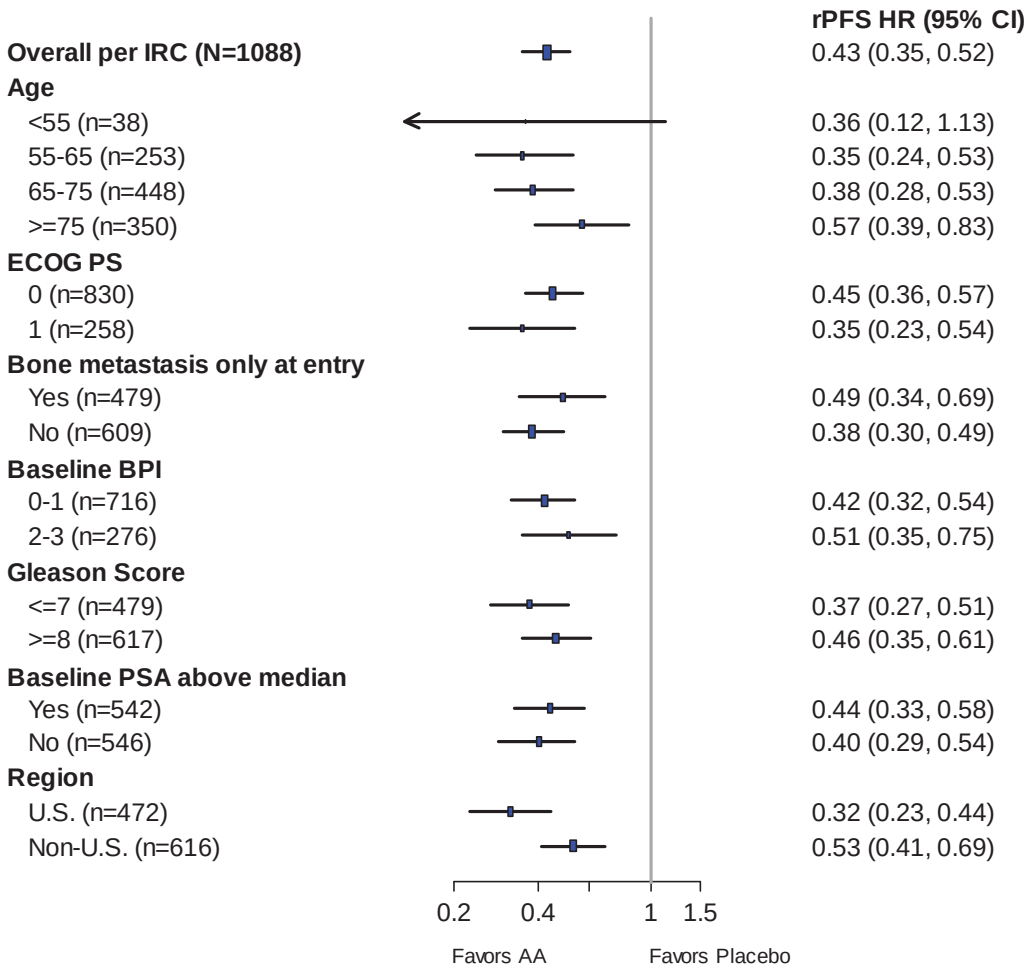
Table 21: Censoring (Independent Review Cutoff 12/20/2010)

		Abiraterone N=546			Placebo N=542		
CENSOR		396		72.5%	291		53.7%
Still at Risk		327			197		
	On Treatment no Event at Cutoff		287	52.6%		151	27.9%
	Discontinued Rx and Alive at Cutoff		40	7.3%		46	8.5%
Permanently Censored		69			94		
	Initiation of Chemotherapy		44	8.1%		67	12.4%
	No baseline and post baseline assessment		10	1.8%		11	2.0%
	Withdrew consent to remain on study		9	1.6%		9	1.7%
	2 consecutive missing scans		6	1.1%		4	0.7%
	No post baseline assessments		0	0.0%		3	0.6%

Source: Dataset [RPFSREAS]

The rPFS benefit was seen across all eight pre-specified subgroups in the applicant's analysis. A smaller subgroup (patients <55 years of age) evaluated in the FDA analysis still favored the abiraterone arm however this 38 patient subgroup's confidence interval exceeded 1.0. (Table 22)

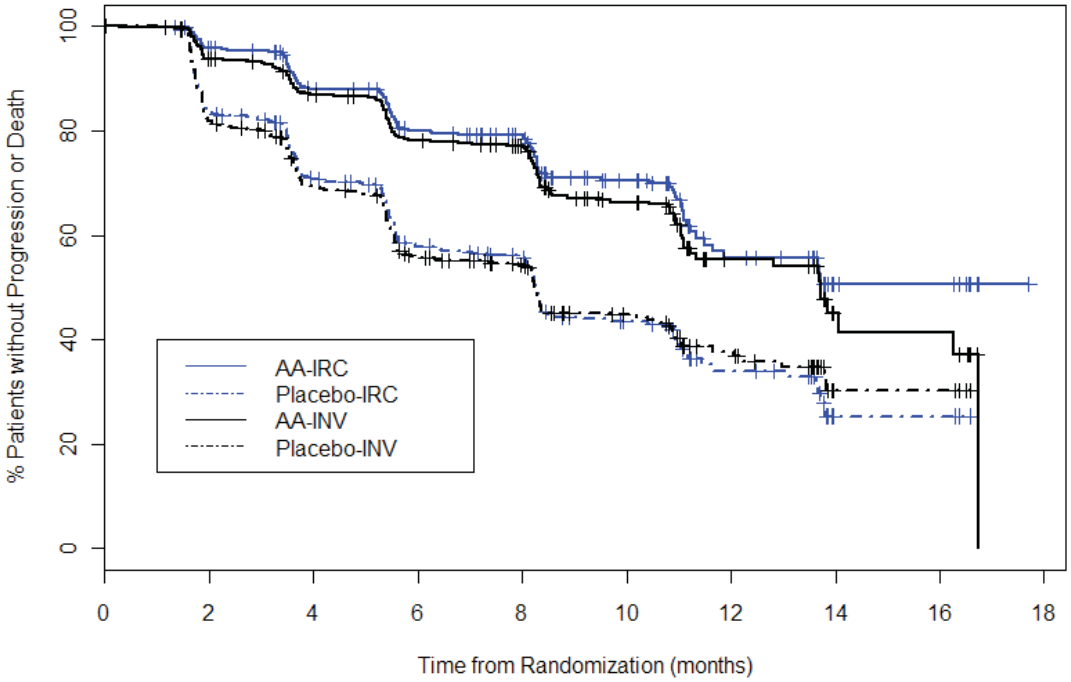
Table 22: FDA rPFS Subgroup Analysis (Independent Review)



Source: rPFS results, IRC data cutoff 12/20/2010

Independent Review - Investigator Review Concordance:
The Kaplan Meier curves for rPFS by investigator review compared with independent review were analyzed by the FDA statistical reviewer and appear consistent (Figure 12).

Figure 12: FDA analysis of Investigator and Independent Review rPFS Concordance



rPFS Sensitivity Analyses:

The FDA statistical reviewer conducted 4 additional sensitivity analyses on the independent radiographic review data to further assess the primary endpoint result of radiographic progression free survival. (Table 23)

- **Sensitivity analysis 1** included unequivocal clinical progression as an event.
- **Sensitivity analysis 2** considered patients who received any new anti-cancer therapy before progression as having disease progression at the next tumor assessment.
- **Sensitivity analysis 3** used earlier time of investigator or independent determination of an event to define rPFS event.
    - If rPFS event types (event vs. censoring) were the same between IRR and INV assessment, the shortest rPFS time was used. For discrepant cases (i.e. cases that have been deemed failure according to one source and censored observation according to the other source), patients were considered as failures and failure time was used.

- **Sensitivity analysis 4** was performed to address potential bias from informative censoring in IRC analysis with the following rules:
  - For patients in the abiraterone arm, who were censored due to "new anti-cancer therapy added" per IRR and were assessed as rPFS events per investigator, rPFS events were imputed and the corresponding rPFS time was extended by 8 weeks from the last non-progression assessment visit, assuming they would have progressed at the next tumor assessment.
  - For patients in the placebo arm, there was no imputation rule applied and patients who were censored for new anti-cancer therapy were not imputed to have an event.

Table 23: FDA rPFS Sensitivity Analyses

rPFS analysis	Median (Months)		HR (95% CI)
	AA	Placebo	
rPFS per IRC	NE	8.3	0.43 (0.35, 0.52)
rPFS per INV	13.7	8.3	0.49 (0.41, 0.60)
Sensitivity Analysis 1	11.9	7.9	0.42 (0.35, 0.51)
Sensitivity Analysis 2	12.1	7.1	0.44 (0.36, 0.52)
Sensitivity Analysis 3	11.1	5.6	0.48 (0.40, 0.57)
Sensitivity Analysis 4	13.7	8.3	0.48 (0.40, 0.59)

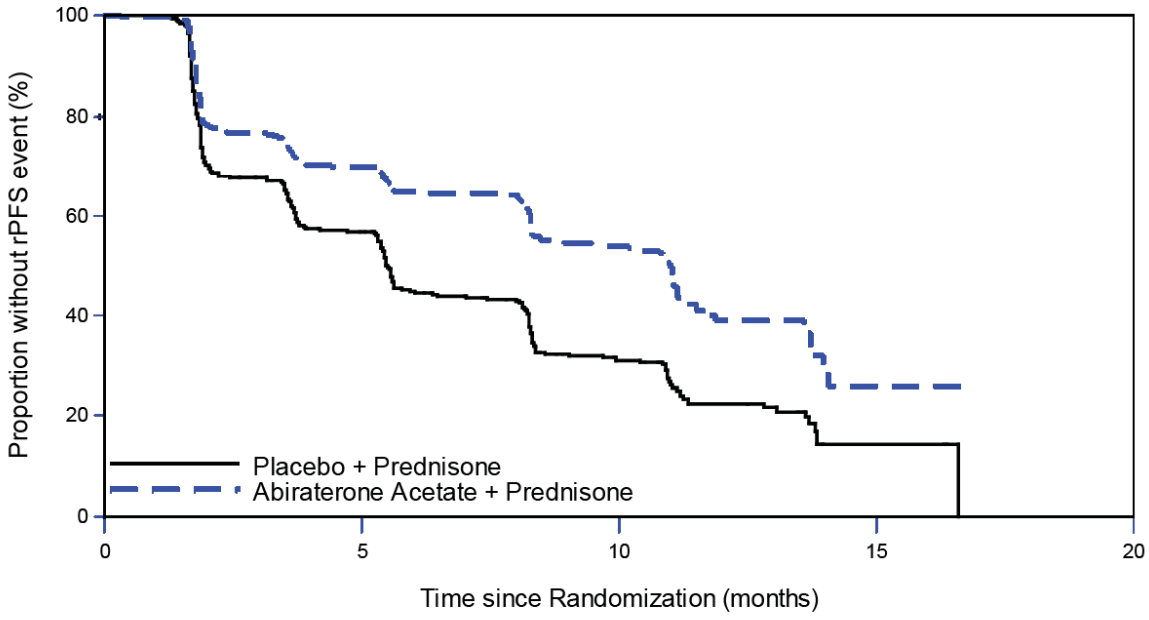
Data Cutoff 12/20/2010. Source [RECIST10] and [RECISTI10]

The results from all four sensitivity analyses favored the abiraterone acetate treatment arm with HR <0.50.

Radiographic Progression Free Survival (rPFS) by first evidence of 2 new lesions:
In an effort to remove the complexity of requiring confirmation of two new lesions, in this analysis 2 new lesions observed at any time without requiring confirmation were deemed an event in the rPFS analysis. The result shows that the benefit continues to favor the abiraterone acetate arm with a HR of 0.57 and a median overall magnitude of benefit of approximately 5.5 months.

Figure 13: rPFS by 2 new bone lesions at any time without confirmation

	AA (N=546)	Placebo (N=542)
Number of total events	247	336
PD	241	331
death	6	5
Median (95%) in months	11.0 (8.9, 11.1)	5.5 (5.4, 5.6)
HR (95% CI)	0.57 (0.49, 0.68)	



Source: Independent radiographic review data from [RECIST10]

Analysis of Bone Scan Events:
Because progression based on bone scans can be problematic, the FDA clinical review focused heavily on bone scan interpretation and its role in providing the data to support this application. With respect to the procedure for confirming bone scan results prior to determining progression, it was confirmed with the applicant via 8/6/2012 information request that the date of progression (DOP) was captured as the scan prior to the scan date that independent reviewers assigned progressive disease (PD).

The FDA clinical and statistical reviewer analyzed the submitted datasets to confirm the interpretation and timing of bone scan progression events. Where there was a question regarding interpretation, comments from the independent radiologist were reviewed from dataset [NEW] (new lesions) and [OVERALLBS] (overall bone scan interpretation results) for specific comments provided by the independent radiologist.

The dataset was queried for those patients who had at least 2 new bone scan lesions from baseline. The 465 patients who met this criterion were subsequently reviewed by the clinical

reviewer with respect to each bone scan assessment and the reported new lesions from baseline, new lesions from prior scan, overall bone scan assessment and the date of progression. Of the 465 patients, the FDA clinical reviewer identified 42 patients for further review based on discrepancies noted between the identification of new lesions from baseline and the determination of progression of disease or date of progression based on IRC rules. (20 patients in the AA arm and 22 patients in the Placebo arm) Two hundred and twenty bone scan assessments from the selected patients were reviewed in depth using IRC comments which were recorded in the dataset [OVERALLBS]. Of these cases, the FDA reviewer determined only 12 cases were felt to warrant a change in the date of progression. It should be noted that these discrepancies were subject to interpretation which highlights the potentially subjective nature of defining progression based on bone scan findings. Nonetheless, these discrepancies were well balanced between the arms (6 per arm) and repeat analysis with the revised progression dates did not lead to a significant change in the outcome of the radiographic progression free survival results.

The review of the bone scan comments by the IRC radiologists suggests that the discrepancies were largely based on known challenges in bone scan interpretation. Given the magnitude of effect demonstrated in this application, the bone scan review did not identify issues which would materially alter the overall risk:benefit determination of this specific supplemental NDA application. However; the review did illustrate the limitations of bone scan assessments in capturing progression events for metastatic prostate cancer, highlighting the importance of a large relative and absolute magnitude of effect on such an endpoint.

Complexity of Determining Progression by Bone Scan:
The pre-specified definition of bone scan progression for COU-AA-302 is based on prostate cancer working group 2 criteria and relies on the timing and confirmation of new bone scan lesions thought to be related to prostate cancer. Challenges identified include:

- **Timing**: If new lesions are seen less than 16 weeks from start of treatment they must be confirmed by an additional two new lesions in order to minimize "bone scan flare" of existing occult lesions.
- **Bone Scan Image Quality**: Poor image resolution and inability to "window" non-digital bone scan images
- **Number of Baseline Bone Scan Lesions**: The more baseline bone lesions, the more challenging it is to identify two NEW lesions
- **Benign Lesions**: Degenerative joint disease and trauma can lead to false positive findings.

Specific examples of the complexity and difficulty related to the timing of bone scan progression from trial COU-AA-302 are provided below:

Figure 14: Bone Scan Interpretation Example 1

Patient with new lesions at first assessment, unconfirmed by subsequent scans					
Subject	Visit	New lesions from Baseline	New lesions from Prior	Bone Scan Assessment	Date of Progression
302-102-2004	BL				

	C3	9	9	NOT PD	
	C5	7	0	NOT PD	
	C7	6	0	NOT PD	
	C10	5	0	NOT PD	

Key: PD- Progressive Disease

In Figure 14 we see that for subject 102-2004, there were 9 new lesions noted in the first follow up scan performed less than 16 weeks from start of treatment. Per prostate cancer working group 2 criteria, these new lesions required confirmatory scan with 2 NEW lesions on subsequent evaluations. Two new lesions were not witnessed for the remainder of study for this patient and the patient did not have a bone scan progression event.

Figure 15: Bone Scan Interpretation Example 2

New lesions <12 weeks (c3) confirmed with 2 new lesions on next scan					
Subject	Visit	New lesions from Baseline	New lesions from Prior	Bone Scan Assessment	Date of Progression
302-106-2001	BL				
	C3	4	4	NOT PD	
	Confirmation	10	6	PD	C3 VISIT

In Figure 15 we see that for subject 302-106-2001, there were 4 new lesions seen at the first assessment (<16 weeks from treatment initiation) which was confirmed by 2 additional new lesions on the subsequent scan. The radiologist called progressive disease per the pre-specified rules on the confirmation scan and the date of progression was recorded as the scan PRIOR to the scan confirming progression (in this case, cycle 3 visit).

Figure 16: Bone Scan Interpretation Example 3

New lesions <12 weeks (c3) not confirmed on subsequent scan, but with progression later in study					
Subject	Visit	New lesions from Baseline	New lesions from Prior	Bone Scan Assessment	Date of Progression
302-121-2002	BL	.	.		
	C3	5	5	NOT PD	
	C5	5	0	NOT PD	
	C7	7	2	PD	C5 Visit

In Figure 16 we see that for subject 302-121-2002, there were 5 new lesions seen at the first assessment (<16 weeks from treatment initiation). The subsequent scan at C5 showed that these lesions persisted, but there were no additional lesions and thus progression was not confirmed. On the next scan (C7), two new lesions appeared, confirming progression. C7 scan was called progressive disease and the date of progression was recorded as the scan prior to this (C5).

As illustrated above, in order to prevent false positive results that may occur from bone scan flare of existing occult bone lesions seen on early (<16 weeks) assessments, rules for calling progression on bone scan can be complex. The nuclear medicine physicians responsible for the

interpretation of progression by bone scan must be carefully trained on the pre-specified criteria for progression.

Interpretation of Bone Scans: PCWG-2 Criteria Confirmation:
PCWG-2 criteria recommends confirmation of an early bone scan progression event by showing an additional two lesions in order to decrease false positive bone scan results early in therapy due to potential existing lesions / bone scan flare phenomena which can be seen by anti-tumor activity. The review of bone scan results from COU-AA-302 supports the notion that early bone scan lesions may be more likely to be false positives in the investigational arm of a trial with an active drug compared with placebo. Table 24 shows that of the patients with 2 or more new bone scan lesions seen at the first assessment (8 weeks), patients on the placebo arm were over twice as likely as the abiraterone arm to have confirmation of progression. This suggests that there may have been more false positive early bone scan results due to antitumor activity (bone scan flare) on the abiraterone treatment arm. Not all unconfirmed patients were false positives however as analysis of the patients with no confirmation at next scan reveals that approximately 17% of these patients had no subsequent scan due to clinical or CT progression, withdrawal or uninterpretable subsequent scan. Nonetheless, it does appear that a large number of patients would have been taken off trial early had the rules stated discontinuation for 2 new bones scan lesions without confirmation.

Table 24: Bone scan confirmation of 2 new lesions at first assessment

	AA	Placebo
# of pts with 2 new lesions at cycle 3 scan	117	145
# of pts with lesions confirmed at next scan	16 (14%)	47 (32%)
# of pts with lesions unconfirmed at next scan	101 (86%)	98 (68%)

Source [RECIST10], independent radiographic review

Bone Scan Image Quality and "Unknown" Bone Scan Overall Assessments:
In addition to complexity regarding the rules for calling bone scan progression with respect to the number of new lesions, the timing of the occurrence of these new lesions and the confirmation of the finding; bone scan interpretation is limited by image quality and extent of bone metastases.

The independent review charter for COU-AA-302, version number 2.0, was reviewed and it is noted that, "If progression cannot be determined due to incompleteness of the data or image quality issues, the nuclear medicine reviewer will assign "Unknown". The dataset [RECIST10] was reviewed to determine the number of post-baseline bone scans with overall bone scan assessment coded as "unknown". The percentage of these bone scans with overall assessment of "UNKNOWN" was relatively well balanced with 4.0% in the AA arm and 5.5% in the placebo arm (Table 25).

Table 25: IRC Post-Baseline Bone Scan Assessments of Bone Lesions

Overall Assessment of IRC Reviewer	**AA = 2165 Bone Scans**		**PBO = 1834 Bone Scans**	
NOT PD	1964	90.7%	1548	84.4%

PD	114	5.3%	185	10.1%
UNK	87	4.0%	101	5.5%

Source: [RECIST10]: 3,999 post-baseline bone scan assessments by variable [OBSASSES]

As a comparison, a similar analysis was done to look at the proportion of post-baseline CT or MRI scans with overall assessment coded as "unknown". When using CT or MRI to assess target lesions, there was an approximately 4- to 5- fold lower incidence of "UNKNOWN" tumor restaging assessments of approximately 1% compared to 4-5% with bone scans (Table 26). This finding is not surprising given the differences in resolution between bone scan and anatomic imaging with CT or MRI.

Table 26: IRC CT/MRI Assessments of Target Lesions

RECIST (CT/MRI)	AA = 876		PBO = 733	
CR	131	15.0%	41	5.6%
PD	36	4.1%	77	10.5%
PR	171	19.5%	88	12.0%
SD	528	60.3%	521	71.1%
UNK	10	1.1%	6	0.8%

Source: [RECIST10]: 1,069 post-baseline assessments of target lesions by variable [TLRESP]

Bone scans were considered to have imaging quality issues 3 times more commonly than CT or MRI in COU-AA-302. Overall bone scan and RECIST datasets were reviewed which provided further scan details including comments by the interpreting physicians. The overall bone scan dataset contains 5,061 bone scan assessments (baseline and post-baseline). Thirty one percent (1,578) of the bone scans were flagged as having "imaging quality issues". This is in comparison to the dataset for CT or MRI evaluations where of the 5,029 CT and MRI evaluations, only 503 (10%) had imaging quality issues flagged.

Is the inability to make a definitive progression assessment (PD vs. SD) on a bone scan a result of image quality alone? While not the only problem with bone scan interpretability, poor image quality appears to be a contributor. Image quality issues flagged for bone scans appear to be associated with an increase in the percentage of assessments recorded as unknown. Of all post-baseline bone scans from the [OverallBS] dataset, approximately 31% of each arm had scans with imaging quality issues. Of 1,229 post-baseline bone scan assessments flagged as "imaging quality issues", 91 (7.4%) had an overall assessment of "Unknown". This compares with about 3-4% of bone scans with an assessment of "Unknown" that did not have image quality issues flagged. However, image quality is clearly not the only issue. Bone scans without any image quality issues still had a nearly 4-fold higher incidence of unknown assessments when compared to the overall CT/MRI assessments (2.8%-4.4% for bones cans not flagged with quality issues compared to 0.8 -1.1% of the overall CT/MRI assessments regardless of image quality).

Review of Independent Radiology Comments:
For unknown assessments of target lesions for CT or MRI modalities, the comments typically related to slices or sections of the imaging that were not available such as "no pelvic images",

"No chest CT", "slices missing", "resected?". Comments regarding the quality of the existing images were uncommon but included, "no IV contrast - can't differentiate from vessels". Beam hardening and pixelation in MRI images was also cited.

By contrast, bone scan comments were frequently related to difficulties differentiating whether a lesion was prostate cancer or another benign etiology (degenerative joint disease or trauma), or assessment challenges based on high disease burden in the bones and whether the lesion was new or pre-existing. Some comments for bone scan interpretation included "confluent lesions", "diffuse disease", "superscans", etc. Furthermore, the comments were generally more descriptive regarding the inability to make a clear determination for bone scans such as:

- "I think the lesions are stable, but impossible to be sure" for subject 11-2002, and;
- "There might be a new r mid femur lesion on the posterior, but there was diffuse disease before, so not sure", for subject 117-2001

Interpretation of Bone Scans: Extent of Baseline Disease:

The amount of baseline bone disease appears to affect the ability to interpret follow up bones cans. The percentage of follow up bone scans that were coded as "unknown" for their overall assessment was higher in patients with more baseline bone scan lesions. Table 27 shows that when patients had less than five baseline bone scan lesions, only 8 (0.4%) of the 2,131 follow up bone scans were interpreted by the radiologist as unknown. The percentage of follow up scans interpreted as "unknown" increases as the number of baseline bone scan lesions goes up to a high of 19% of follow up scans being read as "unknown" for patients with over 20 baseline bone scan lesions. This data supports the notion that high burden of bone disease makes interpretation of progression by bone scan more challenging.

Table 27: Interpretation of Follow-up Bone Scans by Number of Baseline Lesions

	<5 Lesions N=2131 Scans		**5 or more Lesions N=1868 Scans**		**10 or more Lesions N=1277 Scans**		**Over 20 Lesions N=728 Scans**	
NOT PD	2009	94.3%	1503	80.5%	985	77.1%	534	73.4%
PD	114	5.3%	185	9.9%	125	9.8%	56	7.7%
UNK	**8**	**0.4%**	**180**	**9.6%**	**167**	**13.1%**	**138**	**19.0%**

Source [SCRBONE] and [OVERALLBS]

Importantly, the baseline extent of bone metastases appeared well-balanced between the study arms (Table 28). Additionally, approximately 65% of the entire study population had less than 10 bone scan lesions at baseline.

Table 28: Baseline Bone Scan Lesions

# Lesions	AA N=544		Placebo N=542	
None	83	15.3%	91	16.8%

1	54	9.9%	63	11.6%
2-4	130	23.9%	121	22.3%
5-9	84	15.4%	79	14.6%
10-20	83	15.3%	78	14.4%
>20	110	20.2%	110	20.3%

Source [SCRBONE]

In an exploratory analysis conducted by the statistical reviewer, despite smaller numbers of events (note wide confidence intervals), all subsets of baseline bone scan lesions retained a HR of less than 1.0 favoring the AA treatment arm. This held true whether measuring rPFS, bone-only Progression or Overall Survival (Figure 17).

Figure 17: rPFS, bone-only PFS and OS by Baseline Bone Scan Lesions

# of Baseline Bone Scan Lesions	N	AA		Placebo		Hazard Ratio (95% CI)
		# event/n (%)	Median (months)	# event/n (%)	Median (months)	
IRC-based rPFS 12/10/2010						
None	174	23/83 (28)	11.7	52/91 (57)	8.0	0.32 (0.20, 0.53)
1	117	4/54 (7)	NR	28/63 (44)	10.9	0.11 (0.04, 0.33)
2-4	251	36/130 (28)	11.5	49/121 (40)	8.4	0.52 (0.34, 0.80)
5-9	163	30/84 (36)	13.7	34/79 (43)	10.8	0.61 (0.37, 1.00)
10-20	161	24/83 (29)	NR	44/78 (56)	5.5	0.36 (0.22, 0.59)
>20	220	33/110 (30)	13.7	44/110 (40)	8.2	0.50 (0.32, 0.78)
Bone PFS (12/20/2010)						
None	174	2/83 (2)	NR	9/91 (10)	NR	0.21 (0.05, 0.98)
1	117	2/54 (4)	NR	12/63 (19)	NR	0.15 (0.03, 0.65)
2-4	251	22/130 (17)	NR	33/121 (27)	NR	0.49 (0.29, 0.85)
5-9	163	21/84 (25)	13.7	25/79 (32)	13.0	0.61 (0.34, 1.09)
10-20	161	18/83 (22)	NR	34/78 (44)	8.3	0.36 (0.20, 0.64)
>20	220	25/110 (23)	NR	26/110 (24)	NR	0.66 (0.38, 1.14)
OS (12/10/2011)						
None	174	21/83 (25)	26.9	21/91 (23)	NR	0.98 (0.54, 1.78)
1	117	6/54 (11)	NR	15/63 (24)	NR	0.45 (0.17, 1.15)
2-4	251	19/130 (15)	NR	30/121 (25)	27.5	0.58 (0.32, 1.02)
5-9	163	26/84 (31)	25.7	30/79 (38)	26.6	0.81 (0.48, 1.37)
10-20	161	29/83 (35)	NR	33/78 (42)	25.9	0.78 (0.47, 1.28)
>20	220	46/110 (42)	25.1	57/110 (52)	20.5	0.76 (0.52, 1.13)

NR= Not Reached

Reviewer Comments:
Data presented from this application support the notion that interpretation of bone scans for progression events is challenging and more subjective than standard RECIST criteria for progression of target lesions. This is not surprising and the potential variability of bone scan interpretation adds uncertainty regarding radiographic progression endpoints for prostate

cancer applications where the majority of patients have metastatic disease to the bone. Analysis of the bone scan data from COU-AA-302 revealed the following key findings:

1. Bone scans had a 3 times higher incidence of poor image quality compared with CT/MRI
2. The interpretation of progression by bone scan was 4 to 5 times more likely to be "unknown" compared with use of CT/MRI for target lesions.
3. The number of "unknown" interpretations increased with extent of baseline bone metastases.
4. Nuclear Medicine reviewers were unable to provide a definitive assessment for 19% of restaging bone scans in patients who had greater than 20 bone lesions at baseline.

Despite the above limitations, the rPFS result is supported by:

1. Large magnitude of rPFS effect
2. Consistency of rPFS improvement across 8 pre-defined subgroups
3. Only 32% of placebo progression events were from "bone-scan only" progression
4. rPFS benefit appeared to be maintained across all baseline bone scan groups (from no lesions to >20 lesions).
5. rPFS result was consistent across multiple FDA sensitivity analyses

Given the population was restricted to asymptomatic or minimally symptomatic patients, it is important to note that patients with a substantial tumor burden (>20 baseline bone scan lesions) appeared to benefit from abiraterone acetate.

Based on the review of bone scan interpretations in this applications and comments from the reading radiologists, it is this reviewer's opinion that future trials using bone scan results as part of a progression endpoint would benefit from the following:

1. Provide bone scan images to reviewing radiologists in digital format whenever possible to allow "windowing" (adjustment of contrast/brightness)
2. Bone scans should continue to have independent review
3. Bone scans should all include full extremities
4. Patients with "superscans" at baseline should be considered uninterpretable with respect to radiographic progression.
5. Care should be taken to recruit a substantial number of patients with mild to moderate extent of baseline bone metastases given the difficulty in interpretation of progression based on high extent of baseline bone disease.

Summary of rPFS endpoint for metastatic Prostate Cancer:
Given the predominance of bone metastases in metastatic prostate cancer patients, bone scan results are an unavoidable part of the assessment of radiographic progression events. The limitations of bone scan results are highlighted in this clinical review and add uncertainty to rPFS results in prostate cancer and the ability of a delay in bone scan progression events in isolation to predict true clinical benefit. The rPFS results in this application are strengthened by a large magnitude of effect with internal consistency across multiple embedded endpoints more

directly related to clinical benefit. While the rPFS results in this application appear statistically persuasive with a large magnitude, the remainder of the clinical review is dedicated to ensure that the overall survival results, key secondary endpoints and patient reported outcomes data support the statistically significant primary efficacy endpoint outcome for rPFS.

6.1.4.2 Overall Survival

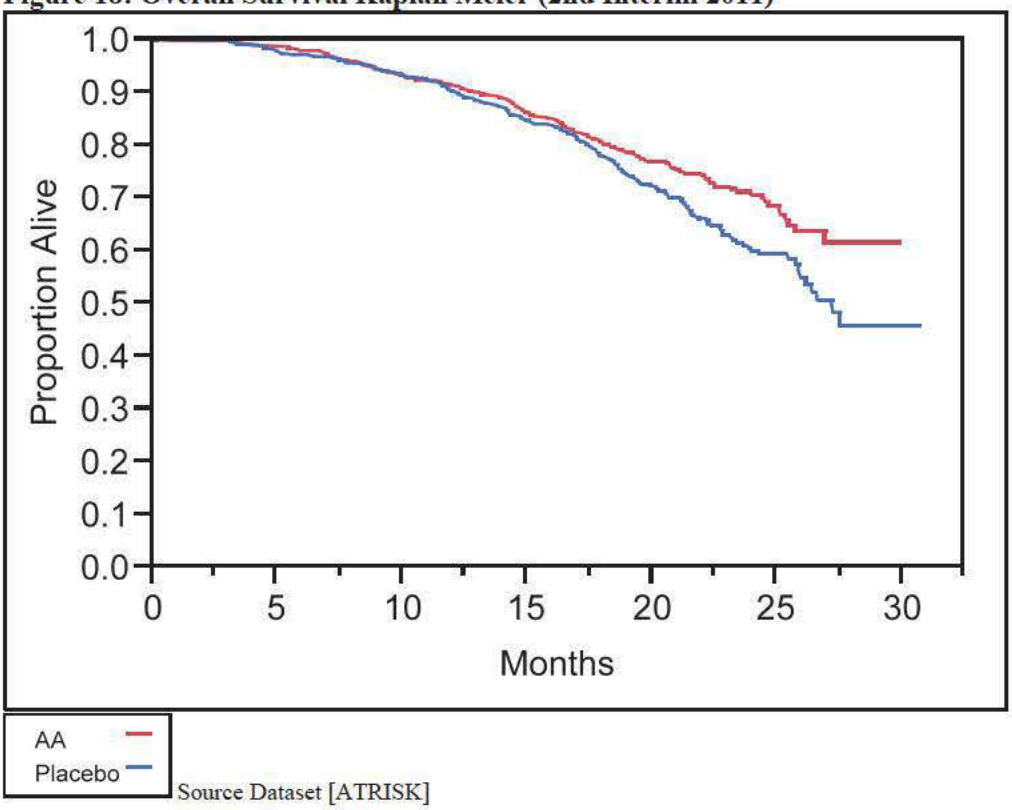
Overall survival was a co-primary endpoint for COU-AA-302. There were 4 planned analyses for overall survival at 15%, 40%, 55% and 100% of the projected observed 773 final overall survival events. The cutoff date for the second interim analysis of OS was 20 December 2011, at which time 333 deaths (43% of the total OS events) were observed with a median follow up of 22 months. The results from the second interim analysis for overall survival are presented below in Table 29 below:

Table 29: Overall Survival: 2nd Interim Analysis 20 Dec 2011 333 (43%) events

	AA (N=546)	Placebo (N=542)
Deaths, n (%)	147 (27%)	186 (34%)
Median (95% CI), in months	not reached	27.2 (25.9, NR)
25% Failures, in months	21.2	18.8
HR (95% CI), stratified	0.75 (0.61, 0.93)	
P-value (2-sided)	0.01*	

Source dataset [ATRISK] *Alpha Significance Level is 0.0008 per O'Brien-Fleming Boundary

Figure 18: Overall Survival Kaplan Meier (2nd Interim 2011)



Source Dataset [ATRISK]

The results for overall survival reveal a delay in time to death from any cause favoring the AA arm; however the P value of 0.01 did not cross the pre-specified O'Brien Fleming boundary for significance. The IDMC met on 27 February 2012 to review the masked efficacy and safety outcomes for the prespecified analysis and unanimously recommended unblinding the treatment and allowing subjects in the placebo group to receive abiraterone acetate. The company sent a letter to the sites with treatment assignments on 26 March 2012. The crossover of the first patient through amendment 3 of protocol COU-AA-302 occurred on 7 May 2012.

Updated Overall Survival Analysis (3rd Interim Analysis):

Updated overall survival results were submitted to the FDA by the applicant on 8/9/2012. The results were from the 3rd interim OS analysis with data cutoff 5/22/2012. At that time the median follow up was reported to be 27.1 months. Four hundred and thirty four (434) death events were observed, which was 56% of the planned 773 death events required for the final analysis. At the third interim analysis, 200 deaths (37%) were reported in the abiraterone acetate arm and 234 (43%) in the placebo arm. An FDA analysis of the submitted dataset [ATRISK] verified the sponsor's reported hazard ratio of 0.79 (95% CI: 0.66, 0.96; p=0.015) revealing a decrease in the risk of death for the abiraterone acetate arm. The p value did not meet the pre-specified statistical boundary of 0.0035 for the 3rd interim analysis.

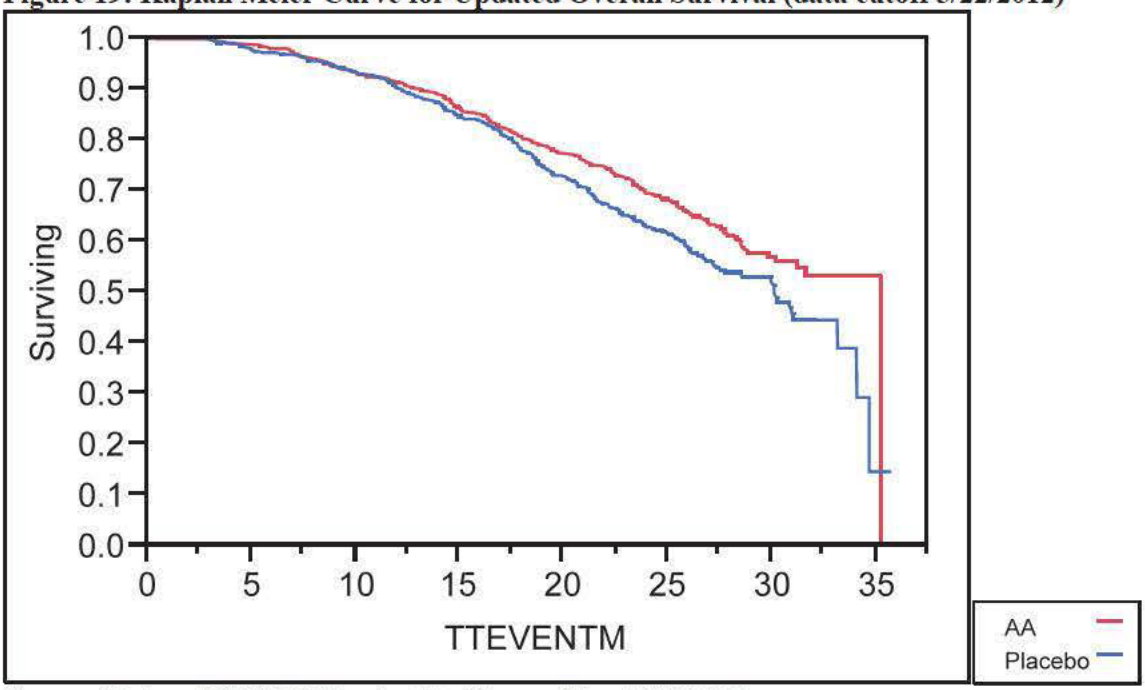
Table 30: Overall Survival (3rd Interim Analysis, 56% Information)

	AA (N=546)	Placebo (N=542)
Deaths, n (%)	200 (37%)	234 (43%)
Median (95% CI), in months	35.29 (31.24, 35.29)	30.13 (27.30, 34.10)
HR (95% CI), stratified	0.79 (0.66, 0.96)	
P-value (2-sided)	0.015*	

Source dataset [ATRISK] submitted 8/9/2012
***Alpha Significance Level is 0.0035 per O'Brien-Fleming Boundary**

The Kaplan Meier curve is presented below (Figure 19):

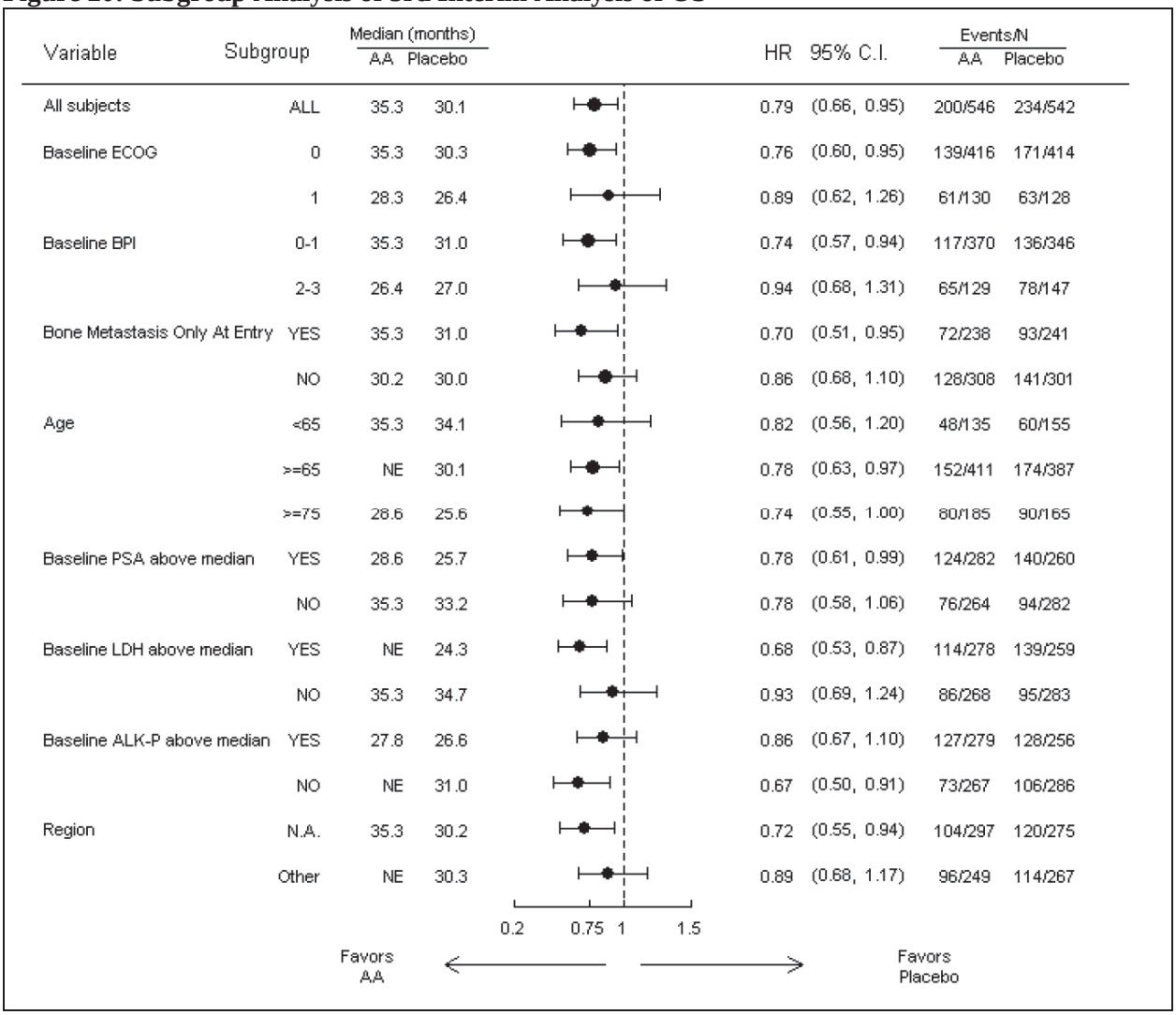
Figure 19: Kaplan Meier Curve for Updated Overall Survival (data cutoff 5/22/2012)



Source: Dataset [ATRISK] submitted by applicant 8/9/2012

The pre-planned 8 subgroups all had estimated hazard ratios below the no treatment effect in favor of abiraterone acetate. (Figure 20)

Figure 20: Subgroup Analysis of 3rd Interim Analysis of OS



Source: Sponsor submission 8/9/2012, confirmed by FDA statistical reviewer.

Further subgroup analyses performed by the statistical reviewer reveal the overall survival for the U.S. population (n=472) was 0.69 (0.52, 0.93). When looking at race, it is noted that the hazard ratio for overall survival in the Black subgroup is 1.32 (95% CI: 0.37, 4.69), however this was based on a very small subset of 28 patients and the PFS hazard ratio for Black patients was 0.72 in favor of the AA arm.

Third Interim Analysis: Update on Subsequent Therapies:
Included in the 3rd interim analysis submission was a dataset for subsequent therapy received by the two arms. Subsequent anti-cancer therapy was received in 64% of the placebo group compared with 50% of the abiraterone acetate group.

Table 31: Subsequent Therapies data cutoff 5/22/2012

	Abiraterone (N=546)		Placebo (N=542)	
Docetaxel	239	43.8%	304	56.1%
Cabazitaxel	60	11.0%	70	12.9%
Ketoconazole	39	7.1%	63	11.6%
Abiraterone Acetate	**38**	**7.0%**	**78**	**14.4%**
Provenge or Sipuleucel-T	33	6.0%	28	5.2%
Anti-Androgen	27	4.9%	36	6.6%
Missing Data	24	4.4%	22	4.1%

Source dataset [SUBSEQTX]

The number of patients who received subsequent abiraterone acetate therapy was 38 (7%) in the AA arm and 78 (14.4%) in the placebo arm (Table 31). Thus, the differential amount of crossover from placebo to abiraterone acetate was not large and adjustment for this effect revealed no substantial change in the analysis.

Reviewer Comment: The majority of this data reflects subsequent therapy prior to study unblinding. The 14% subsequent abiraterone acetate use in the placebo arm likely represents standard of care use either off-label prior to docetaxel or under its currently approved indication after docetaxel rather than cross-over offered at unblinding which occurred only 2 weeks prior to the 5/22/2012 data cutoff.

Therapy after Radiographic Progression:
Patients could continue on study treatment after radiographic progression if they had not experienced unequivocal clinical progression. The number of patients and duration of post-radiographic progression therapy on both abiraterone and placebo arms was evaluated by the clinical and statistical reviewer. Using the investigator radiographic review data, 134/174 (77%) of patients who progressed on abiraterone and 193/261 (74%) of patients who progressed on placebo remained on their respective study treatments at 7 days following radiographic progression. The duration of post-progression therapy was similar between the arms.

Table 32: Duration of Treatment Post-Radiographic Progression

On treatment post radiographic PD, treatment duration post rPD	AA (N=134)	Placebo (N=193)
Median (months)	2.8	2.5
Min, Max	0.26, 14.6	0.26, 14.4

Source: FDA review based on investigator rPFS data cutoff 12/20/2010

Summary of Overall Survival Results:
While the overall survival results did not meet the predefined boundary for statistical significance, the results favored abiraterone acetate and add support to the rPFS findings. There were slightly more patients on placebo who received subsequent therapy with abiraterone acetate however this small amount of "crossover" did not affect the results based on a sensitivity analysis conducted by the applicant (HR unchanged at 0.782 using iterative parameter estimate and rank preserving failure time model). There were no findings in the subsequent therapies /

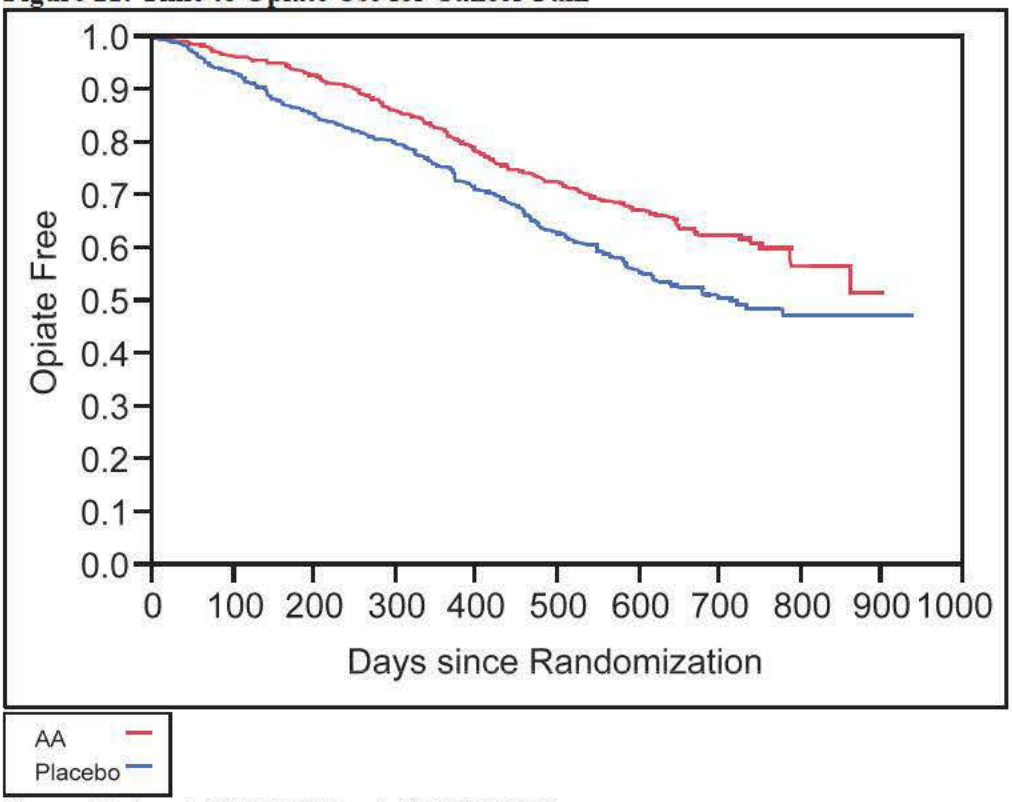
post-radiographic progression treatment patterns that were felt to materially affect the overall survival findings.

6.1.5 Analysis of Secondary Endpoints(s)

6.1.5.1 Time to Opiate Use for Cancer Pain

The time to opiate use for cancer pain was confirmed using source dataset [ATRISK]. There were 183 events in the AA arm and 235 in the placebo arm. The median time to first opiate use was 720 days (23.7 months) for placebo and had not been reached with AA (HR=0.69; 95% CI: 0.57, 0.84; P=0.0002).

Figure 21: Time to Opiate Use for Cancer Pain



Source Dataset: [ATRISK] cutoff 12/20/2011

For an event to be captured, the time to opiate use analysis was based on the attribution of the opiate use to cancer pain which introduces some subjectivity into the endpoint. A sensitivity analysis was conducted for time to opiate use regardless of indication. In this analysis, the use of percocet would be captured as an event even if the indication was "post-procedure" whereas this would not have been captured in the primary analysis as it was not specifically indicated for "prostate cancer pain". The time to opiate use regardless of indication also favors the abiraterone acetate arm (Table 33).

Table 33: Time to Opiate Use Regardless of Indication

	AA (N=546)	Placebo (N=542)
# of events	281 (51%)	321 (59%)
Median (95% CI), months	20.1 (16.8, 22.1)	15.2(13.5, 16.9)
HR (95% CI)	0.76 (0.65, 0.90)	
P-value	0.001	

Source: [CONMED] and [ATRISK10]

Reviewer Comment:
The collection of data in the on-study case report forms for time to opiate use was not optimal. Rather than a yes/no question (i.e. "Did you take any of the following medicines for cancer pain since your last visit"), this analysis relied on a review of collected concomitant medications for any medication that met the criteria for opiate pain medications. It was noted by the statistical reviewer that it was unclear whether the lack of an opiate medication on the concomitant medication list was a true negative (patient did not take an opiate) or was missing data (patient forgot to include it on the list).

Sensitivity Analysis for Missing Data: Time to Opiate Use:
The number of patients who had died on both arms who had not been recorded as having used an opiate was assessed by the FDA review team. One might predict that opiate use would precede death as prostate cancer progresses and the likelihood of disease-related pain increases. If there was bias in the reporting of opiate use we may see more patients dying without recorded opiate use in the abiraterone arm over the placebo arm.

Patients who died never having documented use of an opiate

	AA	Placebo
# of deaths	147	186
Used opiate	87	127
Never used opiate	**60 (41%)**	**59 (32%)**

Data cutoff 12/20/2011

If one believes the assumption that most prostate cancer patients will develop pain requiring an opiate prior to death, these numbers suggest a degree of missing data in the collection of opiate pain medication use. Although the difference is small, a larger proportion of patients who had died in the AA arm (41%) did not have recorded opiate use compared with those in the Placebo arm (32%). Given the small discrepancy, one interpretation of this post-hoc analysis is that there was non-random failure to report opiate use favoring the abiraterone arm. Given that patients and Investigators were likely, based on the adverse event profile of abiraterone, to have remained blinded, the reviewer feels this is unlikely. Furthermore, time to opiate results was supported by patient reported outcomes pain data discussed later in the efficacy review.

Given the concern for potential missing data in the time to opiate use endpoint, an information request was sent to the sponsor with the following question:

FDA Information Request 8/23/2012:
We have a concern regarding the collection of concomitant medications supporting your key secondary endpoints: time to cytotoxic chemotherapy and time to first opiate use. We noted that for the long term quarterly follow-up visits (CRF "FU"), there are specific questions asked for opiate use (yes/no/unknown) and cytotoxic chemotherapy or any other prostate cancer therapies (yes/no/unknown) since last follow-up visit. However, no such questions were found for the on-study treatment visits. Without specifically asking these questions, we rely on the lack of reporting of these medications in an overall concomitant medication list. As such, it is unclear if the lack of opiate or cytotoxic during the prior period was a true negative or missing data.

The sponsor maintains that the lack of opiates on a patient's concomitant medication list is a "true negative" for the following reasons:

- Extensive site monitoring to ensure source documentation captured in CRF
- Cross validation was performed for checkboxes from multiple locations within CRF including:
    - Treatment Discontinuation Reason (Unequivocal Clinical Progression by cytotoxic chemotherapy or chronic opiate pain medication use)
    - Adverse event for pain

- Data elements for opiate use were captured in concomitant medications AND in:
    - Analgesic Use Form (0- no analgesic, 1- non-opioid analgesic, 2- opioid for mod pain, 3- opioid for severe pain)
    - Brief Pain Inventory (BPI) Form (Queried on Question #7: " What treatments or medications are you receiving for your pain? (Please record treatments or medications on Concomitant Medication Form)"
- While there was not a specific yes no question for whether the patient had taken an opioid or not, there was a checkbox on the follow up concomitant medication CRF regarding the indication for the medication: "For prostate cancer related pain" and for cytotoxic chemotherapy "Chemotherapy for prostate cancer".

Reviewer Comment: The concern for missing data in the time to opiate pain medication endpoint is mitigated by site monitoring and multiple cross check validation across multiple CRF forms. The time to first opiate use was further supported by a delay in the time to analgesic progression

Time to Analgesic Progression:

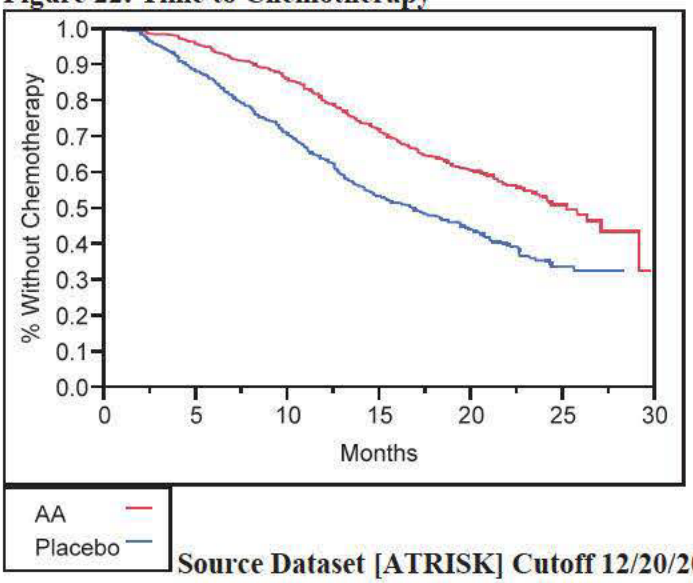
Analgesic use was recorded according to the WHO scale (0 for no medication, 1 for non-opiate pain medication, 2 for opiates for moderate pain, and 3 for opiates for severe pain). The time to analgesic progression was pre-defined in the statistical analysis plan as the time from randomization to a ≥30% increase in analgesic score from baseline observed at two consecutive evaluations ≥4 weeks apart. The applicants analysis revealed a delay in the time to analgesic progression in the abiraterone group compared with the placebo group (HR=0.687; 95% CO: 0.538, 0.878; p=0.003).

Reviewer Summary: Time to Opiate Use for Prostate Cancer Pain:
The key secondary endpoint of time to opiate use for prostate cancer pain favored the abiraterone acetate arm. There are several limitations with this endpoint including lack of a single yes/no answer for each on-study visit with respect to whether a patient had taken an opiate pain medication, variability in investigator and patient threshold for use of opiate pain medications and potential for inadvertent blinding. The duplication and cross-validation of opiate use data throughout multiple case report forms mitigates the potential for missing opiate use data from the concomitant medications CRF. Furthermore, additional trial results including time to analgesic score progression and patient reported outcomes for pain and quality of life support an improvement in the time to opiate use. Given the totality of data, it is this reviewer's determination that the time to opiate use data represents a clinically important result reflective of the benefit of abiraterone acetate in this population.

6.1.5.2 Time to Cytotoxic Chemotherapy

There were 220 chemotherapy events in the AA arm and 298 events in the placebo arm. The median time to initiation of chemotherapy was verified as 25.2 months in the abiraterone acetate arm and 16.8 months in the placebo arm (HR 0.58, 95% CI 0.49-0.69; P<0.0001).

Figure 22: Time to Chemotherapy



Source Dataset [ATRISK] Cutoff 12/20/2011

Time to Cytotoxic Chemotherapy: FDA Repeat Analysis:

The clinical reviewer analyzed the concomitant medications dataset and identified all concomitant medications that were cytotoxic chemotherapy agents. This dataset was then re-analyzed by the statistical reviewer and the results continue to favor the abiraterone acetate arm:

Table 34: Time to Cytotoxic Chemotherapy (FDA Analysis)

	AA (N=546)	Placebo (N=542)
# of events	220 (40%)	301 (56%)
Median (95% CI), months	25.2 (23.3, NE)	16.6 (14.3, 19.3)
HR (95% CI)	0.57 (0.48, 0.68)	
P-value	<0.0001	

FDA Analysis source [CONMED]

Time to Cytotoxic Chemotherapy OR other Prostate Cancer-Related Procedure

The medical officer reviewed a list of on-study procedures from SDTM dataset [YB]. This was done blinded to treatment arm and those procedures likely related to treatment for prostate cancer or prostate cancer related morbidity were flagged and included in the analysis. Some of the more common procedures included: nephrostomy tube *insertion* (revisions/replacements not included), ureteral stenting, radiation therapy, orthopedic procedures, TURP and suprapubic catheter insertion.

The time to chemotherapy or prostate-cancer related procedures favored the abiraterone arm with a hazard ratio of 0.62. (Table 35)

Table 35: Time to chemotherapy OR prostate cancer related procedure

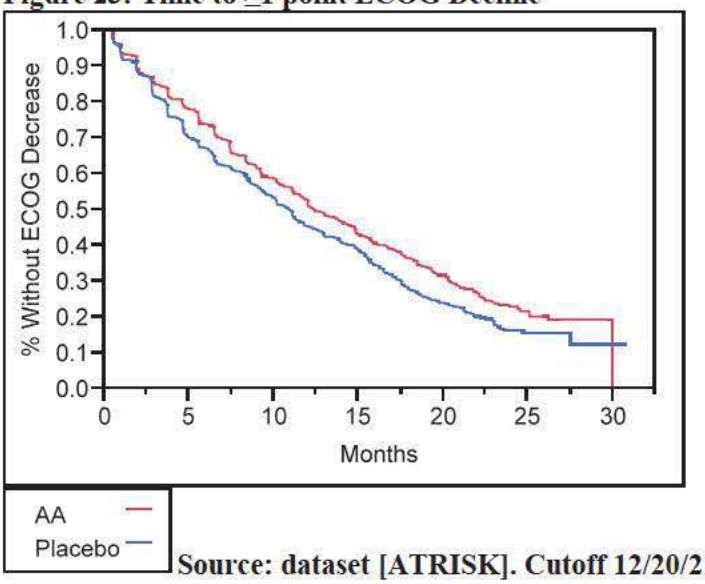
	AA (N=546)	Placebo (N=542)
Number of total events	280 (51%)	353 (65%)
Median (95%) in months	20.07 (17.71, 21.91)	13.21 (12.19, 14.55)
HR (95% CI), P	0.62 (0.53, 0.72), P<0.0001	

Reviewer Comment:
Both the applicant and FDA analyses support the delay in time to cytotoxic chemotherapy with the use of abiraterone acetate. The favorable result was maintained when including cancer-related procedures in an FDA exploratory analysis. While the same concern with respect to data collection methods was brought up with time to cytotoxic chemotherapy (reliance on concomitant medications review rather than a single yes or no question), it is acknowledged by this reviewer that it would be much less likely for a patient to inadvertently forget to list cytotoxic chemotherapy as a concomitant medication. The reviewer's conclusion is that the magnitude of delay in time to cytotoxic chemotherapy appears clinically relevant and statistically persuasive and should be included in the FDA label.

6.1.5.3 Time to ECOG Decline

The time to ECOG decline by ≥1 was confirmed using source dataset [ATRISK]. There were 390 events in the AA arm and 411 in the placebo arm. The median time to ECOG decline was 10.9 months for placebo and 12.3 months for AA (HR=0.82 [95% CI: 0.71 -0.94], P=0.005).

Figure 23: Time to ≥1 point ECOG Decline



Source: dataset [ATRISK]. Cutoff 12/20/2101

The applicant performed a post hoc analysis of time to deterioration in ECOG performance status scale by ≥1 grade ***with confirmation of the ECOG performance status grade at the next visit.*** The median for this analysis was 19.6 months in the AA arm and 15.5 months in the placebo arm (HR=0.754; p=0.0007).

(b) (4)

(b) (4)

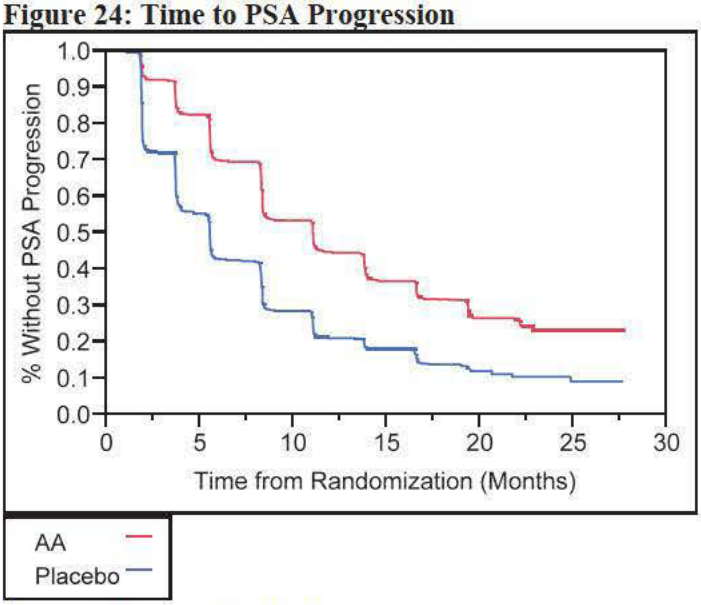
Reviewer Comment: The subjectivity of the investigator assessment and the questionable ability of the instrument to discriminate between ECOG categories are problematic. (b) (4) *Given the limitation of the instrument and the small magnitude of difference between the two arms in the primary analysis of time to ECOG decline, this secondary endpoint is unlikely to be a reliable description of abiraterone acetate's clinical benefit. While it is reassuring that the result favors abiraterone acetate* (b) (4) *the time to ECOG decline results should not be included in the FDA label.*

6.1.5.4 Time to PSA Progression

The time from randomization to PSA progression according to adapted PCWG-2 criteria was delayed in the AA arm when compared with placebo with a hazard ratio of 0.50 (95% CI: 0.43,

0.58) P<0.0001. The median time to PSA progression was 11.1 months in the AA arm versus 5.6 months in the placebo arm.

Figure 24: Time to PSA Progression



Source: Dataset [ATRISK]

Reviewer Comment: Time to PSA progression favors abiraterone and may provide additional support for abiraterone's anti-tumor effect.

6.1.6 Other Endpoints

Antitumor Activity:

Anti-tumor activity was measured in this trial with objective response rate by a modified RECIST 1.0 criteria. Given the eligibility criteria for COU-AA-302 excluded patients with visceral disease, the target lesions for the 438 evaluable patients were nearly all lymph nodes. (Table 36)

Table 36: Location of Target Lesions

Any Target Lesion	Abiraterone N=220		Placebo N=218	
Lymph Nodes	209	95.0%	207	95.0%
Pelvis	11	5.0%	11	5.0%
Lung	4	1.8%	4	1.8%
Liver	8	3.6%	3	1.4%
Adrenal	1	0.5%	2	0.9%
Other	0	0.0%	2	0.9%
Prostate	2	0.9%	1	0.5%
Bladder	0	0.0%	1	0.5%
Retroperitoneum	0	0.0%	1	0.5%

Pancreas	1	0.5%	0	0.0%

Source: dataset [TARGET]

The predominance of lymph node target lesions may be a limitation regarding the objective response results for this trial. Lymph nodes can be challenging as target lesions in that they are normal anatomic structures visible by helical CT scanners even if not involved by malignant disease. Furthermore, they may increase in size due to other non-cancer related processes including infection or other immune-related diseases. Another limitation noted is that the modified RECIST criteria used were based on RECIST 1.0 measurement rules. For instance, the interpretation of measurable disease and of response for target lesions was based on the sum of the diameters in *long axis*. In addition, response criteria could be met regardless of the absolute change in the measurement and thus could be based on increases or decreases of less than 5mm.

The most current RECIST 1.1 criteria were not published prior to the design or initiation of the COU-AA-302 trial. Nonetheless, it should be noted that RECIST 1.1 states that for lymph nodes, the ***short axis*** is the more appropriate measurement and is more predictive of malignant disease. Furthermore, RECIST 1.1 states that a change in the sum of the diameters prompting a PR or PD determination should be a change of ***at least 5mm*** in absolute magnitude.

This limitation was brought to the applicant's attention during the review. The applicant noted that very few patients (only 1 patient on each arm) were affected by progression ONLY based on <5mm changes from nadir measurement (Table 37).

Table 37: PD Based Solely on a <5mm Increase in Target Lesions over Baseline

	AA (N=546) n (%)	Placebo (N=542) n (%)
Progression by CT/MRI or Bone scan criteria	141 (25.8)	240 (44.3)
Progression by target lesion assessment	27 (4.9)	54 (10.0)
PD by < 5 mm change from nadir	3 (0.5)	2 (0.4)
< 5 mm change from nadir & new lesions by CT	1	1
<5 mm change from nadir & PD by bone scan	1	-
< 5 mm change from nadir without other PD	**1**	**1**

Source: CSR attachment table TEFF03C, datasets: RECIST10.xpt and overallr.xpt

Source: Applicant table in response to information request by the FDA during the clinical review, this data was not verified by the clinical reviewer.

Furthermore, the applicant notes that while they did use longest diameter for lymph nodes, in order to increase the likelihood a lymph node target lesion was due to prostate cancer they required target lymph nodes to be 2.0 cm or larger.

With the above limitations in mind, the objective response rates and best overall response for the 438 patients with measurable target lesions are presented below:

Table 38: Objective Response and Best Overall Response (Modified RECIST)

Independent Review	AA		Placebo	
Measurable Baseline Disease	220		218	

Objective Response Rate (PR or CR)*		78	35.5%	34	15.6%
Non-Responder		142	64.5%	184	84.4%
Best Overall Response	CR	24	10.9%	8	3.7%
	PR	54	24.5%	26	11.9%
	SD	135	61.4%	151	69.3%
	PD	5	2.3%	32	14.7%
	NE	2	0.9%	1	0.5%
Source: dataset [RECIST10]. *p<0.0001					

The median duration of response was 10.0 months in the abiraterone acetate arm and 8.6 months in the placebo group based on independent radiographic review. It is notable that the placebo arm enjoyed a 15.6% ORR including 3.7% of patients with a complete response. This is due to the fact that both the AA and the placebo arm used prednisone at 10mg per day which has some activity in prostate cancer.

Reviewer Summary: Anti-tumor Activity:
Despite the limitations regarding the modified RECIST criteria and predominance of lymph node target lesions, the antitumor activity demonstrated by objective response support abiraterone acetate's anti-tumor effect in the chemotherapy naive population. The high response rate to placebo likely reflects the activity of prednisone in prostate cancer.

6.1.7 Subpopulations

Visceral Metastatic Disease:
Patients were excluded from COU-AA-302 if they had evidence of visceral metastatic disease as those patients have typically been offered cytotoxic chemotherapy in standard clinical practice. However, there were 21 patients (12 AA and 9 Placebo) enrolled on COU-AA-302 who did have baseline visceral metastatic disease to the liver, lung, adrenal glands or pancreas (Table 36). There were 3 patients with an objective response in the AA arm with time to response of 59, 164 and 246 days. There was one patient in the placebo arm with a partial response at 53 days.

Table 39: Efficacy Results for Patients from COU-AA-302 With Baseline Visceral Metastases

	AA (n=12)	Placebo (n=9)
# of responders per RECIST (IRC)*	3 (25%)	1 (11%)
# of confirmed PSA responders	9 (75%)	2 (22%)
# of un-confirmed PSA responders	9 (75%)	4 (45%)
rPFS per IRC (2010 cutoff)		
# of rPFS events	3 (25%)	6 (67%)
Median (95% CI) in months	NE	3.7 (1.5, 11.2)
HR (95% CI)	0.25 (0.06, 1.00)	
rPFS per INV (2010 cutoff)		
# of rPFS events	2 (17%)	5 (56%)
Median (95% CI) in months	NE	1.9 (1.5, NE)
HR (95% CI)	0.22 (0.04, 1.12)	

OS (3rd interim, 2012 cutoff)		
# of OS events	6 (50%)	7 (78%)
Median (95% CI) in months	NE (13.1, NE)	17.8 (8.7, NE)
HR (95% CI)	0.43 (0.15, 1.3)	

* All 4 responders are PRs. Time to response: 59, 164, 246 days for the 3 responders in the AA arm, and 53 for the responder in the Placebo arm.

Based on the primary submission datasets with OS cutoff of 12/20/2011, of the 5 patients with visceral metastatic disease in the abiraterone acetate arm who had died, 3 received docetaxel chemotherapy after abiraterone failure. Of the two who died without receiving docetaxel, one patient died on the same day as progression and another died about 5 months following documented progression. No information is provided regarding the reason for not pursuing cytotoxic chemotherapy for that patient. Of the 7 patients who died in the placebo arm with baseline visceral metastatic disease, all 7 received cytotoxic chemotherapy upon progression. This supports the notion that patients with visceral metastatic disease can receive a well-tolerated therapy first and, upon progression, go on to receive docetaxel chemotherapy. There is of course a risk that the window for cytotoxic chemotherapy will close in the meantime. This risk should be discussed with the patient by the treating physician, but the risk does not appear to be unacceptably high based on the limited data reviewed in the COU-AA-302 trial.

Efficacy of AA in Patients with Visceral Metastatic Disease in COU-AA-301:
To further characterize the benefit of abiraterone acetate in patients with visceral metastatic disease, an information request was sent to the applicant asking for an analysis of patients with visceral disease from the COU-AA-301 trial (post-docetaxel). In the post-docetaxel setting, it is noted that there was a similar hazard ratio favoring abiraterone in those with visceral metastatic disease when compared to the overall population with respect to overall survival, rPFS and objective response rate (Figure 25).

Figure 25: COU-AA-301 Visceral Metastatic Disease Summary of Efficacy

	Subjects with Visceral Mets			Total population		
	AA (n=252) median (days)	Placebo (n=101) median (days)	HR+ (95% CI)	AA (N=797) median (days)	Placebo (N=398) Median (days)	HR + (95% CI)
OS	385	257	0.68 (0.49, 0.93)	450	332	0.65 (0.54, 0.77)
rPFS	166	86	0.67 (0.51, 0.88)	171	110	0.67 (0.59, 0.78)
Time to PSA Progression	335	NE	0.96 (0.55, 1.66)	309	200	0.58 (0.46, 0.73)
Time to Pain Progression	NE	NE	0.85 (0.47, 1.56)	NE	NE	0.69 (0.53, 0.90)

+ HR from stratified Cox proportional model

	Subjects with Visceral Mets			Total population		
	AA (n=252)	Placebo (n=101)	Relative Risk (95% CI)	AA (N=797)	Placebo (N=398)	Relative Risk (95% CI)
PSA Response Rate (a)	28%	8%	3.56 (1.78, 7.12)	29%	6%	5.27 (3.46, 8.02)
Objective Response Rate (b)	10%	0%	NE	14%	3%	5.08 (2.07, 12.47)
Pain Palliation Rate (c)	45%	35%	1.28 (0.81, 2.02)	44%	27%	1.65 (1.24, 2.17)

(a) confirmed response
(b) among subjects with measurable disease at baseline
(c) among subjects with pain score ≥ 4 at baseline and at least one post baseline pain score

Applicant's figure in response to FDA information request. This data was not verified by the FDA reviewer.

Summary: AA in chemotherapy naive mCRPC with Visceral Metastatic Disease:
While the numbers are small, AA demonstrated anti-tumor activity in patients with visceral metastatic disease in the pre-docetaxel setting and appeared to benefit from abiraterone acetate compared with placebo. The reviewer believes that treatment of chemotherapy naive patients with visceral metastatic disease with abiraterone acetate should be an option left up to the discretion of the treating physician despite the fact that there was limited data for the efficacy of AA in the pre-docetaxel setting. This determination is based on the following observations:

1. A large subgroup of patients with visceral disease in the post-docetaxel setting showed a benefit (COU-AA-301).
2. Generally, tumors are thought to be as responsive or more responsive to therapy in earlier disease settings compared with more treatment refractory settings.
3. Evidence of antitumor activity and consistency of efficacy findings in the small subset (21 patients) of pre-chemotherapy patients with visceral metastases in COU-AA-302
4. The toxicity profile of abiraterone acetate is such that patients would likely be able to receive docetaxel upon progression following treatment with abiraterone acetate.

Patients with Moderate or Severe Pain at Baseline

Patients with moderate of severe pain (BPI-SF item 3 score of ≥4) were not enrolled on COU-AA-302 trial. (b) (4) (b) (4) Similar to the rationale for the inclusion of patients with visceral metastatic disease in the indication, the reviewer feels that the current efficacy and safety database supports inclusion of chemotherapy naive metastatic CRPC patients regardless of pain status.

In the absence of randomized data directly comparing docetaxel with abiraterone, the reviewer believes that the antitumor activity and safety profile demonstrated by AA in the COU-AA-302 trial provides support that abiraterone is a reasonable option compared with docetaxel in the chemotherapy naive setting regardless of baseline pain. While data is not available for this pain subgroup in the chemotherapy naive population, an information request was sent to the sponsor to review the ability of abiraterone acetate to provide benefit for patients with moderate or severe pain from the COU-AA-301 (post-docetaxel) trial. The subgroup of patients from this trial with BPI-SF ≥4 was provided and is seen in Figure 26 below.

Figure 26: Efficacy of AA in Patients with Moderate/Severe Pain in COU-AA-301

	Subjects with moderate/severe pain			Total population		
	AA (n=357) median (days)	Placebo (n=179) median (days)	HR+ (95% CI)	AA (N=797) median (days)	Placebo (N=398) Median (days)	HR + (95% CI)
OS	385	270	0.67 (0.52, 0.85)	450	332	0.65 (0.54, 0.77)
rPFS	169	87	0.63 (0.51, 0.78)	171	110	0.67 (0.59, 0.78)
Time to PSA Progression	309	172	0.47 (0.32, 0.68)	309	200	0.58 (0.46, 0.73)
Time to Pain Progression	NE	NE	0.73 (0.49, 1.07)	NE	NE	0.69 (0.53, 0.90)

+ HR from stratified Cox proportional model

	AA (n=357)	Placebo (n=179)	Relative Risk (95% CI)	AA (N=797)	Placebo (N=398)	Relative Risk (95% CI)
PSA Response Rate (a)	27%	3%	7.94 (3.55, 17.8)	29%	6%	5.27 (3.46, 8.02)
Objective Response Rate (b)	14%	4%	3.86 (1.20, 12.40)	14%	3%	5.08 (2.07, 12.47)
Pain Palliation Rate (c)	45%	27%	1.70 (1.25, 2.31)	44%	27%	1.65 (1.24, 2.17)

(a) confirmed response
(b) among subjects with measurable disease at baseline
(c) among subjects with pain score ≥ 4 at baseline and at least one post baseline pain score

Source: Applicant subgroup analysis provided. Primary data was unable to be reviewed by the FDA reviewer.

Reviewer Comment:
While there is no direct comparison available for docetaxel versus abiraterone in chemotherapy naive metastatic CRPC with moderate to severe pain, there is no compelling biologic rationale for why abiraterone acetate would be less effective in this subgroup. The data from COU-AA-301 provide support that the moderate/severe pain subgroup does not appear to differ with respect to OS, rPFS or antitumor activity endpoints from the overall COU-AA-301 population. While the FDA did not review the methodology or primary data for the pain palliation rate noted in trial 301 (Figure 26), it is reassuring to note a near doubling of pain palliation by this measure when compared with placebo.

The reviewer believes that treatment of patients with moderate/severe pain with abiraterone should be an option left up to the discretion of the treating physician despite the fact that this specific population was not enrolled on the COU-AA-302 trial. This determination is based on the following observations (similar to rationale for inclusion of visceral metastatic disease):

1. Anti-tumor activity results in the indicated population were robust and compare favorably with docetaxel (limitation of historical cross-trial comparisons are acknowledged).
2. Maintenance of benefit in the moderate/severe pain subgroup of the post-docetaxel patients treated with abiraterone acetate.
3. Generally, tumors are thought to be more responsive to therapy in earlier lines of therapy compared with more treatment refractory settings.
4. The toxicity profile of abiraterone acetate is such that patients would likely be able to receive docetaxel upon progression following treatment with abiraterone acetate.
5. Docetaxel remains an option for chemotherapy-naive metastatic CRPC patients with rapidly progressive disease or with severe pain and may be used prior to abiraterone based on the expertise of the treating physician.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The recommended dose of 1,000mg appears to be safe and effective based on the submitted data from two large phase 3 randomized clinical trials.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The median duration of response was 10.0 months in the abiraterone acetate arm and 8.6 months in the placebo group based on independent radiographic review.

The magnitude of the radiographic progression free survival effect coupled with the median response rate duration of 11.1 months for PSA and 10 months by RECIST support the contention that abiraterone acetate has meaningful persistence of anti-tumor efficacy in the chemotherapy-naive mCRPC population. These findings are supported by favorable overall survival results and

patient reported outcomes data. Nonetheless, patients did progress on AA and further investigation into the etiology for abiraterone resistance will be important.

6.1.10 Additional Efficacy Analyses

Potential Financial Conflict:
The subgroup of patients enrolled to sites with at least one investigator listed in the financial conflicts section, or at sites where there were investigators with missing financial conflict statements was analyzed with respect to the co-primary endpoints. There were no substantial differences in the hazard ratio for OS or rPFS between patients enrolled by sites with documented financial conflicts compared with those without financial conflicts (Table 40).

Table 40: rPFS and OS Analysis for Sites with Potential Financial Conflicts

	N	AA		Placebo		Hazard Ratio (95% CI)
		# event/n (%)	Median (months)	# event/n (%)	Median (months)	
Sites	Radiographic Progression Free Survival (rPFS) IRC Cutoff 12/20/2010					
With financial conflicts	166	19/79 (24)	NR	36/87 (41)	8.21	0.39 (0.22, 0.68)
Without financial conflicts	922	131/467 (28)	13.67	215/455 (47)	8.28	0.44 (0.35, 0.55)
Sites	Overall Survival Cutoff 12/2011					
With financial conflicts	166	22/79 (28)	NR	30/87 (34)	27.5	0.70 (0.40, 1.21)
Without financial conflicts	922	125/467 (27)	NR	156/455 (34)	26.4	0.76 (0.60, 0.96)

Patient Reported Outcomes (PRO):
There were two patient reported outcomes instruments that were utilized in the 302 trial of chemotherapy-naive mCRPC patients. A copy of the BPI-SF and FACT-P instruments can be reviewed in Figure 32 and Figure 33 at the end of this review. The PRO instruments were collected on the schedule listed below:

- Brief Pain Inventory- Short Form (BPI-SF): Screening, Day 1 of each Cycle and End of Study
- Functional Assessment of Cancer Therapy-Prostate (FACT-P): Cycle 1, 3, 5, 7 and 10 then every 3 cycles.

The compliance regarding completion of these instruments was high at over 95% for both the BPI-SF and FACT-P. Due to the limited toxicity of the treatment arm and placebo control, the study was felt to be well-blinded, strengthening the results of the PRO data.

BPI-SF:

Patients enrolled on COU-AA-302 were required to have a pain score no greater than 3 by the BPI-SF worst pain score in the last 24 hours (BPI-SF item3). The distribution of baseline pain scores for patients enrolled in the 302 trial is provided below:

Table 41: Baseline BPI-SF Pain Score for Patients in the 302 Trial

Baseline BPI-SF Pain Score (Worst pain in last 24 hours)	AA	Placebo	Total
n	539	534	1073
0	270 (50%)	260 (49%)	530 (49%)
1	100 (19%)	86 (16%)	186 (17%)
2	76 (14%)	86 (16%)	162 (15%)
3	53 (10%)	61 (11%)	114 (11%)
≥4	40 (7%)	41 (8%)	81 (8%)

Source: dataset [BPI]

There were several time to pain progression endpoints that were analyzed and reported in the COU-AA-302 trial study report. Of the endpoints below, only Time to Average Pain Intensity Progression was prespecified in the statistical analysis plan. The Time to Worst Pain Intensity Progression was prespecified as a sensitivity analysis.

Time to Average Pain Intensity Progression:

Definition: Time from randomization to the first date of BPI-SF increase by 30% from baseline in the average of BPI-SF pain intensity item scores (items 3,4,5 and 6) observed at 2 consecutive evaluations ≥4 weeks apart without decrease in analgesic use score.

Result:
The time to pain progression was delayed by approximately 8 months for abiraterone compared with placebo. (HR 0.817; 95% CI: 0.67-0.99; P=0.049)

Figure 27: Time to Average Pain Intensity Progression

	AA (N=546)	Placebo (N=542)
Subjects randomized	546	542
Event	199 (36.4%)	188 (34.7%)
Censored	347 (63.6%)	354 (65.3%)
Time to event (months)		
25th percentile (95% CI)	7.39 (5.59, 9.13)	5.59 (3.88, 7.39)
Median (95% CI)	26.74 (19.29, NE)	18.40 (14.88, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.0+, 29.6+)	(0.0+, 26.7+)
6-month event-free rate (95% CI)	0.775 (0.736, 0.809)	0.737 (0.694, 0.775)
12-month event-free rate (95% CI)	0.650 (0.604, 0.692)	0.611 (0.558, 0.659)
18-month event-free rate (95% CI)	0.569 (0.518, 0.617)	0.503 (0.441, 0.561)
24-month event-free rate (95% CI)	0.525 (0.470, 0.577)	0.437 (0.366, 0.506)
30-month event-free rate (95% CI)	0.496 (0.419, 0.569)	0.437 (0.366, 0.506)
p value[a]	0.0490	
Hazard ratio (95% CI)[b]	0.817 (0.668, 0.999)	

Note: + =censored observation, NE=not estimable
[a] p value is from a log-rank test stratified by ECOG PS Grade (0 or 1).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors AA.

Source: Applicant Clinical Study Report

Time to Worst Pain Intensity Progression

Definition: Time from randomization to the first date of BPI-SF increase by 30% from baseline in the BPI-SF worst pain intensity item score (items 3) observed at 2 consecutive evaluations ≥4 weeks apart without decrease in analgesic use score.

Result:
There was a trend for the time to worst pain progression being delayed for abiraterone compared with placebo. (HR 0.845; 95% CI: 0.69-1.04; P>0.05).

Reviewer Comment: The definition for pain progression required confirmation of the increase in pain score (by 30% or 2 points) on a consecutive BPI-SF response taken at least 4 weeks later. Because of this requirement, a number of patients experienced a pain event who were subsequently treated with a non-opiate pain medication (i.e. NSAID) who's next consecutive pain score was below the threshold (presumably due to non-opiate pain treatment) and thus was not captured as an event. For instance, a potential scenario includes a baseline worst pain score of 1 going to 8, being treated by NSAID with repeat pain score back to 1. It could be argued that this was a clinically significant pain event. In order to look at this scenario, a sensitivity analysis was conducted changing the definition of the endpoints to first BPI-SF pain score that was greater than 30% or 2 points above baseline. (not requiring confirmation). The results continued to favor abiraterone acetate with HR 95% CI below 1.0. As one might expect by the capture of earlier events, the absolute median difference in time to pain progression was decreased.

Table 42: Time to First Pain Progression (Not requiring Confirmation)

	AA (n=546)	Placebo (n=542)
Time to worst pain PD (1 point)		
# of events	360 (66%)	351 (65%)
Median (95% CI) in months	8.31 (7.33, 9.26)	5.59 (4.70, 6.54)
HR (95% CI)	0.781 (0.674, 0.906)	
Time to worst pain PD (2 points)		
# of events	294 (54%)	282 (52%)
Median (95% CI) in months	12.88 (10.68, 13.90)	8.54 (7.89, 10.61)
HR (95% CI)	0.794 (0.673, 0.936)	
Time to average pain PD (30%)		
# of events	343 (63%)	307 (57%)
Median (95% CI) in months	8.57 (7.43, 10.18)	6.47 (4.83, 8.31)
HR (95% CI)	0.854 (0.731, 0.997)	

Source: datasets [BPI] and [PROBPI]

Reviewer Summary: Pain PRO
While adequate methods for the use of the BPI-SF instrument for pain palliation endpoints have been described, the most appropriate definition for pain progression remains unknown. While we

do not yet have adequate data to define a clinically meaningful pain progression endpoint, the score changes noted in the BPI-SF across BPI items suggest that pain progression was delayed in the AA arm compared with placebo. Because of the lack of a widely agreed upon definition for pain progression and the lack of pre-specified statistical alpha spending, the time to pain progression PRO data for this application, taken in isolation, would not have been persuasive enough to include in the FDA label. However, this well-blinded trial had high compliance for BPI-SF completion and the time to pain progression results were consistent across several definitions and sensitivity analyses. Furthermore, pain results were anchored by multiple other predefined endpoints including overall survival, objective response rate, time to analgesic progression and other measures of progression to more toxic therapies such as opioid pain use and cytotoxic chemotherapy use.

FACT-P:

There was an improvement favoring the abiraterone acetate arm noted in the time to progression for all FACT-P subscales with the exception of Social/Family Well Being. (Figure 28)

Figure 28: Summary of FACT-P Subscale Results

FACT-P Subscale	Median (95% CI) Time to Progression (months)		Hazard ratio of AA/Placebo (95% CI)	p-value
	AA	Placebo		
FACT-P (Total Score)	12.65 (11.07, 14.00)	8.31 (7.39, 10.61)	0.778 (0.659, 0.918)	0.0028
PCS	11.10 (8.64, 13.80)	5.78 (5.49, 8.31)	0.703 (0.598, 0.827)	< 0.0001
TOI	13.86 (11.99, 16.49)	9.26 (8.31, 11.07)	0.745 (0.630, 0.882)	0.0006
FACT-G	16.56 (13.86, 19.35)	11.07 (8.51, 14.75)	0.758 (0.634, 0.906)	0.0023
PWB	14.78 (13.63, 16.82)	11.07 (9.10, 13.80)	0.759 (0.637, 0.904)	0.0020
SFWB	18.40 (13.83, NE)	16.59 (11.07, NE)	0.940 (0.775, 1.139)	0.5283
EWB	22.11 (17.35, NE)	14.16 (13.34, 19.45)	0.714 (0.586, 0.869)	0.0008
FWB	13.34 (11.01, 15.74)	8.35 (7.39, 10.12)	0.760 (0.644, 0.898)	0.0012

EWB=Emotional Well Being; FACT-G=Functional Assessment of Cancer Therapy-General; FACT-P; Functional Assessment of Cancer Therapy-Prostate; FWB=Functional Well Being; PCS=Prostate Cancer Scale; PWB=Physical Well Being; SFWB=Social/Family Well Being; TOI=Total Outcome Index

Source: Clinical Study Report. Data not verified by the clinical reviewer.

The strongest result was in the delay to the time to progression in the Prostate Cancer Scale (PCS).

Figure 29: Time to Progression of FACT-P (PCS) Subscale

	AA (N=546)	Placebo (N=542)
Subjects randomized	546	542
Event	302 (55.3%)	314 (57.9%)
Censored	244 (44.7%)	228 (42.1%)
Time to event (months)		
25th percentile (95% CI)	3.71 (3.65, 3.81)	2.60 (1.97, 3.71)
Median (95% CI)	11.10 (8.64, 13.80)	5.78 (5.49, 8.31)
75th percentile (95% CI)	22.31 (22.08, NE)	16.62 (13.80, NE)
Range	(0.0+, 27.9+)	(0.0+, 27.7+)
6-month event-free rate (95% CI)	0.623 (0.579, 0.665)	0.497 (0.451, 0.543)
12-month event-free rate (95% CI)	0.483 (0.437, 0.529)	0.320 (0.273, 0.368)
18-month event-free rate (95% CI)	0.362 (0.315, 0.410)	0.238 (0.192, 0.288)
24-month event-free rate (95% CI)	0.215 (0.155, 0.282)	0.215 (0.163, 0.272)
p value[a]	< 0.0001	
Hazard ratio (95% CI)[b]	0.703 (0.598, 0.827)	

Note that FACT-P=Functional Assessment Cancer Therapy-Prostate; FACT-P subscales: EWB=emotional well-being; FACT-G=Functional Assessment Cancer Therapy-General; FWB=functional well-being; PWB=physical well-being; PCS=prostate cancer subscale; SFWB=social/family well-being; TOI=total outcome index.
Note: + = censored observation, NE= not estimable.
[a] p value is from a log-rank test stratified by ECOG PS Grade (0 or 1).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favors AA.

Source: Clinical Study Report. Data not verified by the clinical reviewer.

Reviewer Summary: FACT-P

Given the toxicity profile of abiraterone acetate the reviewer believes that inadvertent un-blinding in this trial due to drug toxicity (such as may be seen with an EGFR inhibitor or other agent which may cause noticeable drug-related adverse events) is unlikely which strengthens the PRO results. (b) (4) *Nonetheless, the clinical reviewer feels the results of the FACT-P in this well-blinded randomized clinical trial are supportive of abiraterone acetate's benefit in this population; particularly in the physical and functional well-being subscales.*

It is noted that the prostate subscale has several questions ("I am able to feel like a man, I am able to have and maintain an erection") that would have little likelihood to improve with anticancer therapy in this population of castration resistant prostate cancer patients receiving continuous androgen deprivation therapy. These questions are likely to dilute the ability of the prostate cancer subscale to detect improvements (or delay worsening) in the CRPC population. Despite this limitation, there was a strong benefit seen in the PCS subscale of the FACT-P favoring abiraterone acetate.

In summary, the reviewer considered patient reported outcomes (PRO) results from this well-blinded randomized clinical trial important supportive data for the overall risk:benefit determination and

subsequent approval of this supplemental NDA. The PRO data were of particular importance in this application given the primary surrogate endpoint of asymptomatic radiographic progression.

7 Review of Safety

Safety Summary
The chemotherapy-naive COU-AA-302 safety population includes 542 patients in the abiraterone arm and 540 patients in the placebo arm who have received at least one dose of study medication. The median exposure for trial -302 is 13.8 months which provides the longest exposure data for any trial conducted thus far. The overall safety of abiraterone acetate was also evaluated using integrated data from the combined phase 3 (Trial -301 and -302) datasets of 1,333 AA subjects and 934 placebo subjects. Additionally, available post-marketing surveillance data provided by the applicant and the Office of Surveillance and Epidemiology (OSE) was reviewed which includes submitted reports from over 2 million person-days of worldwide exposure. There is substantial safety data available to adequately conduct this sNDA review.

Key safety results from the COU-AA-302 trial include:

- **Deaths Within 30 days of Last Dose of Study Treatment:**
  There were 18 (3.3%) deaths in the AA arm and 8 (1.5%) in the placebo arm within 30 days of the last dose of study treatment. When removing deaths due to prostate cancer (7 in AA and 3 in placebo), slightly more non-prostate cancer related treatment-emergent adverse events (TEAE) leading to death within 30 days of treatment discontinuation were reported in the AA arm compared with placebo; 11 (2.0%) vs. 5 (0.9%) respectively. There were 5 pulmonary related deaths and 2 related to gastrointestinal ischemia noted in the AA arm. Review of the patient narratives for these deaths as well as review of post-marketing data did not provide sufficient evidence for a causal relationship with AA.

- **Serious Adverse Events and Dose Modifications**:
  Non-fatal SAEs occurred more commonly in the AA arm of COU-AA-302 compared with placebo (33% vs. 26% respectively). SAEs that occurred more frequently in the AA arm were hematuria (1.8%), urinary tract infection (1.5%) and pneumonia (1.3%). There were no deaths due to hematuria or urinary tract infection.

- **Mineralocorticoid-related Adverse Events**:
  Hypertension, hypokalemia and fluid retention/edema continue to occur more frequently in AA arm compared to placebo. The incidence of grade 3-4 hypertension, hypokalemia and edema occurring in the AA arm was 4%, 3% and <1% respectively. There were no reported deaths attributed to these adverse events.

- **Hepatotoxicity:**
  Increased ALT, as a laboratory abnormality, was noted in 42% of patients taking AA compared with 29% of placebo in the COU-302 study. Grade 3-4 ALT was seen in 6% of patients taking AA compared with 0.7% on placebo. Most elevations occurred within the

first 3 months of treatment. Hepatic liver enzyme elevation was the most common reason for treatment interruption and dose reduction occurring in 12 (2.2%) patients in the AA arm compared with 1 (0.2%) in the placebo arm of the -302 trial.

There were no reported hepatic fatalities in clinical trial data. FDA review of the trial -302 laboratory dataset revealed 6 cases of concomitant elevation of ALT and bilirubin, but none were confirmed (based on clinical criteria) to fulfill Hy's Law. The applicant also performed an eDISH and Hy's law analysis which did not reveal any cases fulfilling the criteria for drug-induced liver injury (DILI). Review of the post-marketing data revealed no hepatic deaths clearly related to AA-induced liver injury.

- **Cardiac Events:**
  Events categorized as cardiac disorders occurred more commonly in the AA arm compared with placebo (19% versus 16%). The largest discrepancy occurred in events consistent with cardiac failure (1.8% compared with 0.4% for AA and placebo respectively). Cardiac failure is mechanistically plausible through fluid overload from mineralocorticoid excess.

- **New Adverse Drug Reactions:**
  ADR analysis of COU-AA-302 revealed several adverse events reported with a greater than 2% increase in incidence over placebo. New ADRs occurring in at least 5% of patients that were not included in the -301 ADR table include fatigue, pyrexia, groin pain, constipation, dyspnea, insomnia, contusion, falls, upper respiratory tract infection, nasopharyngitis, hematuria and rash.

- **4-month Safety Update:**
  The 4 month safety update was reviewed. Between the time of sNDA submission and the 4-month update there were no significant changes in the AE profile that would materially affect the conclusion of the primary safety review.

- **Post-Marketing Safety Data:**
  The safety findings in the chemotherapy naive -302 trial were largely consistent with the post-chemotherapy -301 trial population and the integrated safety data. The post-marketing safety data provided by the sponsor and the Office of Surveillance and Epidemiology consult do not provide sufficient evidence for new safety signals that would warrant additional information to the label. The safety database for this supplement is adequate to provide an informed risk:benefit determination for the use of AA in the proposed indication.

7.1 Methods

The safety datasets were reviewed from the COU-302 trial as well as the integrated safety dataset from the primary submission. The primary safety datasets were used for all the major safety

analyses in this review. The 4-month safety update was submitted by the applicant on 9/21/2012 and was reviewed as supportive data. In addition to the standard dataset review, the MedDRA-based Adverse Event Diagnostics (MAED) tool was utilized as an added method to screen for safety signals across all levels of the MEDRA hierarchy as well as select SMQ definitions. Post-marketing data was also reviewed by the primary reviewer, the applicant and through an Office of Surveillance and Epidemiology (OSE) consult.

Treatment emergent adverse events (TEAE) were defined as adverse events occurring during treatment day 1 through end of treatment +30 days. The TEAE definition was verified by cross-validating the treatment start date, end date and adverse event start date and the TEAE flag was verified with the exception of 2 adverse events (Bowen's disease in the AA arm and a case of cataract in the placebo arm) which had no AE start date or imputed start date.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety review of the -302 clinical trial was conducted with support from the integration of the data with the -301 trial. The two large randomized, phase 3, placebo-controlled clinical trials included 2,267 subjects with metastatic castration resistant prostate cancer. Integration of these trials is reasonable given they are similar populations (metastatic castration resistant prostate cancer) and both contained a placebo arm (placebo + prednisone) and the same treatment dose of abiraterone acetate (1,000mg daily). The safety population is defined as all patients who received any part of the study drug (abiraterone acetate or placebo).

Table 43: Randomized Phase 3 Clinical Trials of Abiraterone Acetate

Trial		Arm	Patients
COU-AA-302	Chemotherapy-naive mCRPC, asymptomatic or mildly symptomatic	AA	542
		Placebo	540
COU-AA-301	Post-Chemotherapy mCRPC	AA	791
		Placebo	394

An additional analysis dataset was provided which included safety data from the two phase 3 clinical trials in addition to 8 phase 1/2 clinical studies of men receiving abiraterone acetate for a total of 2,614 patients (1,680 patients receiving AA and 934 patients receiving placebo).

7.1.2 Categorization of Adverse Events

Adverse events were coded to System Organ Class (SOC) and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA) coding system (Version 11.0). The severity of an AE was graded on a scale of 1 to 5 according to the NCI CTCAE (Version 3.0), where higher grades indicated events of greater severity. Adverse events were summarized by grade according to the worst grade experienced.

Accuracy of MEDRA coding:

The integrated safety dataset [ADAE] was reviewed regarding the accuracy of coding reported (verbatim) terms to preferred terms. Of 37,237 reported AEs, 26,237 did not have identical reported terms and coded terms. Approximately 10% of this subset was randomly sampled by the reviewer. There were very few major discrepancies in the coding of reported terms to preferred terms (i.e., reported term "back pain from fall" coded to preferred term "headache" for patient COU-AA-BMA-144-015).

Reviewer Comment: Standard methods were used for categorization of adverse events. The coding of reported terms by investigators to the standardized MEDRA dictionary preferred term did not appear to have a large number of major discrepancies.

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

Pooling of data was performed as described above.

7.2 Adequacy of Safety Assessments

The safety assessments appeared appropriate.

7.2.1 Overall Exposure / Treatment Compliance

Results from COU-AA-302 provide data on prolonged abiraterone acetate (AA) exposure with median AA treatment duration of 13.8 months and placebo exposure of 8.3 months. Over 80% of patients received AA for at least 6 months. By comparison, patients receiving AA in the earlier COU-AA-301 trial of post-chemotherapy patients were exposed to treatment for a median of 7.4 months. Overall treatment compliance was excellent. Based on data obtained at day 1 of each cycle documenting the number of doses (tablets) taken, treatment compliance was >95% in 93% of patients in the AA arm and 91% in the placebo arm.

Table 44: Treatment Exposure

Duration of Treatment	AA	Placebo
N	542	540
Median (months)	13.8	8.3
Range (months)	0.2 - 29.6	0 - 27.7
25%-75% (months)	8.2 - 20.3	3.8 - 16.6

Source: dataset [cycles]

7.2.2 Explorations for Dose Response

All patients received a starting dose of 1,000mg of abiraterone acetate per day.

7.2.3 Special Animal and/or In Vitro Testing

None.

7.2.4 Routine Clinical Testing

The schedule of routine clinical testing and examinations for trial COU-AA-302 can be found in section 5.3 Discussion of Trial COU-AA-302, Figure 5.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please see clinical pharmacology review.

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

Another product used off-label for adrenal suppression of testosterone production is Ketoconazole. Ketoconazole has a black box warning which includes hepatotoxicity including hepatic fatalities. Elevation of AST and ALT has been described with AA and this safety review included an analysis of hepatic toxicity. There have been no hepatic deaths thought to be related to AA reported in clinical trial or post-marketing data.

7.3 Major Safety Results

The overall safety profile for study COU-AA-302 is presented below:

Figure 30: Overall Safety Profile for COU-AA-302 (applicant table)

	AA (N=542)	Placebo (N=540)
Number of Subjects with Treatment-Emergent Adverse Events[a]	537 (99.1%)	524 (97.0%)
Drug-related[b]	424 (78.2%)	413 (76.5%)
Number of Subjects with Grade 3-4 Treatment-Emergent Adverse Events	258 (47.6%)	225 (41.7%)
Drug-related[b]	122 (22.5%)	91 (16.9%)
Number of Subjects with Treatment-Emergent Serious Adverse Events[a]	178 (32.8%)	142 (26.3%)
Drug-related[b]	59 (10.9%)	54 (10.0%)
Grade 3-4	150 (27.7%)	117 (21.7%)
Number of Subjects with Treatment-Emergent Adverse Events Leading to Treatment Discontinuation[c]	55 (10.1%)	49 (9.1%)
Drug-related[b]	29 (5.4%)	23 (4.3%)
Number of Subjects with Treatment-Emergent Adverse Events Leading to Death	20 (3.7%)	12 (2.2%)
Drug-related[b]	5 (0.9%)	4 (0.7%)
All Deaths Within 30 Days of Last Dose	18 (3.3%)	8 (1.5%)
Other	10 (1.8%)	4 (0.7%)
Death due to Prostate Cancer	7 (1.3%)	3 (0.6%)
Unknown	1 (0.2%)	1 (0.2%)

[a] Does not include Grade 5 events.
[b] Adverse events reported as unlikely, possibly, or related for AA/Placebo or Prednisone/Prednisolone or both are classified as drug-related AEs.

Source: Applicant Clinical Study Report COU-AA-302, data verified by clinical reviewer.

7.3.1 Deaths

A total of 333 deaths occurred in COU-AA-302, 147 (27.1%) in AA arm and 186 (34.4%) in the placebo arm:

Table 45: All Deaths in COU-AA-302

	Abiraterone (N=542)		**Placebo (N=540)**	
Total # Deaths	147	27.1%	186	34.4%
Disease Progression	111	20.5%	155	28.7%
Other	28	5.2%	27	5.0%
Unknown	8	1.5%	4	0.7%
Death <=30 days Start	1	0.2%	0	0.0%
Death <=30 days after last Dose	18	3.3%	8	1.5%

Source: Dataset [DEATH]

- For the category of "Unknown" in the AA arm, 7 of the 8 patients died over 90 days from discontinuation of study treatment (range 100-273). The 8th patient, 515-2015, was a 77yo male with history of baseline abdominal pain who had bile duct obstruction study day 268 with US showing compression of portal vein. He was hospitalized and had diagnostic ERCP day 271 and died day 274 of unknown cause (1 day after treatment discontinuation with abiraterone). All events during the hospitalization were thought

unrelated to study drug. There is insufficient data to link this unknown cause of death to treatment with abiraterone acetate.

- For 28 patients with the category of "Other' in the abiraterone acetate arm, 11 were documented as treatment emergent AEs with outcome of death captured in Table 46 below. Of the remaining 17 patients, all died over 60 days from the end of treatment (median 203 days; range 64-446).
- Of the 3 patients who did not have TEAE associated with their death and died less than 90 days from end of treatment, pt 420-2004 died of S. aureus sepsis 64 days after discontinuation, patient 801-2002 died of septic shock due to rectal perforation 77 days after discontinuation and patient 912-2001 died of systemic vasculitis 66 days after treatment discontinuation.

Reviewer Comment: While there were slightly more patients who had death attributed to "other" or "unknown in the AA arm vs. the Placebo arm, none occurred within 2 months of treatment discontinuation lacking temporal associate and were unlikely to be related to therapy.

Deaths Within 30 days of Treatment:
Subjects who died within 30 days of last dose of study medication were reviewed. Of the 18 AA and 8 placebo patients who died within 30 days of treatment discontinuation, 7 in AA and 3 in the placebo arm died of prostate cancer leaving 11 (2.0%) AA subjects and 5 (0.9%) placebo subjects with non-prostate cancer adverse events leading to death within 30 days of study discontinuation. Table 46 lists these events. There were 5 compared to 1 respiratory related deaths and 2 compared to 0 GI necrosis/ischemia related deaths in the AA arm compared with placebo respectively.

Table 46: Deaths Within 30 days of Treatment

Adverse Event	AA N=542		Placebo N=540
Any AE	18 (3.3%)		8 (1.5%)
Prostate Cancer AE	7		3
Non-Prostate Cancer AE	11 (2.0%)		5 (0.9%)
Respiratory	5		1
GI Necrosis/Ischemia	2		0
Cardiac	1		2
Unknown	1		1
Hypothermia	1		0
Suicide	1		0
Stroke	0		1

Source: dataset [DEATH] and datalisting LAE08

Patient narratives for the above deaths in the abiraterone acetate arm were reviewed. Of the 5 respiratory related deaths, one was due to aspiration pneumonia following procedural-related stroke post-cardiac catheterization. One patient was confounded by pre-disposing medical comorbidities of chronic obstructive pulmonary disease (COPD) and asthma. One patient had

concurrent heart failure making attribution to pulmonary infection unclear. Two patients had respiratory infection in the setting of clinical progression occurring on study day 202 and 352.

Reviewer Comment: Death within 30 days due to pulmonary infection was slightly higher in AA than in placebo (5 cases compared with 2). However, the data are insufficient to add death due to pulmonary infections as a significant risk attributed to treatment with abiraterone acetate. Cardiac failure appeared to be a confounder in two cases and is a labeled risk for AA with deaths due to cardiac failure are listed in the label.

Increased upper respiratory tract infection is noted to occur more frequently in the COU-AA-302 trial (see Table 53: Adverse Events > 5% in patients taking AA in COU-AA-302), and this adverse reaction will be included as an ADR under that study. The incidence of pneumonia was 2.2% for AA and 1.9% for placebo. There did not appear to be a significant safety signal noted in post-marketing data concerning pneumonia, or pulmonary events.

GI necrosis / ischemia:

Patient 523-2001
Death on study day 3 admitted with anorexia and fatigue. Study day 5 obstruction, thought *secondary to strangulated inguinal hernia*. Exploratory laparotomy revealed extensive mesenteric ischemia complicated by peritonitis and perforation.

Unlikely due to medication given the strangulated inguinal hernia.

Patient 620-2009
77yo with past history of hypertension, diabetes and gastroesophageal reflux disease (GERD) presented on day 115 with intestinal ischemia and study medication discontinued. Differential diagnosis reported as ischemic bowel versus urosepsis. Patient not considered a surgical candidate and progressed to multiorgan failure and died day 116.

Post-marketing data was reviewed and revealed a total of 3 cases intestinal infarction and 1 of intestinal ischemia were noted in over 2.2 million patient days of exposure to AA.

Reviewer Comment: There is insufficient evidence for a causal relationship between abiraterone acetate and the development of gastrointestinal ischemia.

Cardiac: Myocardial infarction leading to ischemic cardiac failure in Patient 231-2007

Patient 231-2007
89 yr old with cardiac risk factors of gender, age, smoking, coronary artery disease and hypercholesterolemia. On study day 278 the patient presented with scapular fracture and was hospitalized. On study day 279 the patient had grade 3 renal failure and on day 280 grade 3 respiratory distress. On day 281 he was reported to suffer a grade 5 myocardial infarction (MI) event and grade 4 congestive heart failure (CHF) and died.

Reviewer Comment: This case has multiple confounders including advanced age, additional medical stressors including recent fracture and renal failure leading up to his MI and CHF. Causality is unlikely related to study medication.

Cardiac Failure:

Patient 812-2009:

This is a 77 yr old with past history of "hyperglycemia" on metformin and hypertension taking atenolol. Baseline echocardiogram read as abnormal but not clinically significant with EF 69%. On study day 328 he had grade 2 respiratory failure. On study day 335 he experience grade 3 cardiac failure, respiratory failure and pneumonia. Bilateral rales and pitting edema noted and study medication interrupted. Atrial fibrillation was reported and sputum culture was positive for pseudomonas. He was treated with antibiotics and digoxin. He was discharged and on study day 430 he had grade 4 dyspnea, grade 4 atrial fibrillation and a SAE of cardiac failure. He died of multiorgan failure with reported Mallory-Weiss tear with GI bleed, renal failure, pneumonia and heart failure.

Reviewer Comment: There were no reports of cardiac echo in either narrative or in the cardiac echo dataset [ECHO]. Given the narrative however, it appears that the multiorgan failure was most likely related to heart failure complicated by pneumonia. Cardiac failure is a labeled risk for abiraterone acetate and has a plausible mechanistic rationale. Deaths due to heart failure will be documented in the proposed label.

Adverse events documented as leading to death that were not flagged as Treatment-Emergent in the AE dataset occurred in 8 patients in AA and 11 patients in the placebo arm. AEs were largely disease progression and typically began several months after discontinuation of either placebo or AA making association with AA unlikely.

Table 47: Non-treatment related AEs Resulting in Death

	AA	N=542	Placebo	N=540
Any	8	1.5%	11	2.0%
Disease Progression[1]	7	1.3%	10	1.9%
Atrial Fibrillation		0.0%	1	0.2%
Myocardial Infarction	1	0.2%	0	0.0%

[1] Includes euthanasia in one patient on Placebo and general physical health deterioration in one patient on AA arm.

Summary of Patient Deaths:

An in depth analysis of death events from the COU-AA-302 arm did not reveal any clear evidence of new safety signals. There were an increased number of patients who died following a pulmonary or GI adverse event in the AA arm however most cases had alternative explanations and attribution to study drug could not be clearly confirmed. There is insufficient evidence from this review to attribute excess pulmonary deaths or GI ischemic deaths to AA.

7.3.2 Nonfatal Serious Adverse Events (SAE)

Nonfatal serious adverse events occurred more frequently in the AA arm (33%) than placebo (26%). The most common nonfatal SAEs (>1%) that were more frequent in the AA arm compared with placebo were hematuria (1.8%), urinary tract infection (1.5%), and pneumonia (1.3%). Hematuria was seen more frequently in the AA arm and is included in the adverse reactions table for the COU-AA-302 trial in the FDA proposed labeling. There were no deaths attributed to hematuria or UTI. There was one death due to pneumonia on the AA arm.

Table 48: Nonfatal Serious Adverse Events Occurring in ≥5 patients on the AA Arm of COU-AA-302

	AA N=542		**Placebo N=540**	
	Any Grade	**%**	**Any Grade**	**%**
Any Subject with SAE	**178**	**32.8%**	**142**	**26.3%**
Hematuria	**10**	**1.8%**	**4**	**0.7%**
Pulmonary embolism	8	1.5%	11	2.0%
Urinary tract infection	**8**	**1.5%**	**3**	**0.6%**
Atrial fibrillation	7	1.3%	8	1.5%
Pneumonia	**7**	**1.3%**	**4**	**0.7%**
Anemia	5	0.9%	5	0.9%
Angina pectoris	5	0.9%	1	0.2%
Dehydration	5	0.9%	1	0.2%
Gastroenteritis	5	0.9%	1	0.2%
General physical health deterioration	5	0.9%	0	0.00%
Spinal cord compression	5	0.9%	4	0.7%
Syncope	5	0.9%	1	0.2%

SAEs by System Organ Class:

There were higher numbers of infections, cardiac disorders and nervous system disorder SOC SAEs noted in AA arm.

Table 49: Nonfatal SAE by System Organ Class (SOC)

COU-AA-302	**AA**		**Placebo**	
System Organ Class (SOC)	N=542		N=540	
Infections and infestations	45	8.3%	31	5.7%
Cardiac disorders	29	5.4%	14	2.6%
Nervous system disorders	29	5.4%	13	2.4%
Renal and urinary disorders	27	5.0%	25	4.6%
Gastrointestinal disorders	16	3.0%	13	2.4%
Injury, poisoning and procedural complications	16	3.0%	15	2.8%
Respiratory, thoracic and mediastinal disorders	15	2.8%	21	3.9%
General disorders and administration site conditions	14	2.6%	12	2.2%
Musculoskeletal and connective tissue disorders	14	2.6%	19	3.5%

Metabolism and nutrition disorders	13	2.4%	6	1.1%
Investigations	11	2.0%	1	0.2%

Nervous System Disorders SOC:
The nervous system disorder SAEs were reviewed. The most common nervous system SAEs were cerebral ischemia/CVA/embolic stroke (6 vs. 2 patients), syncope/presyncope (6 vs. 2 patients) and spinal cord compression (5 vs. 4 patients) in AA compared with placebo respectively. The most common SAE with SOC Investigations was elevated AST or ALT (5 patients).

Review of the 6 patients with CVA/Embolic Stroke (patient ID 170-2008, 144-2003, 157-2032, 170-2008, 921-2004 and 422-2016) was performed. Five of 6 events occurred after 200 days on study (range 77-598). One 58 yr old patient had a history of stroke with ASD repair. Four of the remaining 5 patients were 67 years of age or older and all had at least 2 risk factors for stroke. Given the increased time on study for the AA arm and the older age and comorbidities of the study population, there is insufficient evidence to support an attribution to AA for the slight increase in stroke SAEs.

Review of the 6 patients on the AA arm experiencing syncope/presyncope was performed. Two patients had a history of syncope in the past. One patient had syncope related to atrial fibrillation. Four patients had syncope in the setting of stress or vagal stimulus. There is insufficient evidence to support an attribution to AA for the slight increase in syncope/presyncope SAEs.

Reviewer Comment: The review of serious adverse events does not provide any significant data to suggest new or unlabeled safety issues. Cardiac and infectious SOC adverse events are further reviewed in section 7.3.5 Submission Specific Primary Safety Concerns.

7.3.3 Discontinuations / Dose Modifications

Treatment discontinuations due to adverse events occurred more commonly in the AA arm (9.8%) compared with placebo (7.8%) as shown in Table 50. The specific adverse events that lead to treatment discontinuations were reviewed including patient narratives when necessary. For treatment discontinuations resulting from multiple adverse events, the adverse event of highest grade or of most clinical relevance was selected as the reason for discontinuation. The adverse events leading to treatment discontinuation for both arms is listed in the table below.

Table 50: AE Categories Leading to Treatment Discontinuation

		AA	Placebo
		542	540
Any Adverse Event Leading to Treatment Discontinuation		53 (9.8%)	42 (7.8%)
	Hepatic Adverse Events[1]	12 (2.2%)	1 (0.2%)
	General Disorders[2]	10	5
	Cardiovascular Adverse Events[3]	9	9
	Pain[4]	7	9
	Infections[5]	5	2
	Neoplasms	3	6
	Gastrointestinal disorders[6]	2	3
	Other	12	8

[1] Includes terms alanine and aspartate aminotransferase increased, Alanine aminotransferase abnormal and hepatotoxicity.
[2] Includes terms fatigue, general physical health deterioration, non-cardiac chest pain, hypothermia, death, asthenia, disease progression and performance status decrease.
[3] Includes terms myocardial infarction, cerebral ischemia, cerebral vascular accident, cardiac arrest, cardiac failure, coronary artery disease, hypertension, peripheral vascular disorder, pulmonary embolism and venous thrombosis.
[4] Includes arthralgia, back pain, groin pain, pain in extremity, cancer pain
[5] Includes lung infection, urinary tract infection, herpes zoster, hepatitis C (AA), and biliary sepsis and bacteremia (Placebo).
[6] Includes terms (Placebo): Lipase increased, pancreatitis necrotizing and oesophageal mass. (Abiraterone): gastrointestinal necrosis and intestinal ischemia.

Reviewer Comment: TEAE resulting in discontinuation was assessed by evaluating the AE dataset for those AEs with a flag for treatment discontinuation. The major discrepancy in adverse events leading to discontinuation occurred in liver function test abnormalities and cardiac failure. Both of these adverse reactions are risks cited in the FDA label. No novel safety signal was appreciated. Treatment discontinuation due to cardiac failure occurred in 2 patients in the abiraterone arm and no patients in the placebo arm.

Dose Modifications:

Table 51: Dose modifications in COU-AA-302

	AA (N=542)	Placebo (N=540)
Number of Dose Reductions		
0	507 (93.5%)	530 (98.1%)
1	25 (4.6%)	10 (1.9%)
2	10 (1.8%)	0
Reason for Dose Reduction[a]	35 (6.5%)	10 (1.9%)
Adverse Event or Toxicity	5 (0.9%)	1 (0.2%)
Other	1 (0.2%)	1 (0.2%)
Restart Dosing	29 (5.4%)	8 (1.5%)
Number of Dose Interruptions		
0	439 (81.0%)	475 (88.0%)
1	71 (13.1%)	50 (9.3%)
2	24 (4.4%)	12 (2.2%)
3	5 (0.9%)	2 (0.4%)
4	2 (0.4%)	1 (0.2%)
5	1 (0.2%)	0
Reason for Dose Interruption[a]	103 (19.0%)	65 (12.0%)
Adverse Event or Toxicity	71 (13.1%)	35 (6.5%)
Other	12 (2.2%)	12 (2.2%)
Serious Adverse Event or Hospitalization	34 (6.3%)	26 (4.8%)

[a] Subjects having multiple dose modifications are counted only once on each line, but may be represented on more than one line.
PROD\RE571 [TEXP02.SAS], 02MAR2012 23:56
Note that "Restart Dosing" refers to dosing reinitiation after an AE.

Source: Applicant clinical study report, verified by reviewer with dataset [DOSEMOD]

There were more dose interruptions (19% vs. 12%) and dose reductions (6.5% vs. 1.9%) in the AA arm compared with placebo. The most common TEAEs leading to treatment interruption or modification included increases in ALT and AST, hypertension, vomiting, dehydration and dyspnea.

Table 52: TEAE leading to dose interruption or modification occurring in 5 or more patients in the AA arm (COU-AA-302)

	AA		**Placebo**	
Preferred Term	**N=542**		**N=540**	
Alanine aminotransferase increased	24	4.4%	4	0.7%
Aspartate aminotransferase increased	18	3.3%	3	0.6%
Hypertension	6	1.1%	5	0.9%
Vomiting	6	1.1%	3	0.6%
Dehydration	5	0.9%	1	0.2%
Dyspnea	5	0.9%	2	0.4%

Source: Dataset [AE]

Reviewer Comment: The majority of dose modifications due to treatment emergent adverse events occurred due to AST or ALT elevations. For details regarding dose modifications due to ALT elevation in the COU-AA-302 trial see section 7.3.5, Submission Specific Primary Safety Concerns under hepatotoxicity.

7.3.4 Adverse Drug Reactions

The most common (>5%) adverse events reported in the COU-AA-302 trial are presented in Table 53 below with the absolute difference between arms noted in the far right column. Those AEs with ≥2% difference favoring AA are highlighted in bold.

Table 53: Adverse Events > 5% in patients taking AA in COU-AA-302

	Abiraterone		Placebo		Difference
		542		540	
ANY AE	**537**	**99.1%**	**524**	**97.0%**	
Fatigue	**212**	**39.1%**	**185**	**34.3%**	**4.9%**
Back pain	173	31.9%	173	32.0%	-0.1%
Arthralgia	**154**	**28.4%**	**129**	**23.9%**	**4.5%**
Edema peripheral	**134**	**24.7%**	**108**	**20.0%**	**4.7%**
Constipation	**125**	**23.1%**	**103**	**19.1%**	**4.0%**
Hot flush	**121**	**22.3%**	**98**	**18.1%**	**4.2%**
Nausea	120	22.1%	118	21.9%	0.3%
Diarrhea	**117**	**21.6%**	**96**	**17.8%**	**3.8%**
Hypertension	**117**	**21.6%**	**71**	**13.1%**	**8.4%**
Bone pain	106	19.6%	103	19.1%	0.5%
Cough	**94**	**17.3%**	**73**	**13.5%**	**3.8%**
Hypokalemia	**91**	**16.8%**	**68**	**12.6%**	**4.2%**
Pain in extremity	90	16.6%	85	15.7%	0.9%
Musculoskeletal pain	78	14.4%	78	14.4%	-0.1%
Muscle spasms	75	13.8%	110	20.4%	-6.5%
Insomnia	**73**	**13.5%**	**61**	**11.3%**	**2.2%**
Contusion	**72**	**13.3%**	**49**	**9.1%**	**4.2%**
Headache	72	13.3%	66	12.2%	1.1%
Dizziness	70	12.9%	70	13.0%	0.0%
Upper respiratory tract infection	**69**	**12.7%**	**43**	**8.0%**	**4.8%**
Vomiting	**69**	**12.7%**	**58**	**10.7%**	**2.0%**
Dyspnea	**64**	**11.8%**	**52**	**9.6%**	**2.2%**
Alanine aminotransferase increased	**63**	**11.6%**	**27**	**5.0%**	**6.6%**
Dyspepsia	**60**	**11.1%**	**27**	**5.0%**	**6.1%**
Anemia	58	10.7%	50	9.3%	1.4%
Aspartate aminotransferase increased	**58**	**10.7%**	**26**	**4.8%**	**5.9%**
Nasopharyngitis	**58**	**10.7%**	**44**	**8.1%**	**2.6%**
Hematuria	**56**	**10.3%**	**30**	**5.6%**	**4.8%**
Pollakiuria	54	10.0%	54	10.0%	0.0%
Pyrexia	**47**	**8.7%**	**32**	**5.9%**	**2.7%**

Urinary tract infection	46	8.5%	39	7.2%	1.3%
Hyperglycemia	45	8.3%	41	7.6%	0.7%
Rash	**44**	**8.1%**	**20**	**3.7%**	**4.4%**
Asthenia	43	7.9%	45	8.3%	-0.4%
Anorexia	39	7.2%	36	6.7%	0.5%
Abdominal pain	37	6.8%	43	8.0%	-1.1%
Groin pain	**36**	**6.6%**	**22**	**4.1%**	**2.6%**
Weight decreased	33	6.1%	25	4.6%	1.5%
Fall	**32**	**5.9%**	**18**	**3.3%**	**2.6%**
Urinary incontinence	32	5.9%	25	4.6%	1.3%
Muscular weakness	31	5.7%	40	7.4%	-1.7%
Myalgia	31	5.7%	31	5.7%	0.0%
Nocturia	31	5.7%	28	5.2%	0.5%
Decreased appetite	28	5.2%	30	5.6%	-0.4%
Weight increased	28	5.2%	39	7.2%	-2.1%

Source: Dataset [AE]

*** NOTE:** Adverse events describing laboratory abnormalities (hypokalemia, AST/ALT increases) are evaluated in the laboratory analysis and are labeled based on laboratory abnormality incidence from the lab datasets.

Combined Preferred Terms of Interest in trial -302:
For the initial NDA submission of abiraterone acetate, the COU-AA-301 trial had preferred term events combined to reflect clinically relevant groupings. Combined preferred term events that were noted to occur more frequently in the abiraterone arm compared to placebo during the COU-AA-301 study were re-analyzed for the COU-AA-302 study. These combined terms are presented below:

Table 54: Combined AE Terms of Interest for COU-AA-302

	Abiraterone (N=542)				Placebo (N=540)			
	Grade 1-4[1]		Grade 3-4		Grade 1-4		Grade 3-4	
Joint swelling / discomfort [2]	164	30.3%	11	2.0%	136	25.2%	11	2.0%
Muscle discomfort [3]	173	31.9%	4	0.7%	197	36.5%	7	1.3%
Edema [4]	136	25.1%	2	0.4%	112	20.7%	6	1.1%
Fracture [5]	38	7.0%	11	2.0%	36	6.7%	6	1.1%
Arrhythmia [6]	49	9.0%	11	2.0%	45	8.3%	6	1.1%
Chest pain or chest discomfort [7]	18	3.3%	2	0.4%	15	2.8%	4	0.7%
Cardiac failure [8]	10	1.8%	7	1.3%	2	0.4%	0	0.0%

[1] Adverse events graded according to CTCAE version 3.0
[2] Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness
[3] Includes terms Muscle spasms, Musculoskeletal pain, Myalgia, Musculoskeletal discomfort, and Musculoskeletal stiffness
[4] Includes terms Edema, Edema peripheral, Pitting edema, and Generalized edema
[5] Includes all fractures with the exception of pathological fracture
[6] Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradycardia, Atrioventricular block complete, Conduction disorder, and Bradyarrhythmia
[7] Includes terms Angina pectoris, Chest pain, and Angina unstable. Myocardial infarction or ischemia occurred more commonly in the placebo arm than in the AA arm (1.3% vs. 1.1% respectively).
[8] Includes terms Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, and Ejection fraction decreased

Based on these analyses, the following table of adverse reactions for COU-AA-302 will be recommended for the FDA label:

Table 55: Adverse Drug Reactions in ≥5% of Patients on AA arm in COU-AA-302

	AA with Prednisone (N=542)		Placebo with Prednisone (N=540)	
System/Organ Class	All Grades[1]	Grade 3-4	All Grades	Grade 3-4
Adverse reaction	%	%	%	%
General disorders				
Fatigue	39.1	2.2	34.3	1.7
Edema[2]	25.1	0.4	20.7	1.1
Pyrexia	8.7	0.6	5.9	0.2
Musculoskeletal and connective tissue disorders				
Joint swelling/ discomfort[3]	30.3	2.0	25.2	2.0
Groin pain	6.6	0.4	4.1	0.7
Gastrointestinal disorders				
Constipation	23.1	0.4	19.1	0.6
Diarrhea	21.6	0.9	17.8	0.9
Dyspepsia	11.1	0.0	5.0	0.2
Vascular disorders				
Hot flush	22.3	0.2	18.1	0.0
Hypertension	21.6	3.9	13.1	3.0
Respiratory, thoracic and mediastinal disorders				
Cough	17.3	0.0	13.5	0.2
Dyspnea	11.8	2.4	9.6	0.9
Psychiatric disorders				
Insomnia	13.5	0.2	11.3	0.0
Injury, poisoning and procedural complications				
Contusion	13.3	0.0	9.1	0.0
Falls	5.9	0.0	3.3	0.0
Infections and infestations				
Upper respiratory tract infection	12.7	0.0	8.0	0.0
Nasopharyngitis	10.7	0.0	8.1	0.0
Renal and urinary disorders				
Hematuria	10.3	1.3	5.6	0.6
Skin and subcutaneous tissue disorders				
Rash	8.1	0.0	3.7	0.0

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

Reviewer Comment:
Combined terms for muscle discomfort, fracture, arrhythmia and chest pain or chest discomfort had a smaller discrepancy between the arms in the COU-AA-302 trial suggesting their attribution to AA may be less likely.

Adverse Reactions Analysis in Overall Combined Phase 3 Population:
A similar analysis was performed on the combined phase 3 dataset and these results are presented below (AEs with a >2% increase in incidence in the AA arm are bolded and these AEs were considered adverse drug reactions):

Table 56: TEAE in >10% of patients taking AA in the Combined Phase 3 Trial Data

Combined Phase 3	**Abiraterone**		**Placebo**		
	N=1333		N=934		Difference
Fatigue	584	43.8%	359	38.4%	**5.4%**
Back pain	435	32.6%	314	33.6%	-1.0%
Arthralgia	393	29.5%	224	24.0%	**5.5%**
Nausea	378	28.4%	248	26.6%	1.8%
Constipation	348	26.1%	229	24.5%	1.6%
Edema peripheral	346	26.0%	183	19.6%	**6.4%**
Bone pain	322	24.2%	220	23.6%	0.6%
Hot flush	275	20.6%	166	17.8%	**2.9%**
Diarrhea	273	20.5%	154	16.5%	**4.0%**
Vomiting	260	19.5%	159	17.0%	**2.5%**
Anemia	256	19.2%	160	17.1%	**2.1%**
Pain in extremity	246	18.5%	167	17.9%	0.6%
Hypokalemia	234	17.6%	104	11.1%	**6.4%**
Musculoskeletal pain	212	15.9%	134	14.3%	1.6%
Cough	195	14.6%	105	11.2%	**3.4%**
Hypertension	193	14.5%	98	10.5%	**4.0%**
Anorexia	182	13.7%	111	11.9%	1.8%
Dyspnea	180	13.5%	103	11.0%	**2.5%**
Headache	175	13.1%	108	11.6%	1.6%
Asthenia	165	12.4%	99	10.6%	1.8%
Insomnia	163	12.2%	112	12.0%	0.2%
Dizziness	159	11.9%	109	11.7%	0.3%
Urinary tract infection	151	11.3%	68	7.3%	**4.0%**
Muscle spasms	149	11.2%	147	15.7%	-4.6%
Abdominal pain	139	10.4%	90	9.6%	0.8%
Contusion	134	10.1%	71	7.6%	**2.5%**

Source: Integrated safety dataset [ADAE]

*** NOTE:** Adverse events describing laboratory abnormalities (hypokalemia, AST/ALT increases) are described in the laboratory analysis and are labeled based on laboratory abnormality incidence from the lab datasets.

Combined Preferred Terms of Interest in Combined Phase 3 Population:
The combined term analysis was performed on the integrated phase 3 datasets and is presented below:

Table 57: Combined AE Terms of Interest for Both Phase 3 Trials

	AA N=1333				Placebo N=934			
	Grade 1-4[1]		Grade 3-4		Grade 1-4		Grade 3-4	
Joint swelling / discomfort [2]	423	31.7%	51	3.8%	234	25.1%	28	3.0%
Muscle discomfort [3]	402	30.2%	30	2.3%	293	31.4%	16	1.7%
Edema [4]	363	27.2%	18	1.4%	190	20.3%	8	0.9%
Fracture [5]	87	6.5%	27	2.0%	47	5.0%	7	0.7%
Arrhythmia[6]	116	8.7%	23	1.7%	63	6.7%	10	1.1%
Chest pain or chest discomfort [7]	49	3.7%	7	0.5%	27	2.9%	4	0.4%
Cardiac failure [8]	28	2.1%	21	1.6%	6	0.6%	1	0.1%

Source: Integrated safety dataset [ADAE]

[1] Adverse events graded according to CTCAE version 3.0
[2] Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness
[3] Includes terms Muscle spasms, Musculoskeletal pain, Myalgia, Musculoskeletal discomfort, and Musculoskeletal stiffness
[4] Includes terms Edema, Edema peripheral, Pitting edema, and Generalized edema
[5] Includes all fractures with the exception of pathological fracture
[6] Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradycardia, Atrioventricular block complete, Conduction disorder, and Bradyarrhythmia
[7] Includes terms Angina pectoris, Chest pain, and Angina unstable. Myocardial infarction or ischemia occurred more commonly in the placebo arm than in the AA arm (1.3% vs. 1.1% respectively).
[8] Includes terms Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, and Ejection fraction decreased

Adverse Events Standardized for Exposure

Because treatment duration in the abiraterone acetate arm was longer than that of the placebo arm (median treatment duration 13.8 months in AA arm and 8.3 months for placebo), the applicant standardized the adverse event rates by treatment exposure (AEs per 100 patient-years) for the COU-AA-302 data as part of their adverse reaction analysis. Using an absolute difference of 5 or more events/100PY occurring in the AA arm compared with placebo, the following adverse events were highlighted: alanine aminotransferase increased (24 vs. 9), aspartate aminotransferase increased (17 vs. 8), dyspepsia (11 vs. 6), and hematuria (14 vs. 8). As would be expected, this methodology attenuated the absolute differences seen between AE incidence between the treatment arms. These adverse reactions were captured as part of the FDA adverse reaction analysis and are included in the revised FDA label for the -302 trial results.

As was mentioned in the safety review of the COU-AA-301 trial for the initial 202379 NDA application, it should be pointed out that standardization by treatment exposure (event/100PY) has not 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 labeling purposes in this submission.

Reviewer Comment: Joint swelling / Discomfort and combined term Edema continue to occur more frequently in the abiraterone arm by approximately 5%. Cardiac failure continues to be more common in the abiraterone arm (see cardiac failure analysis below) and has mechanistic

plausibility due to potential for fluid retention from mineralocorticoid excess. The safety signal for the remaining combined terms muscle discomfort, non-pathologic fractures, arrhythmia and chest pain has been attenuated. Adverse events or combined terms occurring more than 2% more frequently in the abiraterone arm of the combined phase 3 clinical trial integrated dataset will be included in the overall adverse reactions component of the highlights section of the FDA label.

7.3.5 Submission Specific Primary Safety Concerns

Several adverse reactions of special interest were reviewed including those associated with mineralocorticoid excess (hypokalemia, hypertension and edema), hepatic toxicity, cardiac events and combined terms found to occur more often in AA compared to placebo in the -301 trial including joint swelling/discomfort, muscle discomfort, edema, fractures, arrhythmia, chest pain or discomfort and cardiac failure. In addition, based on the review of the safety data from COU-AA-302, infectious events and venous thromboembolic events were further reviewed.

Fluid Retention/Edema:
Trial -302: The combined term edema occurred more commonly in AA than placebo (25% vs. 21%). Grade 3-4 edema occurred in <1% of patients taking AA and there were no deaths or discontinuations for the combined term of edema.

Combined Phase 3 Data: In the combined phase 3 data, preferred terms consistent with edema occurred more commonly in the AA group than placebo (27% vs. 20%). These events were largely grade 1-2 in severity and grade 3-4 edema events occurred in 1.4% and 0.9% of abiraterone and placebo patients respectively. Only 7 serious edema events were recorded in the combined phase 3 trials for AA and one patient was discontinued from therapy.

The incidence of pleural effusion or ascites was rare in the chemotherapy naive trial -302 and well balanced with 4 patients reporting pleural effusion in both arms and 1 patient with ascites in both arms. This is in contrast to the post-chemotherapy -301 trial where there were 18 patients with pleural effusion in AA versus 6 in placebo.

Hypokalemia:
Trial -302: Hypokalemia was reported as an adverse event more commonly in the AA arm compared with placebo in the -302 trial (18% vs. 9%). This was also seen with laboratory data with low potassium being seen in 17% of AA patients compared with 10% in the placebo arm.

Combined Phase 3 Data: The rate of hypokalemia seen in the integrated phase 3 laboratory data was 24.3% in the abiraterone arm compared with 14% seen in placebo. Grade 3-4 incidence was also higher in the abiraterone arm (4.4% vs. 1.8%). While hypokalemia may predispose patients to arrhythmias, the review of cardiac arrhythmias revealed an attenuation of the difference in arrhythmias between the arms in trial COU-AA-302 compared with the post-chemotherapy COU-AA-301 trial. (See cardiac events discussed later in the review)

Hypertension:
Trial -302: Hypertension continued to occur more commonly in the abiraterone arm of study -302 compared with placebo (22% vs. 13%). Grade 3-4 hypertension occurred in 3.9% of patients receiving AA in study -302. One 80 year old patient with multiple cardiac comorbidities (AA-302-411-2007) experienced a hypertensive crisis with blood pressure of 212/110 which resolved with treatment.

Combined Phase 3 Data: In the integrated phase 3 data, 4 patients in the AA arms had SAE of hypertension, with 1 patient (from study 302) discontinuing treatment due to grade 3 hypertension. There were no deaths in the integrated phase 3 data due to hypertension.

Fracture:
Trial -302: In the chemotherapy naive -302 trial, non-pathologic fractures occurred at approximately the same frequency in both treatment arms (7% AA and 6.7% Placebo) with a higher rate of grade 3-4 fractures in the abiraterone acetate arm (2.0% vs. 1.1%). This is in contrast to the results from the -301 trial showing an increase in reports of non-pathologic fractures occurring in the AA arm compared with placebo (6% vs. 2%).

Combined Phase 3 Data: In the integrated safety database, the combined term for fractures occurred in 87 patients (6.5%) receiving AA of which 25 were considered serious events and 5 patients were discontinued from treatment. There were no deaths in the integrated phase 3 data due to non-pathologic fracture. There was no data provided regarding osteopenia. Bone density is difficult to obtain in patients with diffuse bone metastases.

Hepatotoxicity:
Trial -302: Grade 3-4 elevation of ALT occurred in 6% vs. 0.7% and AST in 3% vs. 1% of patients receiving AA compared with placebo respectively. Integrated laboratory datasets confirmed an imbalance with grade 3 or higher elevations in ALT and AST occurring at 3% of AA and 2% of placebo in the entire 1,680 patient integrated safety database. There were less than 1% of patients who required drug discontinuation due to increases in ALT or AST. There were no drug-related hepatotoxicity deaths reported. A Hy's Law and eDISH analysis for drug-induced liver injury (DILI) was performed by the sponsor and the FDA and did not reveal any clear cases of DILI. Post-marketing evaluation of the adverse event reporting database by the appicant and the reviewer did not reveal any hepatic related deaths clearly attributed to drug-induced liver injury.

Reviewer Comment: Hepatic enzyme elevation continues to be seen in patients receiving AA. Dose interruption for increased hepatic serum AST or ALT should be followed per labeled recommendation. Appropriate dose modification guidelines for hepatic enzyme elevation are included in the FDA label.

Adrenocortical Insufficiency:

Given the mechanism of action of abiraterone acetate, adrenocortical insufficiency is of particular interest. There were 2 cases of adrenal insufficiency in the abiraterone arm and 2 cases in the placebo arm of COU-AA-302. Brief narratives for the cases in the AA arm are below:

Patient 125-2003:
69yo male with past history of myocardial infarction, diarrhea, constipation, smoking, DM-2, dizziness, obesity, sleep apnea and syncope. He experienced syncope on study day 106 and was diagnosed with grade 2 adrenal insufficiency on study day 146. Random cortisol was 6, cortisol stimulation test results were baseline 12.4, 30min 11.8 and 60 min 11.4 (in healthy individuals, baseline cortisol levels should double by 60 minutes). The patient's dose of steroids was increased.

Patient 906-2003:
76 year old with past history of night sweats was hospitalized for nephrolithiasis, but no mention of adrenal insufficiency was found. The event was of grade 1 severity and occurred on study day 438 and ended day 450 with AE outcome of "resolved".

The safety database was queried for preferred terms containing either adrenal insufficiency or hypotension and the following results were obtained:

Table 58: Adrenal Insufficiency or Hypotension

	COU-AA-302					**Integrated Phase 3**				**Integrated AA including Ph1/2**	
	AA (N=542)		PBO (N=540)			AA (N=1333)		PBO (N=934)		AA (N=1680)	
Any AI or Hypotension	19	3.5%	22	4.1%		57	4.3%	42	4.5%	76	4.5%
Adrenal Insufficiency	2	0.4%	2	0.4%		6	0.5%	2	0.2%	9	0.5%
Hypotension	14	2.6%	17	3.1%		46	3.5%	35	3.7%	62	3.7%
Orthostatic Hypotension	4	0.7%	5	0.9%		7	0.5%	8	0.9%	8	0.5%

Source: Dataset [AE] and [ADAE]
AI: Adrenal Insufficiency; PBO: Placebo

Reviewer Comment: Adrenal insufficiency remains a mechanistically plausible safety concern although this adverse reaction has been infrequently reported in clinical trial data. Neither of the patients with documented adrenal insufficiency had prior prednisone dose reductions.

Cardiac Events:
Combined terms for COU-302 for cardiac events were analyzed in the same fashion as the COU-301 study:

COU-AA-302	Abiraterone (N=542)				Placebo (N=540)			
	All		Gr 3-4		All		Gr 3-4	
Arrhythmia[1]	49	9.0%	11	2.0%	45	8.3%	6	1.1%
Chest pain[2]	18	3.3%	2	0.4%	15	2.8%	4	0.7%
Cardiac Failure[3]	10	1.8%	7	1.3%	2	0.4%	0	0.0%

[1] Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradycardia, Atrioventricular block complete, Conduction disorder, and Bradyarrhythmia
[2] Includes terms Angina pectoris, Chest pain, and Angina unstable. Myocardial infarction or ischemia occurred more commonly in the placebo arm than in the AA arm (1.3% vs. 1.1% respectively).
[3] Includes terms Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, and Ejection fraction decreased

The combined phase 3 results for cardiac events is presented below:

Combined Phase 3 Data	Abiraterone (N=1333)				Placebo (N=934)			
	Any Grade	%	Grade 3-4	%	Any Grade	%	Grade 3-4	%
Arrhythmia[1]	139	8.3%	28	1.7%	71	7.6%	11	1.2%
Chest Pain[2]	60	3.6%	9	0.5%	27	2.9%	4	0.4%
Cardiac Failure[3]	28	2.1%	21	1.6%	7	0.7%	2	0.2%

[1] Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradycardia, Atrioventricular block complete, Conduction disorder, and Bradyarrhythmia
[2] Includes terms Angina pectoris, Chest pain, and Angina unstable. Myocardial infarction or ischemia occurred more commonly in the placebo arm than in the AA arm (1.3% vs. 1.1% respectively).
[3] Includes terms Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, and Ejection fraction decreased

Treatment discontinuations due to cardiac failure occurred in 5 patients in the abiraterone group and no patients in the combined placebo group.

Deaths due to Cardiac Events:

- The applicant notes there were 2 cases of **heart failure** resulting in death in the abiraterone acetate group and 1 death in the combined placebo group.

  AA: COU-AA-302_812-2009
  AA: COU-AA-302_106-2009
  Placebo: COU-AA-301_507-0043

- There were 7 deaths due to **cardiorespiratory arrest or cardiac arrest** in the AA group and 3 deaths in the placebo group.
- There was 1 death associated with **arrhythmia** and 1 sudden death in the AA arm and none in the placebo arm.
- There were 2 deaths associated with **myocardial ischemia/infarction** in the AA arm 3 deaths in the placebo group.

Table 59: Cardiac AE with Outcome of Death in Combined Phase 3 Data

Combined Phase 3 Data	Abiraterone (N=1333)		Placebo (N=934)	
AEs with outcome of DEATH	131	9.8%	87	9.3%
Cardiac	12		8	
Cardiac Arrest / Cardio- respiratory Arrest	7		3	

Myocardial Infarction	2		3	
Arrhythmia	1		1	
Heart Failure	1		1	
Sudden Death	1		0	

Source: Dataset [ADAE]

Reviewer Comment:
The 7 cardiac arrest events were reviewed. Events occurred a median of 164 days after study drug initiation (64-344) and were considered unrelated by the investigator. Six of the 7 occurred in the COU-AA-301 trial and one occurred in the -302 trial. Five events occurred in the setting of hospitalization for acute complications including illeus, grade 5 renal failure, COPD exacerbation requiring intubation, MRSA wound infection and heart failure in the intensive care unit, and one with sepsis and congestive heart failure. Of the two patients who died at home, one patient had a history of deep vein thrombosis and hypertension and died at home on study day 164, another had diabetes, coronary artery diseaes, hypertension and hyperlipidemia and died at home on study day 68. The slight increase in patients taking AA who suffered cardiac arrest compared to placebo is confounded by multiple alternative explanations for cardiac arrest. There is insufficient data to support an association between the use of AA and cardiac arrest events.

Echocardiograms:
A dataset for echocardiograms performed in COU-AA-302 was included in this submission. Of the 1094 echocardiograms, 1,084 were baseline exams with median EF 64% in both arms. Only 10 post-baseline exams were performed in 10 patients. Two had missing ejection fraction data, but neither report describes LV dysfunction. The other 8 exams (5 in AA and 3 in Placebo) had ejection fraction equal to or greater than 55%.

Cardiac Adverse Event Summary:
Based on a review of the applicant's safety summary and the analysis of the integrated datasets, the strongest imbalance in cardiac disorders occurred in the cardiac failure subcategory. Cardiac failure occurred more frequently in the abiraterone group and this discrepancy persisted in an exposure-standardized analysis with 5 events / 100PY in abiraterone treated patients versus 1 event / 100PY in the combined placebo group (applicant data). The applicant notes that study COU-AA-301 included regular multiple gated acquisition scans/echocardiograms; 6% of subjects in the abiraterone acetate group and 5% of subjects in the placebo group were found to have a decrease in left ventricular ejection fraction (LVEF) of at least 15% from baseline at any time during the study. In Study COU-AA-302, these assessments were not required post-baseline.

Reviewer Comment:
While cardiac disorders were slightly more common in the abiraterone group, deaths were uncommon. Given the potential for fluid accumulation in the setting of mineralocorticoid excess, cardiac failure has a mechanistic rationale and is more likely an adverse drug reaction.

Information regarding cardiac failure and cardiac events is noted in the safety section of the label.

Pulmonary Embolism and Deep Vein Thrombosis:
Review of the integrated phase 3 safety database revealed 4 fatal cases of pulmonary embolism (PE) in the AA arm compared with 0 in the placebo group. All 4 cases occurred in the COU-AA-301 clinical trial and there were no fatal cases of pulmonary embolism noted in the chemotherapy naive -302 trial. The overall incidence of venous thromboembolic events (DVT or PE) was 3.9% in the placebo arm and 3.5% in the AA arm of the integrated phase 3 datasets. The overall incidence of nonfatal PE and DVT are provided below:

Table 60: Venous Thromboembolic Events (VTE) in the Integrated Phase 3 Datasets

	Abiraterone N=1333				**Placebo N=934**			
Preferred Term	**Grade 1-4**		**Grade 3-4**		**Grade 1-4**		**Grade 3-4**	
Deep vein thrombosis (DVT)	24	1.8%	18	1.4%	8	0.9%	7	0.7%
Pulmonary embolism (PE)	22	1.7%	17	1.3%	31	3.3%	25	2.7%

Source: Dataset [ADAE]

There were 26 reported cases of pulmonary embolism in the post-marketing adverse event reporting database which is based on over 2,200,000 person days of worldwide exposure. The interpretation of this finding is challenging due to the increased risk of VTE in the advanced metastatic indication for which abiraterone is currently approved (after failure of docetaxel chemotherapy).

Reviewer Comment:
Advanced malignancy is a known risk for development of venous thromboembolic events. While there was an imbalance of fatal pulmonary embolism events in the AA arm versus placebo in the more advanced -301 trial, the remainder of the integrated phase 3 data suggest that overall VTE events occurred more frequently in the placebo arm. There were no fatal VTE events in the submitted chemotherapy naive clinical -302 trial. While the incidence of DVT was higher in the AA arm of the integrated safety database, the incidence of PE was higher in the placebo arms (1.7% for AA and 3.3% for placebo). Given the increased exposure and time on study in the AA arms, the known increased risk of VTE in advanced malignancy and the overall higher incidence of VTE in the placebo arm of the integrated safety dataset, there is felt to be insufficient data to attribute the deaths due to pulmonary embolism in the COU-AA-301 trial to abiraterone acetate.

Infections and Infestations:
Adverse events due to infection were higher in the AA arm compared with placebo (SOC infections and infestations 55% AA and 39% for placebo. Preferred terms in the infection SOC that occurred at >2% higher incidence in the AA arm were upper respiratory tract infection

(12.7%), nasopharyngitis (10.7%), bronchitis (4.8%) and sinusitis (4.4%). Of the 156 patients who had any of those 4 events, only 1 patients had a grade 3 event. There were no grade 3 or higher upper respiratory tract infection in either arm. Overall, grade 3 or higher AEs with SOC of infections/infestations occurred in 55 (7.4%) of patients in the AA arm and 33 (6.1%) of placebo.

Table 61: Grade 3-4 Infections in COU-AA-302

	Abiraterone Acetate N=542		Placebo N=540	
Urinary tract infection	8	1.5%	3	0.6%
Pneumonia	7	1.3%	4	0.7%
Sepsis	4	0.7%	2	0.4%
Cystitis	3	0.6%	0	0.0%
Gastroenteritis	3	0.6%	1	0.2%
Cellulitis	2	0.4%	3	0.6%
Herpes zoster	2	0.4%	1	0.2%
Pyelonephritis	2	0.4%	1	0.2%
Respiratory tract infection	2	0.4%	0	0.0%
Urosepsis	2	0.4%	2	0.4%

Source: [AE]

There were 3 deaths (lung infection, pneumonia and respiratory tract infection) in the AA arm and no deaths in the placebo arm. Pulmonary deaths have already been discussed earlier in this sNDA review.

An Empirica analysis of the post-marketing data reveals

Reviewer Comment: Infections occurred more commonly in the AA arm of COU-AA-302. The most common preferred terms seen more commonly in the AA arm compared with placebo in the infection SOC, upper respiratory tract infection and nasopharyngitis, are included in the FDA label as ADRs occurring in over 10% of subjects in COU-AA-302. The majority of infection events were of low grade. Given the increased exposure in the abiraterone acetate arm, the low grade and lack of obvious mechanistic/biologic rationale, it is the reviewers determination that a causal relationship between AA and general infections can not be established and a specific warning for increased risk for general infections is not warranted at this time.

7.4 Supportive Safety Results

7.4.1 Laboratory Findings

The laboratory datasets were analyzed by the review team with the following results displayed in the table below:

Table 62: Laboratory data from COU-AA-302

	Abiraterone	Placebo

	N = 542		N = 540	
	Grade 1-4	Grade 3-4	Grade 1-4	Grade 3-4
Hematology				
Neutropenia	26 (5%)	4 (0.7%)	29 (5%)	6 (1%)
Lymphocytopenia	**207 (38%)**	**47 (9%)**	**171 (32%)**	**40 (7%)**
Anemia	342 (63%)	10 (2%)	325 (60%)	13 (2%)
Thrombocytopenia	59 (11%)	3 (0.6%)	45 (8%)	4 (0.7%)
Chemistry				
ALT	**227 (42%)**	**33 (6%)**	**157 (29%)**	**4 (0.7%)**
AST	**202 (37%)**	**17 (3%)**	**155 (29%)**	**6 (1%)**
Bilirubin	**67 (12%)**	**3 (0.6%)**	**29 (5%)**	**1 (0.2%)**
Alkaline Phosphatase	293 (54%)	43 (8%)	273 (51%)	43 (8%)
Creatinine	82 (15%)	4 (0.7%)	82 (15%)	3 (0.6%)
Amylase	31 (6%)	3 (0.6%)	23 (4%)	0
Cholesterol	37 (7%)	0	44 (8%)	1 (0.2%)
Triglycerides	123 (23%)	0	100 (19%)	0
Hypoalbuminemia	120 (22%)	1 (0.2%)	104 (19%)	1 (0.2%)
Hypophosphatemia	**56 (10%)**	**32 (6%)**	**24 (4%)**	**13 (2%)**
Hypokalemia	**93 (17%)**	**15 (3%)**	**55 (10%)**	**9 (2%)**
Hyperkalemia	27 (5%)	1 (0.2%)	29 (5%)	5 (0.9%)
Hypomagnesemia	10 (2%)	0	9 (2%)	0
Hypermagnesemia	100 (18%)	2 (0.4%)	96 (18%)	1 (0.2%)
Hypocalcemia	46 (8%)	0	43 (8%)	6 (1%)
Hypercalcemia	**54 (10%)**	**1 (0.2%)**	**24 (4%)**	**1 (0.2%)**
Hypoglycemia	44 (8%)	1 (0.2%)	34 (6%)	0
Hyperglycemia	**307 (57%)**	**35 (6%)**	**275 (51%)**	**28 (5%)**
Hyponatremia	79 (15%)	10 (2%)	78 (14%)	16 (3%)
Hypernatremia	**178 (33%)**	**2 (0.4%)**	**135 (25%)**	**1 (0.2%)**
Hyperuricemia	20 (4%)	6 (1%)	38 (7%)	11 (2%)

Laboratory abnormalities that occurred at a greater than 5% increase in incidence in the abiraterone acetate arm include lymphocytopenia, elevation of AST, ALT and bilirubin, hypophosphatemia, hypokalemia, hypercalcemia, hyperglycemia and hypernatremia.

The most clinically significant laboratory abnormalities based on mechanism of action and grade appear to be changes related to liver toxicity (high AST and ALT) and mineralocorticoid excess (hypokalemia) which are labeled adverse reactions for AA. Interestingly, high ALT occurred more commonly in the chemotherapy naive population of trial -302 compared with trial -301 (42% vs. 11%). Grade 3 or higher ALT was also higher, occurring in 6% of patients taking AA in the -302 trial compared with 1.4% of -301 patients. This may be due to the longer period of treatment exposure seen in the chemotherapy naive trial -302 or may be due to differences in the laboratory analysis conducted for the two trials. Laboratory assessments were performed more frequently in the -302 trial and the -302 trial had more stringent eligibility requirements for baseline AST/ALT.

While increased glucose occurred more commonly on the AA arm, grade 3-4 hyperglycemia was seen in approximately equal rates in both arms and is likely attributed to concomitant prednisone use. There were no treatment discontinuations or deaths due to hyperglycemia.

Reviewer Comment:
Hypokalemia and elevation of hepatic transaminases continue to be seen at a higher rate in patients treated with AA compared with placebo. For labeling purposes, a threshold of grade 1-4 laboratory abnormality incidence >5% occurring in AA compared with placebo will be used to select adverse laboratory findings more likely to be attributed to treatment with AA for labeling purposes for COU-AA-302.

7.4.2 Vital Signs

Vital sign data including systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate and temperature were collected from trial COU-AA-302. The applicant's analysis was reviewed from the study report. Baseline vital signs appeared to be well-balanced between the arms. Vital sign findings were similar between AA and placebo with the exception of blood pressure findings. Heart rate >120bpm with >30 bpm increase from baseline occurred in only 4 patients on each arm. Hypertension appeared to be predominantly systolic based on vital sign findings. Systolic blood pressure >170mmHg with >40mmHg increase from baseline occurred at a higher rate in the AA arm (9%) when compared with placebo (4%) whereas diastolic blood pressure >100mmHg with >30mmHg increase from baseline occurred in only 6 patients on the AA arm and 8 patients on placebo. The increase in systolic blood pressure noted in the vital sign analysis is consistent with the increase in hypertension noted in the adverse event reporting and is adequately reflected in labeling.

7.4.3 Electrocardiograms (ECGs)

Three studies have formally assessed the affect of AA on QTc including one formal QT study (COU-AA-006). None of the studies has shown an effect of abiraterone acetate on QTc prolongation. Section 12.6 of the FDA label states,

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

Study COU-AA-302 obtained ECGs pre-dose and 2 hours post-dose at cycles 1, 2 and 5. The study was not intended as a controlled QTc study. It is noted that QTcF prolongation >30ms occurred in 16% of patients taking AA compared with 10% taking placebo. QTcF prolongation >60ms occurred in 6% of patients taking AA compared with 4% taking placebo. QTcF >450ms occurred in 27% vs. 20% in AA and placebo respectively.

Reviewer Comment: The COU-AA-302 study was not intended as a controlled QTc study and has multiple limitations with respect to interpretation of QTc results. The increases in QTc

prolongation seen in AA compared with placebo are difficult to interpret. The current labeling based on the more controlled QTc studies is thought to be appropriate.

7.5.1 Dose Dependency for Adverse Events

All patients received 1,000mg per day of abiraterone acetate with dose reduction permitted to 750mg and 500mg per day based on toxicity.

7.5.2 Time Dependency for Adverse Events

Dose Modification for Patients with Elevated ALT:
The COU-AA-302 protocol specified dose interruption for grade 3 or higher AST or ALT elevation. If the level resolved to grade 1 or less, the investigator was to resume dosing at the first reduced dose level (750mg per day). A second dose reduction to 500mg per day was allowed.

Dose modifications for ALT elevation were reviewed. There were 44 episodes of grade 3-4 ALT elevation occurring in 33 patients.

- Median day of onset for the first elevation was day 43 (range 15-533).
- Twenty nine of 33 (88%) of patients had elevated ALT prior to day 90.
- Ten of the 33 patients **discontinued** treatment.
- Ten patients had **one dose interruption.**
- Twelve patients had **two dose interruptions**.
- Median time to resolution to grade 1 ALT was 13 days. (range 1-99)

7.5.3 Drug-Demographic Interactions

Key safety findings were summarized by age group by the applicant and are presented in Table 63 below. Treatment emergent grade 3-4 AEs, SAEs and AEs leading to drug discontinuation all increase with the age group of the treatment subjects. Importantly, treatment emergent adverse events leading to death considered drug-related by the investigators did not increase substantially with age group.

Table 63: Key Safety Data by Age Group in COU-AA-302

	COU-AA-302					
	AA			Placebo		
	Age<65 (N=135)	Age 65-74 (N=225)	Age>=75 (N=182)	Age<65 (N=154)	Age 65-74 (N=222)	
Treatment-Emergent Adverse Events (TEAEs) [a]	133 (98.5%)	222 (98.7%)	182 (100.0%)	147 (95.5%)	214 (96.4%)	1
Drug-related [b]	107 (79.3%)	176 (78.2%)	141 (77.5%)	114 (74.0%)	166 (74.8%)	1
Grade 3-4 TEAEs	53 (39.3%)	104 (46.2%)	101 (55.5%)	53 (34.4%)	85 (38.3%)	
Drug-related [b]	19 (14.1%)	54 (24.0%)	49 (26.9%)	22 (14.3%)	32 (14.4%)	
Serious TEAEs [a]	36 (26.7%)	63 (28.0%)	79 (43.4%)	30 (19.5%)	47 (21.2%)	
Drug-related [b]	9 (6.7%)	23 (10.2%)	27 (14.8%)	11 (7.1%)	19 (8.6%)	
Grade 3-4	32 (23.7%)	51 (22.7%)	67 (36.8%)	20 (13.0%)	40 (18.0%)	
Drug-related Grade 3-4 [b]	9 (6.7%)	19 (8.4%)	25 (13.7%)	9 (5.8%)	14 (6.3%)	
TEAEs Leading to Treatment Discontinuation [c]	8 (5.9%)	18 (8.0%)	29 (15.9%)	5 (3.2%)	19 (8.6%)	
Drug-related [b]	3 (2.2%)	9 (4.0%)	17 (9.3%)	4 (2.6%)	10 (4.5%)	
TEAEs Leading to Death	2 (1.5%)	5 (2.2%)	13 (7.1%)	1 (0.6%)	3 (1.4%)	
Drug-related [b]	1 (0.7%)	2 (0.9%)	2 (1.1%)	1 (0.6%)	2 (0.9%)	
All deaths within 30 days of last dose	1 (0.7%)	6 (2.7%)	11 (6.0%)	1 (0.6%)	2 (0.9%)	
Underlying Disease	1 (0.7%)	2 (0.9%)	4 (2.2%)	0	1 (0.5%)	
Other	0	4 (1.8%)	6 (3.3%)	1 (0.6%)	1 (0.5%)	
Unknown	0	0	1 (0.5%)	0	0	

[a] Grade 5 event is not included.
[b] Adverse events reported to be unlikely related, possibly related, or related to AA/Placebo or Prednisone/Prednisolone are classified as drug-rela
events with missing relationship are considered as drug-related AEs.
[c] Discontinuation of study medication includes discontinuation of AA/Placebo and/or Prednisone/Prednisolone or both.
PROD\RE534 [AE01A.SAS], 16MAR2012 20:02

Source: Applicant integrated safety summary. Data verified by the clinical reviewer.

Reviewer Comment: Adverse events occur more frequently in both the AA and placebo arm for patients ≥75 compared with patients <65. While drug-related adverse events are reported in a higher percentage of elderly patients, deaths due to TEAEs considered drug-related by the investigator do not increase substantially. Elderly patients are typically at higher risk for adverse events in general and the reviewer considers the overall risk:benefit of AA favorable in elderly patients with prostate cancer. This conclusion is supported by the subgroup analysis of overall survival for which the most favorable hazard ratio belongs to the subgroup of patients >=75 years of age (Figure 20).

7.6.1 Human Carcinogenicity

Adverse events in system organ class "neoplasms, benign, malignant and unspecified" occurred in 54 patients (10%) in the AA arm compared with 54 (10%) in the placebo arm. The most common adverse event in this SOC was cancer pain in 14 patients in AA and 18 in placebo. There were 4 cases of malignant melanoma in AA compared with 0 in the placebo arm. The incidence of new solid tumor malignancies overall were well-balanced between the arms.

Table 64: Neoplastic adverse events in COU-AA-302

	AA N=542	Placebo N=540
Squamous/Basal Cell/Skin Cancer	20	11
New Solid Tumor Malignancy	12	10
Hematologic Malignancy	1	1

Source: dataset [AE]. Cancer pain and adverse events not consistent with new secondary malignancy were excluded (colon adenomas, metastatic pain, cancer pain, etc.)

Melanoma:
The applicant notes in their summary of clinical safety that of the total of 6 melanomas seen in the integrated safety database, 2 patients had a history of melanoma and 1 a history of basal cell carcinoma. A fourth subject had a history of "scattered lesions on skin/body". A review of the post-marketing adverse event reporting system was performed using the Empirica tool and there were no reports of melanoma listed in 774 post-marketing reports submitted from both the U.S. and foreign sources.

Reviewer Comment: The development of slightly more skin cancers in the AA arm is confounded by the increased time on study and the age of the population. There is no clear biologic rationale for increased risk of malignancy through AA mechanism of action. There have been no findings in the non-clinical program that would suggest an increased risk of carcinogenicity. The post-marketing safety data does not contain any cases of malignant melanoma. It is the reviewer's determination that there is insufficient data to conclude that abiraterone acetate use results in an increase risk of malignant melanoma or other malignant tumors.

7.6.2 Human Reproduction and Pregnancy Data

There are no human data on the use of abiraterone in pregnancy and this medication is intended currently for men with prostate cancer. Nonclinical studies abiraterone did have effects on pregnancy and the applicant recommends contraception with a condom along with another effective contraception method for men engaging in sexual activity as it is not known whether abiraterone or its metabolites are present in semen.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is no evidence to suggest AA has the potential for addiction or abuse. There are no reported cases of overdose in the clinical trial database. The applicant notes a medically confirmed case of a 66 year old who self-administered abiraterone acetate 1,000mg twice daily for 3 days with adverse events of hypokalemia, asthenia, nausea and vomiting. No studies have been performed to specifically assess withdrawal or rebound effects.

7.7 Additional Submissions / Safety Issues

120-day Safety Update:
The 120 day safety update was received and reviewed. The clinical data cutoff for the primary submission was 12/20/2011. The data cutoff for the 120 day safety update is 5/22/2012 providing

an additional 5 months of drug exposure. Between the time of sNDA submission and the 4-month update there were 3 additional placebo patients with a death within 30 days of the last dose of study treatment and none on the AA arm. Narratives for deaths and serious adverse events were reviewed.

Table 65: Overall safety profile for 4-month Safety Update

	sNDA		Safety Update	
	AA (N=542)	Placebo (N=540)	AA (N=542)	Placebo (N=540)
Number of Subjects with Treatment-Emergent Adverse Events[a]	537 (99.1%)	524 (97.0%)	538 (99.3%)	524 (97.0%)
Drug-related[b]	424 (78.2%)	413 (76.5%)	426 (78.6%)	414 (76.7%)
Number of Subjects with Grade 3-4 Treatment-Emergent Adverse Events	258 (47.6%)	225 (41.7%)	267 (49.3%)	235 (43.5%)
Drug-related[b]	122 (22.5%)	91 (16.9%)	127 (23.4%)	97 (18.0%)
Number of Subjects with Treatment-Emergent Serious Adverse Events[a]	178 (32.8%)	142 (26.3%)	188 (34.7%)	146 (27.0%)
Drug-related[b]	59 (10.9%)	54 (10.0%)	63 (11.6%)	55 (10.2%)
Grade 3-4	150 (27.7%)	117 (21.7%)	156 (28.8%)	123 (22.8%)
Number of Subjects with Treatment-Emergent Adverse Events Leading to Treatment Discontinuation[c]	55 (10.1%)	49 (9.1%)	58 (10.7%)	53 (9.8%)
Drug-related[b]	29 (5.4%)	23 (4.3%)	32 (5.9%)	24 (4.4%)
Number of Subjects with Treatment-Emergent Adverse Events Leading to Death	20 (3.7%)	12 (2.2%)	21 (3.9%)	16 (3.0%)
Drug-related[b]	5 (0.9%)	4 (0.7%)	6 (1.1%)	6 (1.1%)
All Deaths Within 30 Days of Last Dose	18 (3.3%)	8 (1.5%)	18 (3.3%)	11 (2.0%)
Other	10 (1.8%)	4 (0.7%)	11 (2.0%)	6 (1.1%)
Death due to Prostate Cancer	7 (1.3%)	3 (0.6%)	6 (1.1%)	4 (0.7%)
Unknown	1 (0.2%)	1 (0.2%)	1 (0.2%)	1 (0.2%)

AA=abiraterone acetate
[a] Does not include Grade 5 events.
[b] Adverse events reported as unlikely, possibly, or related for AA/Placebo or Prednisone/Prednisolone or both are cla ssified as drug-related AEs.
[c] Discontinuation of study medication includes discontinuation of AA/Placebo or Prednisone/Prednisolone or both.
PROD\RE_IA3 [TAE01.SAS], 23JUL2012 11:01

Source: Applicant submission. Clinical reviewer verified several portions of the 4-mo safety update data with the datasets provided.

Reviewer Comment: No significant safety issues were found upon review of the 4-month safety update that would materially affect the review of the primary submission.

8 Postmarket Experience

Marketing approval for abiraterone acetate was granted on April 28, 2011 in the United States and since that time the applicant estimates 2,245,830 person-days of worldwide exposure. Post-marketing data were reviewed by the Office of Surveillance and Epidemiology (OSE), as well as

the clinical reviewer. In addition, an information request was sent to the applicant to specifically review their post-marketing AA database for adverse events of interest in this review including identification of any fatal liver failure cases, diarrhea, pulmonary related deaths, cardiac failure and rash events including any cases of Stevens Johnson syndrome or DRESS. The most frequently reported preferred terms in the post-marketing analysis performed by OSE is presented in Table 66 below. Based on the review of the available post-marketing safety data, there were felt to be insufficient data to warrant additional labeling changes.

Table 66: Most Frequently Reported Adverse Events in Post-Marketing OSE Analysis

Most Frequently Reported MeDRA Preferred Terms(PT)- Top 25		
Event-Preferred Terms(PTs)	**Total Cases**	**Percent of Total**
PROSTATIC SPECIFIC ANTIGEN INCREASED	49	11.75
DEATH	43	10.31
DYSPNOEA	42	10.07
OEDEMA PERIPHERAL	40	9.59
FATIGUE	39	9.35
ANAEMIA	35	8.39
PAIN	33	7.91
DRUG INEFFECTIVE	27	6.47
NAUSEA	27	6.47
HYPOKALAEMIA	26	6.24
PULMONARY EMBOLISM	26	6.24
DECREASED APPETITE	25	6
VOMITING	24	5.76
ASTHENIA	23	5.52
CONFUSIONAL STATE	23	5.52
BLOOD ALKALINE PHOSPHATASE INCREASED	21	5.04
PROSTATE CANCER	21	5.04
THROMBOCYTOPENIA	21	5.04
DISEASE PROGRESSION	19	4.56
PYREXIA	19	4.56
PROSTATE CANCER METASTATIC	18	4.32
RENAL FAILURE	18	4.32
RENAL FAILURE ACUTE	18	4.32
DIARRHOEA	17	4.08
WEIGHT DECREASED	17	4.08

Source: OSE consult review of FAERs database.

The majority of the adverse events reported above are either labeled risks of AA or frequent prostate cancer-related complications. Pulmonary embolism and thrombocytopenia are not labeled risks of AA. Both of these AEs can be side effects of prostate cancer itself. Pulmonary embolism risk was reviewed in section 7.3.5: Submission Specific Primary Safety Concerns with the conclusion that there is insufficient data to support a causal relationship. Thrombocytopenia was evaluated in the laboratory section of the safety review and occurred in 11% of patients taking AA compared with 8% in the placebo arm. Grade 3 or higher thrombocytopenia occurred in less than 1% of patients on either arm. There is insufficient evidence by randomized trial data and mechanistic / biologic plausibility to conclude that AA has a causal relationship to thrombocytopenia.

9 Appendices

9.1 Labeling Recommendations

The applicant proposed [redacted]:

Applicant's initial proposed indication:
ZYTIGA is a CYP17 inhibitor, in combination with prednisone indicated for:

- the treatment of patients with metastatic castration-resistant prostate cancer [redacted]

Based on the review of this submission, the clinical review team has recommended the following single indication:

FDA revised indication labeling recommendation:
ZYTIGA is a CYP17 inhibitor in combination with prednisone indicated for
the treatment of patients with metastatic castration-resistant prostate cancer. (1)

The full rationale and analysis providing support for the [redacted] indication which includes two populations which were excluded in COU-AA-302 trial (moderate or severe symptoms and patients with visceral metastases) is provided in the efficacy section of this review.

To summarize, the reviewer believes that the use of abiraterone acetate as a treatment for patients with moderate/severe pain or with visceral metastases prior to the use of docetaxel should be an option left up to the discretion of the treating physician. This determination is based on the following observations:

1. Anti-tumor activity results in the indicated population were robust and compare favorably with docetaxel (limitation of historical cross-trial comparisons are acknowledged).
2. Benefit in the moderate/severe pain and visceral metastases subgroups of the post-docetaxel patients treated with abiraterone acetate.
3. Generally, tumors are thought to be more responsive to treatment in earlier lines of therapy compared with more treatment refractory settings.
4. The toxicity profile of abiraterone acetate is such that patients would likely be able to receive docetaxel upon progression following treatment with abiraterone acetate.
5. Docetaxel remains an option for chemotherapy-naive metastatic CRPC patients with rapidly progressive disease or with severe pain and may be used prior to abiraterone based on the discretion of the treating physician.

9.2 Advisory Committee Meeting

The use of radiographic progression free survival (rPFS) as the sole primary efficacy endpoint meeting statistical significance has no regulatory precedence in prostate cancer approvals. For approvals using novel regulatory endpoints in a particular disease setting, an advisory committee meeting is typically held. However; as was stated in the risk:benefit determination of this review, the design of the pivotal trial included multiple measures intended to evaluate clinical benefit. Significant and consistent corroborating evidence of direct clinical benefit was provided including a strong overall survival trend and statistically significant improvements in key secondary endpoints including time to opiate use, time to ECOG decline and time to initiation of cytotoxic chemotherapy as well as supportive patient reported pain and quality of life assessments. Furthermore, AA is already commercially available and approved based on an overall survival advantage in a later stage of the same disease for which this indication is being sought. Finally, a large amount of safety data was available from both placebo controlled clinical trials as well as post-marketing data.

Taken as a whole, the review team felt confident that the application fulfilled the regulatory requirement to provide substantial evidence of safety and efficacy and an advisory committee meeting was not deemed necessary.

9.3 Additional Figures

Figure 31: ECOG Performance Scale

ECOG Grade Scale (with Karnofsky conversion)	
0	Fully active, able to carry on all pre-disease performance without restriction. (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work on a light or sedentary nature, eg., light housework, office work. (Karnofsky 70-80)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. (Karnofsky 50-60)
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours. (Karnofsky 30-40)
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. (Karnofsky 10-20)
5	Dead

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/s/

PAUL G KLUETZ
11/20/2012

VIRGINIA E MAHER
11/21/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 202379/ S005

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW

1. ORGANIZATION CDER/ONDQA Division of Post-Marketing Evaluation HFD-150	**2. NDA #** 202-379 Original NDA approved: 04/28/11
3. NAME AND ADDRESS OF APPLICANT Janssen Research & Development, LLC 920 Route 202, P.O. Box 300 Raritan, NJ 08869 On behalf of: Janssen Biotech, Inc.	**4. SUPPLEMENT** S-005 13 -JUN-2012 (Rec. 14-JUN-2012)
	5. Name of the Drug Zytiga
	6. Nonproprietary Name abiraterone acetate
7. SUPPLEMENT PROVIDES for clinical changes to the label.	**8. AMENDMENT** --

9. PHARMACOLOGICAL CATEGORY Metastatic advanced prostate cancer	**10. HOW DISPENSED** Rx	**11. RELATED**
12. DOSAGE FORM IR Tablets	**13. POTENCY** 250 mg	

14. CHEMICAL NAME AND STRUCTURE See previous CMC reviews.
(3β)-17-(3-pyridinyl)androsta-5,16-dien-3-yl acetate

15. COMMENTS This application is submitted as a PA Supplement (SDN 145, eCTD0056; SND 162, eCTD0061 7/16/2012). The original labeling for Zytiga was approved on 28 April 2011. The Applicant seeks approval of Zytiga 250 mg tablets, in combination with prednisone, for the treatment of patients with metastatic castration-resistant prostate cancer (b) (4) (b) (4) Cross reference is made to the previously approved CMC content of NDA 202-379. The categorical exclusion (21 CFR 25.31 [b]) from the requirements to prepare an environmental assessment is granted.

16. CONCLUSIONS AND RECOMMENDATIONS The CMC sections of the proposed label that were reviewed are the Highlights of Prescribing Information and Full Prescribing Information (Section 3 Dosage Form and Strengths, Section 11 Description, Section 16 How Supplied/Storage and Handling). The labeling was provided as an annotated ('tracked') and proposed ('clean') version. In the Description section, the inactive ingredients have been re-ordered alphabetically according to USP 1 May 2012 USP 35/NF30, <1091> Labeling of Inactive Ingredients. No CMC changes are proposed to the container label. From a CMC perspective, this Supplement can be Approved. OND will issue the Action Letter.

17. REVIEWER NAME (AND SIGNATURE) Sharon Kelly, PhD
DATE COMPLETED 21-AUG-2012
R/D INITIALED BY
filename: 202-379#05 NDA

DISTRIBUTION: Original: NDA 202-379#05 cc: Division File CSO Reviewer

1 Pages(s) of Draft Labeling has been Withheld in Full as b4 (CCI/ TS) immediately following this page.

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/s/

SHARON L KELLY
08/21/2012

HASMUKH B PATEL
08/21/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 202379/ S005

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	202379/S-005
Supporting document/s:	145
Submission date:	6/13/12
Received date:	6/14/12
Product:	Abiraterone Acetate; Zytiga™
Indication:	treatment of patients with metastatic castration-resistant prostate cancer
Applicant:	Janssen Research & Development Raritan, NJ
Review Division:	DHOT (for DOP1)
Reviewer:	Kimberly Ringgold, PhD
Acting Supervisor:	Todd Palmby, PhD
Division Director:	John Leighton, PhD, DABT (DHOT) Robert Justice, MD (DOP1)
Project Manager:	Amy Tilley

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

This efficacy supplement was submitted by the Applicant in an effort to change the indicated population to include patients with metastatic castration-resistant prostate cancer who have not yet received treatment with docetaxel based on new clinical data included in the submission. The Applicant submitted a number of nonclinical study reports to the NDA with this supplement, which included reports for embryo-fetal developmental toxicity studies, nonclinical reproductive and fertility studies and genetic toxicity studies conducted with impurities. These studies were not requested by FDA to support approval of this efficacy supplement. Rather, the Applicant stated that these studies were complementary to the previous nonclinical toxicology package with abiraterone acetate, and support other indications that are being pursued by the Applicant in clinical trials.

1.2 Brief Discussion of Nonclinical Findings

When administered orally to male rats once daily for 28 days, fertility index was reduced in males at 300 mg/kg/day abiraterone acetate. Abiraterone acetate administration also resulted in small size of the reproductive organs, reduced sperm count and motility, and increased sperm morphological abnormalities. Evaluation of untreated females that were mated with treated males showed a decrease in live fetus per pregnant animal at ≥ 30 mg/kg/day, which is related to increased pre- and post-implantation losses. Abiraterone acetate administration to females daily starting 2-weeks prior to mating until day 7 of pregnancy resulted in no differences in mating, fertility, and litter parameters in female rats that received abiraterone acetate. Reduced bodyweight gain during was noted at ≥ 30 mg/kg. There was a dose-dependent increase in irregular and extended cycles and in pre-implantation loss in female rats.

In an embryo-fetal developmental toxicity study in rats, developmental toxicity occurred with abiraterone acetate administration during gestation at doses ≥ 10 mg/kg/day as was evident by embryo-fetal lethality and fetal developmental delay. Fetal ano-genital distance was decreased in males at ≥ 30 mg/kg. No NOAEL was established in the fertility or embryofetal development studies.

(b) (4) is a potential synthesis impurity that was not previously characterized under the original NDA approval in 2011. Under the conditions tested, (b) (4) does not have mutagenic potential.

1.3 Recommendations

1.3.1 Approvability

There is nothing in the nonclinical studies submitted to this efficacy supplement that preclude the approval of abiraterone acetate for the proposed indication of treatment of patients with metastatic castration-resistant prostate cancer.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

The sections in the current FDA approved package insert for Zytiga that can contain nonclinical data and that were revised during the review of this efficacy supplement are as follows:

4 CONTRAINDICATIONS
4.1 Pregnancy
ZYTIGA may cause fetal harm when administered to a pregnant woman. ZYTIGA is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Pregnancy Category X [see Contraindications (4.1)].
ZYTIGA is contraindicated in women who are or may become pregnant while receiving the drug. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus and the potential risk for pregnancy loss. Women of childbearing potential should be advised to avoid becoming pregnant during treatment with ZYTIGA.

8.4 Pediatric Use
ZYTIGA is not indicated in children.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility
Long-term animal studies have not been conducted to evaluate the carcinogenic potential of abiraterone acetate.

Abiraterone acetate and abiraterone did not induce mutations in the microbial mutagenesis (Ames) assay and was not clastogenic in both the in vitro cytogenetic assay using primary human lymphocytes and in the in vivo rat micronucleus assay.

Developmental or reproductive toxicology studies were not conducted with abiraterone acetate. In studies in rats (13-and 26-weeks) and monkeys (39-weeks), atrophy, aspermia/hypospermia, and hyperplasia in the reproductive system were observed at ≥50 mg/kg/day in rats and ≥250 mg/kg/day in monkeys and were consistent with the antiandrogenic pharmacological activity of abiraterone [see Nonclinical Toxicology (13.2.)]. These effects were observed in rats and monkeys at approximately 1.14 and 0.6-fold greater than the human clinical exposure based on AUC, respectively.

13.2 Animal Toxicology and/or Pharmacology

In 13- and 26-week studies in rats and 13- and 39-week studies in monkeys, a reduction in circulating testosterone levels occurred with abiraterone acetate at approximately one half the human clinical exposure based on AUC. As a result, decreases in organ weights and toxicities were observed in the male and female reproductive system, adrenal glands, liver, pituitary (rats only), and male mammary glands. The changes in the reproductive organs are consistent with the antiandrogenic pharmacological activity of abiraterone acetate. A dose-dependent increase in cataracts was observed in rats at 26 weeks starting at ≥50 mg/kg/day (1.14-fold greater than the human clinical exposure based on AUC). In the 39-week monkey study, no cataracts were observed at higher doses (2-fold greater than the clinical exposure based on AUC). All other toxicities associated with abiraterone acetate reversed or were partially resolved after a 4-week recovery period.

The revised version of sections 4.1, 8.1, 8.4, 13.1 and 13.2 for the Zytiga package insert to incorporate the results of the fertility and embryo-fetal developmental toxicology studies and to comply with 21 CFR 201.57 is as follows:

4 CONTRAINDICATIONS

4.1 Pregnancy

ZYTIGA can cause fetal harm when administered to a pregnant woman. ZYTIGA is not indicated for use in women. ZYTIGA is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss *[see Use in Specific Populations (8.1)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X *[see Contraindications (4.1)].*

ZYTIGA can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. While there are no adequate and well-controlled studies with ZYTIGA in pregnant women and ZYTIGA is not indicated for use in women, it is important to know that maternal use of a CYP17

inhibitor could affect development of the fetus. Abiraterone acetate caused developmental toxicity in pregnant rats at exposures that were lower than in patients receiving the recommended dose. ZYTIGA is contraindicated in women who are or may become pregnant while receiving the drug. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss. Advise females of reproductive potential to avoid becoming pregnant during treatment with ZYTIGA.

In an embryo-fetal developmental toxicity study in rats, abiraterone acetate caused developmental toxicity when administered at oral doses of 10, 30 or 100 mg/kg/day throughout the period of organogenesis (gestational days 6-17). Findings included embryo-fetal lethality (increased post implantation loss and resorptions and decreased number of live fetuses), fetal developmental delay (skeletal effects) and urogenital effects (bilateral ureter dilation) at doses ≥10 mg/kg/day, decreased fetal ano-genital distance at ≥30 mg/kg/day, and decreased fetal body weight at 100 mg/kg/day. Doses ≥10 mg/kg/day caused maternal toxicity. The doses tested in rats resulted in systemic exposures (AUC) approximately 0.03, 0.1 and 0.3 times, respectively, the AUC in patients.

8.4 Pediatric Use

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of abiraterone acetate.

Abiraterone acetate and abiraterone did not induce mutations in the microbial mutagenesis (Ames) assay and was not clastogenic in both the *in vitro* cytogenetic assay using primary human lymphocytes and in the *in vivo* rat micronucleus assay.

ZYTIGA has the potential to impair reproductive function and fertility in humans based on findings in animals. In repeat-dose toxicity studies in male rats (13- and 26-weeks) and monkeys (39-weeks), atrophy, aspermia/hypospermia, and hyperplasia in the reproductive system were observed at ≥ 50 mg/kg/day in rats and ≥ 250 mg/kg/day in monkeys and were consistent with the antiandrogenic pharmacological activity of abiraterone [*see Nonclinical Toxicology (13.2.)*]. These effects were observed in rats at systemic exposures similar to humans and in monkeys at exposures approximately 0.6 times the AUC in humans.

In fertility studies in rats, reduced organ weights of the reproductive system, sperm counts, sperm motility, altered sperm morphology and decreased fertility were observed in males dosed for 4 weeks at ≥ 30 mg/kg/day. Mating of

untreated females with males that received 30 mg/kg/day abiraterone acetate resulted in a reduced number of corpora lutea, implantations and live embryos and an increased incidence of pre-implantation loss. Effects on male rats were reversible after 16 weeks from the last abiraterone acetate administration. Female rats dosed for 2 weeks until day 7 of pregnancy at ≥ 30 mg/kg/day had an increased incidence of irregular or extended estrous cycles and pre-implantation loss (300 mg/kg/day). There were no differences in mating, fertility, and litter parameters in female rats that received abiraterone acetate. Effects on female rats were reversible after 4 weeks from the last abiraterone acetate administration. The dose of 30 mg/kg/day in rats is approximately 0.3 times the recommended dose of 1000 mg/day based on body surface area.

13.2 Animal Toxicology and/or Pharmacology

In 13- and 26-week studies in rats and 13- and 39-week studies in monkeys, a reduction in circulating testosterone levels occurred with abiraterone acetate at approximately one half the human clinical exposure based on AUC. As a result, decreases in organ weights and toxicities were observed in the male and female reproductive system, adrenal glands, liver, pituitary (rats only), and male mammary glands. The changes in the reproductive organs are consistent with the antiandrogenic pharmacological activity of abiraterone acetate. A dose-dependent increase in cataracts was observed in rats at 26 weeks starting at ≥50 mg/kg/day (similar to the clinical exposure based on AUC). In the 39-week monkey study, no cataracts were observed at higher doses (2 times the clinical exposure based on AUC). All other toxicities associated with abiraterone acetate reversed or were partially resolved after a 4-week recovery period.

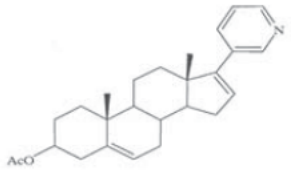
The clinical steady-state AUC value in patients receiving 1,000 mg abiraterone acetate daily that was used to calculate the exposure multiple in animals compared to humans was 1173 ng*hr/mL.

2 Drug Information

2.1 Drug

Trade name: Zytiga™
Generic Name: abiraterone acetate
Code Name: CB7630; JNJ-212082-AAA
Chemical Name: 3β-Acetoxy-17-(3-pyridyl) androsta-5, 16-diene
CAS Name: 154229-18-2
Molecular Formula/Molecular Weight: $C_{26}H_{33}NO_2$/391.5 g/mol

Structure:



Pharmacologic class: CYP17 inhibitor

2.2 Relevant IND/s, NDA/s, and DMF/s

NDA 202379

2.3 Clinical Formulation

2.3.1 Drug Formulation: supplied in white to off-white tablets containing 250 mg abiraterone acetate

Composition of Abiraterone Acetate 250-mg Tablet (Formulation JNJ-212082-AAA-G-002)

Component	Reference to Quality Standard[a]	Function	mg/tablet
Abiraterone Acetate	(b) (4)	Active	250.00
Lactose Monohydrate			(b) (4)
Microcrystalline Cellulose			
Croscarmellose Sodium			
Povidone (b) (4)			
Sodium Lauryl Sulfate			
Colloidal Silicon Dioxide			
Magnesium Stearate			
(b) (4)			
Total Tablet Weight:			(b) (4)

2.4 Comments on Novel Excipients

none

2.5 Comments on Impurities/Degradants of Concern

The following information requests were sent to the Applicant regarding reports for impurity qualification studies (TOX9749, TOX9744 and TOX9780) that were submitted with this supplemental NDA:

1. FDA COMMENT 1

Please provide clarification as to the purpose of the impurity qualification studies TOX9749, TOX9744 and TOX9780 that were submitted as final study reports on June 14, 2012, with your efficacy supplement-5. It is unclear if there was a proposed change in manufacturing or specifications that prompted conducting these studies since the current specifications appear to be the same as those proposed in the original NDA, which were acceptable based on data in the original NDA submission.

The Applicant replied that there was no change in manufacturing or specifications, and that these studies were conducted to complement the toxicological qualification of these impurities. The levels of these impurities were acceptable during review of the original NDA submission. Since no additional changes were made to the specifications for the drug substance or drug product, the levels remain acceptable.

2. FDA COMMENT 2
To understand the significance of TOX9780, as the Specification for Drug substance and Drug product do not have a limit set for (b) (4) please provide clarification regarding the structure and origin of impurity (b) (4) and why limits were not included in the specifications. Alternatively, please provide a reference to earlier NDA submissions that may have this information.

The Applicant clarified that (b) (4) is a potential drug substance impurity that might originate from (b) (4) This impurity was not detected in batches of active pharmaceutical ingredient (API). The genotoxic potential of (b) (4) was tested in an *in vitro* bacterial reverse mutation (Ames) assay, the results of which were submitted in the current supplemental NDA. Under the conditions tested, (b) (4) was not mutagenic in an Ames assay (see review of this study report in section 7). Since this impurity was not mutagenic in an Ames assay, there was no specification included in the drug substance or drug product to control this impurity. The current specifications, including "Each Unspecified Impurity" of (b) (4) in the drug substance, are acceptable to control the levels of this impurity.

2.6 Proposed Clinical Population and Dosing Regimen

ZYTIGA® in Combination with Prednisone for the Treatment of Patients with Metastatic Castration-Resistant Prostate Cancer

- The recommended dose of abiraterone acetate is 1,000 mg administered as four 250 mg tablets or 4 placebo tablets orally once daily and prednisone or prednisolone 5 mg orally twice daily.

2.7 Regulatory Background

Zytiga was FDA approved in 2011 for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC) in patients who have received prior chemotherapy containing docetaxel.

3 Studies Submitted

3.1 Studies Reviewed

Study Title	Study No.
Genotoxicity	
In Vitro Bacterial Reverse Mutation Test with [redacted] (b) (4) n *Salmonella typhimurium*	TOX9780
Reproductive and Developmental Toxicity	
Oral Fertility Study of JNJ-212082-AAA in the Male Rat	TOX10095
Oral Fertility Study of JNJ-212082-AAA in the Female Rat	TOX10096
Pilot Oral Developmental Toxicity Study in the Rat	TOX10066
Oral Developmental Toxicity Study of JNJ-212082-AAA in the Rat	TOX10115

3.2 Studies Not Reviewed

Study Title	Study No.
Pharmacokinetics	
Validation of a Method for the Determination of Abiraterone and Abiraterone Acetate in Mouse Plasma Samples	BA1729
Pharmacokinetics and relative bioavailability of abiraterone JNJ-589485 in male beagle dogs after single oral administration at 50 mg/kg of 4 different formulations of JNJ-212082-AAA.	FK7653
Pharmacokinetics and exposure of abiraterone (JNJ-47838830) and abiraterone acetate (JNJ-212082) in male beagle dogs after single oral administration at 25, 50 mg/kg or at 250, 500 mg/dog or single intravenous administration at 5 mg/kg of different formulations of JNJ-212082	FK10014
Pharmacokinetics and relative bioavailability of abiraterone in male beagle dogs after single oral administration of a microsuspension (50 mg/kg), a nanosuspension (44.6 mg/kg) or after single intravenous administration of a SBE-□-CD formulation (5 mg/kg) of JNJ-47838830-AAA.	FK10060
Pharmacokinetics, food effect and relative bioavailability of abiraterone in male beagle dogs after single oral administration of different formulations of abiraterone acetate at 25 mg/kg, 250 mg/dog or 500 mg/dog or after intravenous administration of abiraterone or abiraterone acetate at 5 mg/kg.	FK10118
Comparison of the exposure of selected metabolites of JNJ-212082 (abiraterone acetate) between human and animal species used for safety evaluation of JN-212082.	BA1732
Pharmacokinetics of abiraterone acetate and abiraterone in portal vein catheterized male CEDS beagle dogs after single oral administration of a 20% HP-□-CD solution of abiraterone acetate (JNJ-212082-AAA) at 10 mg/kg (fasted) and 25 mg/kg (fed/fasted)	FK10121

An *In Vitro* Investigation of the Potential of Abiraterone Acetate and Abiraterone to Inhibit CYP2B6 and CYP2C19 in Human Liver Microsomes	FK10147
Toxicology	
28-Day Repeated Dose Oral Toxicity and Toxicokinetic Study in CByB6F1 Mice	TOX9688
Abiraterone Acetate (JNJ-212082-AAA): Preliminary Juvenile Toxicity Study in the Crl:CD(SD) Rat by Oral Gavage Administration	TOX10036
2-Week repeated dose study (hormone profiling) of JNJ-212082-AAA in the rat.	TOX10066
1-month Repeated Dose Oral Toxicity Study of JNJ-212082-AAA in the Rat (Impurity Qualification).	TOX9744
In Vitro Mammalian Chromosome Aberration Test with JNJ-212082-AAA spiked with 2.6% JNJ-47838804-AAA in Human Lymphocytes	TOX9749

3.3 Previous Reviews Referenced

Non-clinical reviews under NDA 202379

4 Pharmacology

Abiraterone acetate belongs to a class of CYP17 inhibitors. This classification captures the inhibitory activity of abiraterone towards CYP17 which has both 17-α hydroxylase and C17, 20 lyase activities. CYP17 is a key enzyme in the production of androgens. Pharmacology studies were reviewed under NDA 202379.

5 Pharmacokinetics/ADME/Toxicokinetics

Studies reviewed under NDA 202379.

6 General Toxicology

Studies reviewed under NDA 202379

7 Genetic Toxicology

Studies have been performed with abiraterone acetate using bacterial and mammalian systems. These studies provided no evidence of mutagenic or clastogenic potential. See information available in the approved package insert and nonclinical reviews under NDA 202379.

Study title *In Vitro* Bacterial Reverse Mutation Test with (b) (4) in *Salmonella typhimurium*
Study report No: TOX9780
Testing Laboratory: Drug Safety Sciences; B-2340 Beerse, Belgium
Date of study initiation: 11 Oct 2010
Date of study report: 18 Nov 2010
GLP Compliance: Statements included and signed
QA-report: Statements included and signed
Drug Batch No.: tvanhoeg-07-040-1

Key Findings: (b) (4) was negative in this Ames Test under the conditions tested.

Methods:

(b) (4)

(b) (4)

(b) (4)

Results:

Study validation: The positive controls significantly increased the number of colonies compared to the solvent controls indicating the capacity of the system to indentify mutagens.

Study outcome: (b) (4) did not significantly increase the number of colonies as compared to the vehicle control (b) (4). The results were summarized in the following tables.

(b) (4)

(b) (4)

(tables excerpted from Applicant's submission)

8 Carcinogenicity

Due to the indication, long-term animal studies have not been conducted to evaluate the carcinogenic potential of abiraterone acetate.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study title: Oral Fertility Study of JNJ-212082-AAA in the male rat

Study no.:	TOX10095
Study report location:	eCTD 4.2.3.5.1
Conducting laboratory and location:	Drug Safety Sciences B-2340 Beerse, Belgium
Date of study initiation:	05 May 2011
GLP compliance:	Statement included and signed
QA statement:	Statement included and signed
Drug, lot #, and % purity:	JNJ-212082-AAA, Lot # ZR102164PUA071, 100%

Key Study Findings:

- Fertility index was reduced in males at the abiraterone 300 mg/kg dose.
- Small male reproductive organs were noted at both dose levels with reduced epididymides and testis weights
- Sperm count and motility were reduced by 99% and 98% at 300 mg/kg, respectively
- Increased morphological abnormalities in sperm were evident at 300 mg/kg of abiraterone (6-fold greater than control)
- In females mated with treated males, there was a decrease in live fetuses per pregnant animal at 30 mg/kg, which appears to be due to increased pre- and post- implantation loss
- A NOAEL was not established

Methods

Route of administration:	Oral (gavage)
Formulation/Vehicle:	0.5% (w/v) Methocel A4M (methylcellulose 4000 mPa.s), 0.1% (w/v) Tween 80 in demineralized water (aqueous suspension)
Species/Strain:	Rat, Sprague-Dawley
Age:	56 – 63 days old
Weight:	320 – 372 g (males);
Frequency:	Once daily for 28 days. Recovery period for 8 and 16 weeks.
Study Design:	Male rats were dosed by oral gavage at doses of 0, 30, or 300 mg/kg/day. The first subset of animals (subset I) were euthanized after 4 weeks of treatment without pairing and sperm quality was assessed. The second and third

subset of males (subsets II and III) were dosed throughout the pre-pairing and initial pairing periods and allowed a recovery of 8 or 16 weeks, respectively, before pairing for a second time with untreated females, and/or euthanized and sperm quality assessed. The pre-coital interval was noted and the untreated females were sacrificed on Day 14 of pregnancy for evaluation of pregnancy status.

(Excerpted from sponsor)

Table 1: Dosage group assignment

Parameter		V Vehicle (blue)	L Low (red)	H High (green)
Dose level (mg/kg/day)		0	30	300
Concentration (mg/ml)		0	3	30
Dose volume (ml/kg/day)		10	10	10
Male Numbers	Subset I	1 - 12	41 - 52	81 - 92
	Subset II	13 - 24	53 - 64	93 - 104
	Subset III	25 - 36	65 - 76	105 - 116
Female Numbers	Subset II+III	201 - 224	261 - 284	321 - 344
	Subset II	225 - 236	285 - 296	345 - 356

Observations and Results

Mortality

Animals were checked at least once daily. No drug-related mortalities observed

Clinical Signs

Males			
	Incidence		
Dose (mg/kg)	0	30	300

No. animals	36	36	36
3 to 5 copulation plugs	20	11	6**
Plug in female	9	6	5
Aggression	12	0***	0***

**: statistically significant from controls $p \leq 0.01$; ***: $p \leq 0.001$

Bodyweight

Animals were checked daily during dosing and weekly during recovery

Mean bodyweights compared to vehicle controls

	Dosage Group (mg / kg) Males			
Week/Day	Vehicle	Low:30	High:300	
0 / 0	351 (1.7)	349 (2.1)	353 (1.8)	
1 / 7	386 (3.3)	379 (3.5)	370 (2.5)	***
2 / 14	419 (4.7)	415 (4.5)	400 (3.2)	***
3 / 21	443 (5.6)	441 (4.8)	417 (4.0)	***
4 / 28	462 (6.4)	461 (5.9)	434 (4.2)	***

***: Statistically significant compared to controls $p \leq 0.001$

Mean bodyweight gain compared to vehicle controls

Week/Day	Dosage Group (mg / kg) Males Vehicle	Low:30	High:300
1 / 7	36 (2.2)	30 * (1.9)	17 *** (1.6)
2 / 14	69 (3.7)	66 (2.8)	47 *** (2.4)
3 / 21	93 (4.7)	92 (3.2)	65 *** (3.2)
4 / 28	111 (5.6)	112 (4.4)	81 *** (3.5)

*: Statistically significant compared to controls $p \leq 0.05$; ***: $p \leq 0.001$

(Excerpted from Applicant's submission)

Food Consumption

Unremarkable

Fertility Data

Males			
	Incidence		
Dose (mg/kg)	0	30	300
# of pregnant females	24/24	22/24	-
No sperm found	0/24	2/24	17/24
No. Mated	24	22	7
No. corpora lutea	17.4	15.9	-
No. of implantations/pregnant	16.2	14.2**	-
Pre-implantation loss (%)	6.06	11.22*	-
Total resorptions/pregnant animal	0.77	1	-
Post-implantation loss (%)	4.94	7.25	-
No of live fetus/pregnant animal	15.4	13.2***	-

*: statistically significant compared to controls $p \leq 0.05$; **: $p \leq 0.01$; ***: $p \leq 0.001$

Organ Weights

Samples were taken at scheduled necropsy. Unremarkable findings for recovery animals at 8 & 16 weeks.

Relative to Bodyweight	Male		
	Control	% change from control	
Dose (mg/kg)	0	30	300
No. animals	12	12	12
Epididymides-L	0.13875	↓20*	↓59**
Epididymides-R	0.13620	↓20*	↓60**
Testis-L	0.34606	↓15*	↓29**
Testis-R	0.35162	↓16**	↓27**

*: statistically significant compared to controls $p \leq 0.05$; **: $p \leq 0.01$

Gross Pathology

Samples were taken at scheduled necropsy. Unremarkable findings for recovery animals at 16 weeks.

Macroscopic Findings-Terminal		Males			Females		
		Incidences			Incidences		
Dose (mg/kg)		0	30	300	0	30	300
No. animals		12	12	12	24	24	24
Coagulating glands	Small	-	8	12	-	-	-
Epididymides	Small	-	8	12	-	-	-
Liver	Discoloration	-	-	7	-	-	-
	Swollen	-	2	7	-	-	-
Prostate	Small	-	8	12	-	-	-
Seminal vesicles	Small	-	8	12	-	-	-
Testes	Small	-	7	12	-	-	-
	Soft	-	-	9	-	-	-
Spleen	Irregular	-	-	-	-	1	1
	Swollen	-	-	-	-	1	1
Uterus	Watery contents	-	-	-	-	-	1
	Dilatation	-	-	-	-	-	1

Macroscopic Findings-	Males	Females

		Incidences			Incidences		
Dose (mg/kg)		0	30	300	0	30	300
No. animals		12	12	12	24	24	24
Liver	Swollen	-	-	2	-	-	-
Kidneys	Discoloration: pale	-	-	1	-	-	-
	Pelvic dilatation	-	-	1	-	-	-
Vagina	Abnormal contents	-	-	-	-	-	1
	Obstruction	-	-	-	-	-	1
	Dilatation	-	-	-	-	-	1

Sperm Assessment

Terminal Necropsy *(Excerpted from Applicant's submission)*

Treatment unit: mg / kg	Vehicle 0	Low 30	High 300
Sperm Motility			
Animals: Examined/Total	12 / 12	12 / 12	12 / 12
Motile sperm (%)	88.9 (9.8)	83.2 (8.6)	1.5 (4.9)
	-	0.0459*	0.0000***
Progressively motile sperm (%)	70.7 (12.2)	63.3 (8.1)	0.0 (0.0)
	-	0.0402*	0.0000***
Sperm Concentration: Cauda epididymidis			
Animals: Examined/Total	12 / 12	12 / 12	12 / 12
Weight (g)	0.281 (0.040)	0.199 (0.029)	0.094 (0.019)
	-	0.0002***	0.0000***
Sperm count (millions/g)	639.2 (146.2)	596.4 (132.7)	21.4 (13.0)
	-	0.4529	0.0000***
Total (million)	177.8 (40.0)	120.1 (37.9)	2.1 (1.4)
	-	0.0042**	0.0000***
Sperm Concentration: Testis			
Animals: Examined/Total	12 / 12	12 / 12	12 / 12
Weight (g)	1.512 (0.145)	1.244 (0.131)	0.887 (0.083)
	-	0.0004***	0.0000***
Sperm count (millions/g)	87.3 (9.7)	88.2 (13.4)	43.8 (17.6)
	-	0.8661	0.0000***
Total (million)	132.3 (21.6)	110.1 (22.5)	38.9 (16.6)
	-	0.0130*	0.0000***

*: statistically significant compared to controls $p \leq 0.01$; **: $p \leq 0.05$; ***: $p \leq 0.001$

Treatment unit: mg / kg	Vehicle 0	Low 30	High 300
Sperm Morphology			
Animals: Examined/Total	12 / 12	10 / 12	12 / 12
Mean number of sperm cells examined per animal	200.0	200.0	36.2
p-val Sign.	-	-	0.0000***
Normal number (%)	89.0	86.2	20.7
p-val Sign.	-	0.2911	0.0001***
Abnormal number (%)	11.0	13.8	79.3
p-val Sign.	-	0.2911	0.0001***

***: statistically significant compared to controls p ≤ 0.001

Recovery Necropsy - 8 weeks *(Excerpted from Applicant's submission)*

Treatment unit: mg / kg	Vehicle 0	Low 30	High 300
Sperm Motility			
Animals: Examined/Total	11 / 12	12 / 12	12 / 12
Motile sperm (%)	71.3 (13.6)	74.0 (14.4)	63.6 (29.6)
	-	0.3242	0.7816
Progressively motile sperm (%)	50.7 (14.0)	49.2 (11.3)	40.2 (20.7)
	-	0.6885	0.1649
Sperm Concentration: Cauda epididymidis			
Animals: Examined/Total	11 / 12	12 / 12	12 / 12
Weight (g)	0.354 (0.057)	0.342 (0.050)	0.330 (0.042)
	-	0.7119	0.1757
Sperm count (millions/g)	675.0 (76.8)	699.8 (103.3)	686.7 (99.2)
	-	0.9020	0.9509
Total (million)	239.3 (42.5)	238.8 (47.7)	227.7 (45.2)
	-	0.6666	0.3889
Sperm Concentration: Testis			
Animals: Examined/Total	11 / 12	12 / 12	12 / 12
Weight (g)	1.538 (0.107)	1.610 (0.199)	1.706 (0.110)
	-	0.5383	0.0026**
Sperm count (millions/g)	71.8 (5.7)	77.7 (8.7)	73.8 (9.0)
	-	0.1396	0.5796
Total (million)	110.4 (11.0)	124.0 (10.4)	125.9 (17.6)
	-	0.0097**	0.0226*
Sperm Morphology			
Animals: Examined/Total	11 / 12	12 / 12	12 / 12
Mean number of sperm cells examined per animal	200.0	200.0	191.7
p-val Sign.	-	-	0.3384
Normal number (%)	87.0	94.2	86.2
p-val Sign.	-	0.0041**	0.4976
Abnormal number (%)	13.0	5.8	13.8
p-val Sign.	-	0.0041**	0.4976

*: statistically significant compared to controls p ≤ 0.05; **: p ≤ 0.01;

Recovery necropsy at 16 weeks was unremarkable.

Stability and Homogeneity

Adequate

Study Summary

Abiraterone acetate was administered to male rats via oral (gavage) at doses of 0, 30, and 300 mg/kg. No drug-related mortalities were reported. General clinical signs included a reduction in aggression and female copulatory plugs amongst treated animals. Decreased bodyweights and body weight gain were also observed without corresponding decreases in food consumption. Mating and fertility parameters were

similar amongst control and 30 mg/kg groups. In the 300 mg/kg group, only 7 of the pairs mated with none resulting in pregnancy. Macroscopic findings in males include small reproductive organs (coagulating glands, epididymides, prostate, seminal vesicles, & testes). Corresponding decreases in the weights of the epididymides and testes (relative to bodyweight) were observed in both treatment groups. A decrease in sperm motility, sperm counts, and normal sperm were also noted in the 30 and 300 mg/kg groups. All results were reversible by 16 weeks. In the 30 mg/kg treatment group, females mated with treated males had decreased corpora lutea, implantations, and live embryos compared to vehicle controls. There was also a 47% increase in the number of post-implantation losses in females mated with males that received 30 mg/kg compared to controls. The findings were consistent with the pharmacology of abiraterone. A NOAEL was not established.

Study title: Oral Fertility Study of JNJ-212082-AAA in the female rat

Study no.:	TOX10096
Study report location:	eCTD 4.2.3.5.1
Conducting laboratory and location:	Drug Safety Sciences, Beerse site B-2340 Beerse, Belgium
Date of study initiation:	05 May 2011
GLP compliance:	Statement included and signed
QA statement:	Statement included and signed
Drug, lot #, and % purity:	JNJ-212082-AAA, Lot # ZR102164PUA071, 100%

Key Study Findings:

- No differences in mating, fertility, and litter parameters were observed
- Reduced bodyweight gain was observed at ≥ 30 mg/kg
- Dose-dependent increase in irregular and extended estrous cycles at ≥ 30 mg/kg
- Increased incidence of pre-implantation loss at 300 mg/kg
- A NOAEL was not established

Methods

Route of administration:	Oral (gavage)
Formulation/Vehicle:	0.5% (w/v) Methocel A4M (methylcellulose 4000 mPa.s), 0.1% (w/v) Tween 80 in demineralized water (aqueous suspension)
Species/Strain:	Rat, Sprague-Dawley
Age:	49 – 56 days old
Weight:	182 – 227 g (females);
Frequency:	Subset I: Once daily for 2-week pre-pairing period, throughout the pairing period and until Day 7 of pregnancy. Subsets II & III: once daily for days 0 – 14 followed by a 4 or 8 weeks non-

dosing period pre-pairing.
Recovery: 4 and 8 weeks

(Excerpted from sponsor)

Table 1: Dosage group assignment				
Parameter		**V** Vehicle (blue)	**L** Low (red)	**H** High (green)
Dose level (mg/kg/day)		00	30	300
Concentration (mg/ml)		0	3	30
Dose volume (ml/kg/day)		10	10	10
Female Numbers	Subset I	1 - 16	61 - 76	121 - 136
	Subset II	17 - 32	77- 92	137 - 152
	Subset III	33 - 48	93 - 108	153 - 168

Observations and Results

Mortality

Animals were checked at least once daily. No drug-related mortalities observed.

Clinical Signs

Animals were checked at least once daily. Unremarkable

Bodyweight

Animals were checked daily during dosing and weekly during recovery. No drug-related in changes in bodyweight during the treatment period. There was a reduced bodyweight gain after 3 & 4 weeks from the beginning of treatment. Changes were unremarkable after 4 and 8 week recovery.

Mean bodyweight gain compared to vehicle control

Females			
	Control	% change over control	
Dose (mg/kg)	0	30	300
Week 1	16	-	-
Week 2	30	-	-
Week 3	17	↓29*	↓47***
Week 4	28	↓18*	↓25**

*: Statistically significant compared to controls $p \leq 0.05$; **: $p \leq 0.01$; ***: $p \leq 0.001$

Food Consumption

Unremarkable

Fertility Data

Estrous cycles

Females			
	Incidence		
Dose (mg/kg)	0	30	300
	16	16	16
Irregular cycles	0	3	9
Extended cycle length	2	6	14

Changes were unremarkable after 4 and 8 weeks of recovery.

Fertility Indices

Females			
	Incidence		
Dose (mg/kg)	0	30	300
No. of mated animals	16	16	16
# of pregnant females (subset I)	16	14	15
# of pregnant females (subset II)	14	14	15

Body weight gain during pregnancy

Females			
	Control	% change over control	
Dose (mg/kg)	0	30	300
Day 0 – 7 Subset I Subset II	 44.2 36.8	 ↓14* -	 ↓17* -
Day 8 – 13 Subset I Subset II	34.4 32.3	- -	- -

*: Statistically significant compared to controls $p \leq 0.05$

Litter Parameters

Unremarkable

Gross Pathology

Samples were taken at schedule necropsy. Unremarkable

Stability and Homogeneity

Adequate

Study Summary

Abiraterone acetate was administered to female rats via oral (gavage) at doses of 0, 30, and 300 mg/kg for a 2-week pre-pairing period, throughout the pairing period, and until day 7 of pregnancy. Additional subsets of animals were dosed throughout the 2-week pre-pairing period, and then allowed to recover for 4 or 8 weeks before pairing. No drug-related mortalities were reported. Decreased body weight gain was observed at 3 and 4 weeks without corresponding decreases in food consumption. No differences in mating, fertility, and litter parameters were observed between controls and abiraterone acetate groups. There was a statistically significant decrease in bodyweight gain amongst pregnant females administered 30 and 300 mg/kg during days 0 – 7 of pregnancy for subset I. There was a dose–dependent increase in irregular and extended estrous cycles (≥ 30 mg/kg) and pre-implantation loss (300 mg/kg) in females administered abiraterone acetate compared to controls. These findings were consistent with the pharmacology of abiraterone.

9.2 Embryonic Fetal Development

Studies in this section were reviewed by Dr. Eias Zahalka in the Division of Hematology Oncology Toxicology.

Study title: Pilot oral developmental toxicity study of JNJ-212082-AAA in the rat

Study no.:	TOX10066
Study report location:	eCTD 4.2.3.5.2
Conducting laboratory and location:	Drug Safety Sciences, Beerse siteTurnhoutseweg 30B-2340 Beerse, Belgium
Date of study initiation:	24 March 2011
GLP compliance:	Non-GLP
Drug, lot #:	JNJ-212082-AAA, lot # ZR102164PUA071

Key Study Findings

- Mortalities: 2 females at 300 mg/kg were found dead, with no notable clinical signs
- Increased late resorptions, total resorptions, & post implantation loss at ≥ 30 mg/kg
- Decreased live fetuses, uterine weight, & percent of male fetus at ≥ 30 mg/kg
- External fetal evaluation resulted in one fetus with umbilical hernia at 300 mg/kg and a dose-related reduction in male ano-genital distance in all treated groups
- No NOAEL for embryofetal effects could be identified

Objectives:

To evaluate the potential toxicity of JNJ-212082-AAA when administered orally by gavage to pregnant Sprague- Dawley rats once daily from Day 6 to 17 and to establish the doses for the subsequent main Developmental Toxicity study.

Methods:

- Species: Male and female Rats
- Strain: SPF Sprague-Dawley (Crl: CD®)
- Supplier: (b) (4)
- Age: 54-63 days
- Weight: 226-253 g
- Mating procedure: One male was housed with two females. Females were examined for the presence of spermatozoa by conducting vaginal smears each day. Evidence of a sperm positive vaginal smear was detected, males and female were separated.

Study design:

	Dose mg/kg	Dose Volume (ml)	Number of Rats
Group 1	Vehicle	10	5
Group 2	30	10	5

Group 3	100	10	5
Group 4	300	10	5

- *Vehicle/Formulation:* 0.5% w/v Methocel, 0.1% w/v Tween 80 in demineralized water.
- Dosing: Daily from Day 6 to 17 (Day 0= Day 1 of gestation). Males were not dosed.
- Route: Orally by gavage
- Cesarean section (C-section): Day 21
- In-life end points: Mortalities, clinical observations, Body weight and food consumption.
- Litter end points: Uterus weight, number of corpora lutea, number of live fetuses, number of dead fetuses, resorptions and fetal weights.
- Fetal end points: Sex, external examination and ano-genital distance.

Results:

Maternal data:

- Mortalities: Two animals at 300 mg/kg were found dead on Day 20. Prior to death, one animal had red vaginal discharge.
- Clinical observations: Red vaginal discharge was observed on Days 17 to 21, in 1, 3 and 5 females at 30, 100 and 300 mg/kg, respectively.
- Body weights:

  At 300 mg/kg, animals gained less body weight (up to 54%) than controls, during Days 6-13 of pregnancy. Even after the cessation of drug administration (Days 18-20 of pregnancy) animals continued to gain less body weight than controls (38.8 g (control) vs. -11.8 g at 300 mg/kg).

  At 100 mg/kg, animals gained less body weight than controls during Days 6-9 (17%) and on Days 18 to 20 (37%) of gestation.

  At 30 mg/kg, animals gained less body weight than controls during Days 18-20 (36%).
- Food consumption:

  At 300 mg/kg, animals consumed 50% less food than controls during Days 18-20 of gestation.

  At 100 mg/kg, animals consumed 19% less food than controls during Days 18-20 of gestation.

Litter data:

- At 300 mg/kg, one of the four surviving litters had no live fetuses at the time of the C-section
- At 300 mg/kg, the following C-Section findings were reported relative to the control group: 35% decrease in uterus weight, 18X increase in number of late and total resorptions, 17X increase in post-implantation loss, 68% decrease in number of live fetuses, 26% decrease in weight of live fetuses and decrease in percent of male fetuses. The fetal losses probably

contributed to the observed reduction in body weight gain and the observed red vaginal discharge can be attributed to the post implantation loss.

- At 100 mg/kg, the following litter findings were reported relative to the control group: 8X increase in number of late and total resorptions, 8X increase in post-implantation loss and 23% decrease in number of live fetuses. Individual litter data showed that litter # 46 with 15 implants but only 6 live fetuses; litter # 43 with 15 implants and only 8 live fetuses; litter # 42 with 13 implants and only 5 live fetuses. The fetal losses probably contributed to the observed reduction in body weight gain and the observed red vaginal discharge can be attributed to the post implantation loss.
- At 30 mg/kg, the following litter findings were reported relative to the control group: 9X increase in the number of late and total resorptions, 9X increase in the post-implantation loss and 33% decrease in the number of live fetuses. Individual litter data showed that litter # 26 had 11 implants and only one live fetus; litter # 24 had 13 implants and only 4 live fetuses; litter # 22 had 16 implants and only 10 live fetuses. The fetal losses probably contributed to the observed reduction in body weight gain and the observed red vaginal discharge can be attributed to the post implantation loss.
- There was a dose related reduction in male ano-genital distance in all treated groups with the mean distance being 85, 76 and 64% in the groups receiving 30, 100 or 300 mg/kg in comparison with the vehicle controls.
- External fetal evaluation resulted in one fetus with umbilical hernia at 300 mg/kg.

(Excerpted from Applicant's submission)

Treatment unit: mg/kg		Vehicle 0	Low 30	Medium 100	High 300
LITTER DATA					
Number of corpora lutea of pregnancy/pregnant animal	(3)	16.0	18.2	17.5	13.8
Number of implantations/pregnant animal	(3)	13.7	13.5	14.7	13.5
Pre-implantation loss (%)	(3)	15.16	21.64	13.83	1.67
Number of early resorptions / pregnant animal	(3)	0.50	0.33	0.33	0.00
Number of late resorptions / pregnant animal	(3)	0.00	4.33	4.17 *	9.00 **
Total number of resorptions / pregnant animal	(3)	0.50	4.67	4.50	9.00 **
Post-implantation loss (%)	(3)	4.07	36.79	31.37	69.79 **
Number of live fetuses/pregnant animal	(3)	13.2	8.8	10.2	4.2 **
Number of dead fetuses/pregnant animal	(3)	0.0	0.0	0.0	0.2
Weight of live fetuses (g)	(3)	5.23	4.82	5.17	3.89
Sex ratio (% male fetuses)	(3)	56.2	39.4	51.1	6.7 *
Incidence of malformed fetuses	(1)	0/79	0/53	0/61	1/17

Summary:

Two animals at 300 mg/kg were found dead. Clinical observations (red vaginal discharge), decreases in body weight gain and food consumption were evident at

all dose levels tested. The reported litter data showed increases in number of late, total resorptions, post-implantation loss, decrease in number of live fetuses and a reduction in male ano-genital distance at all dose levels tested, relative to the control group. Additionally, decreases in uterus weight, of live fetuses and in percent of male fetuses were reported at 100 mg/kg only. In contrast to the sponsor's conclusion stating that maternal and fetal toxicity were limited to the highest dose level, this reviewer concludes that maternal and embryo-fetal lethality were evident at all dose levels. An unequivocal NOAEL was not established for this study.

Study title: Oral developmental toxicity study of JNJ-212082-AAA in the rat

Study no.:	TOX10115
Study report location:	eCTD 4.2.3.5.2
Conducting laboratory and location:	Drug Safety Sciences, Beerse site Turnhoutseweg 30 B-2340 Beerse, Belgium
Date of study initiation:	12 May 2011
GLP compliance:	OECD GLP
QA Statement	Yes
Drug, lot #:	JNJ-212082-AAA, lot # ZR102164PUA071

Key Findings:

- Mortalities: 3 pregnant females at 100 mg/kg were found dead, with clinical signs limited to red vaginal discharge
- Decreased live fetuses, fetal bodyweight, and fetal ano-genital distance at ≥ 30 mg/kg
- Increased total resorptions, & post implantation loss at ≥ 10 mg/kg
- External fetal evaluation show no reported treatment related fetal malformations
- No NOAEL for embryofetal effects could be identified

Objectives:
To evaluate the potential toxicity of JNJ-212082-AAA when administered orally by gavage to pregnant Sprague- Dawley rats once daily from Day 6 to 17. In addition, the toxicokinetics (TK) profile was evaluated using a satellite group of animals.

Methods:

- Species: Male and Female Rats
- Strain: SPF Sprague-Dawley (Crl: CD®)
- Supplier: (b) (4)
- Age: 63-72 days
- Weight: 173-265 g
- Mating procedure: One male was housed with two females. Females were examined for the presence of spermatozoa by conducting vaginal smears

each day. Evidence of a sperm positive vaginal smear was detected and males and female were separated.

Study design:

	Dose mg/kg	Dose Volume (ml)	Main Study Rats	TK Study Rats
Group 1	Vehicle	10	22	3
Group 2	10	10	22	3
Group 3	30	10	22	3
Group 4	100	10	22	3

- *Vehicle/Formulation:* 0.5% w/v Methocel, 0.1% w/v Tween 80 in demineralized water.
- Analysis: concentration, homogeneity and stability were evaluated.
- Dosing:
  Main study rats: Daily from Day 6 to 17 (Day 0= Day 1 of gestation). Males were not dosed.
  TK study rats: Daily from Day 6 to 14 (Day 0= Day 1 of gestation).
- Route: Oral gavage
- Cesarean section (C-section):
  Main study rats: Day 21
  TK study rats: Day 15; uterine contents examined only to confirm pregnancy status.
- TK blood sampling on Day 14:
  Group 1 (vehicle) - Blood was collected at 1, 7, and 24 hours post dose.
  Groups 2, 3 and 4 – Blood was collected at 1, 2, 4, 7 and 24 hours post dose.
- In-life end points: Mortalities and clinical observations
  Body weight - Days 0, 4, 6, 10, 14, 18, and 21.
  Food consumption - Days 0, 6, 10, 14, 18 and 21.
- Litter end points (Main study rats): Uterus weight, number of corpora lutea, number of live fetuses, number of dead fetuses, resorptions and fetal weight.
- Fetal end points (Main study rats): Sex, external examination, ano-genital distance, visceral and skeletal examination.

Results:

Analysis of test formulations:

Concentration and homogeneity of the test article in the formulations were within the acceptable criteria. The formulation was stable for up to 18 days after preparation at (2-8°C) and for at least one day at room temperature.

Toxicokinetics:

Dose level/Group	C_{max} (ng/ml)	T_{max} (h)	$AUC_{0-24\ hr}$ (ng.h/ml)
10 mg/kg	10.8	1-2	34.0
30 mg/kg	33.8	1-2	109
100 mg/kg	55.7	1-2	367

- Peak plasma concentrations (Tmax) were observed at 1-2 hours post dose at all dose levels.
- A dose proportional increase was reported for C_{max} between the 10 and 30 mg/kg, and a less than dose proportional increase between 30 and 100 mg/kg.
- A dose proportional increase was reported for AUC between all doses.

Maternal data (Main study rats):

At 100 mg/kg:

- Three pregnant females were found dead during Days 18 to 21. Prior to death, females were reported to have red vaginal discharge.
- An additional eight surviving females had red vaginal discharge.
- Other clinical observations included: anemia, decreased general activity, dyspnea, hypothermia, piloerection, dark urine and/or ataxia.
- Body weights were decreased by 37%, 13% and 62% during Days 6-9, 14-17 and 18-20, respectively, relative to the control group.
- Food consumption was decreased by 5%, 14% and 30% during Days 10-13 and 18-20, respectively, relative to the control group.

At 30 mg/kg:

- Six females had red vaginal discharge.
- Body weight gain was decreased by 25% and 15% during Days 6-9 and 18-20, respectively, relative to the control group.
- Food consumption was decreased by 10% and 11% during Days 14-17 and 18-20, respectively, relative to the control group.

At 10 mg/kg:

- Body weight gain was decreased by 27% during Days 6-9, relative to the control group.
- Food consumption was decreased by 6% and 7% during Days 14-17 and 18-20, respectively, relative to the control group.

Litter data:

- There were 22/22, 22/22, 21/22 and 18/22 pregnant females evaluated at C-section at the vehicle, 10, 30 and 100 mg/kg, respectively.

- One animal at 100 mg/kg was found to be not pregnant at C-section
- At 30 mg/kg and 100 mg/kg, the number and mean number of live fetuses decreased by up to 23% and 54%, respectively.
- Mean gravid uterus weight was decreased by 20% at 100 mg/kg.
- Mean number of total resorptions was increased by 5.7X, 8.8X and 17.6X at 10, 30 and 100 mg/kg, respectively. The reported increases in total resorptions were attributed to the increases in mean number of early and late resorptions.
- Mean post implantation losses increased with the dose. Post implantation loss at 10, 30 and 100 mg/kg were 5.7X, 9.9X and 20X, respectively.
- Mean fetal body weight at 100 mg/kg was decreased by 22%. There were no reported decreases in fetal body weights at doses ≤ 30 mg/kg; however, in light of the decrease in mean number of fetuses in each litter as a result of implantation loss, increase in resorptions and/or abortions, which are normally associated with an increase in litter fetal weight, it is possible that an effect on fetal weight occurred but was not detected due to the above reasons.

The reported decrease in maternal body weights can be attributed to the possible abortion (red vaginal discharge), implantation loss, increase in resorptions, decrease in mean fetal weight and/or decrease in the number of live fetuses.

Fetal Data:

- There were no reported treatment-related fetal malformations at all dose levels.
- Significant increases in skeletal variation were observed: 6^{th} sternebra incomplete ossification (at all dose levels), scapula bent (at ≥ 30 mg/kg), and more than 1 metatarsal bone not ossified (at 100 mg/kg). These effects are generally associated with developmental delay, and were probably the result of the decrease in fetal body weights observed at all dose levels.
- Bilateral ureter dilation was the only visceral anomaly reported at 100 mg/kg.
- Fetal ano-genital distance was decreased in males relative to the control group by 11% and 20% at 30 and 100 mg/kg, respectively.

Summary:

- Three pregnant females were found to be dead at 100 mg/kg. Clinical observations that included red vaginal discharge, decreases in body weight gain (up to 27%, 25% and 62% at 10, 30 and 100 mg/kg) and food consumption (up to 7%, 11% and 30% at 10, 30 and 100 mg/kg) were reported at all dose levels.

- At 30 mg/kg and 100 mg/kg, number and mean number of live fetuses decreased by up to 23% and 54%, respectively; Mean number of total resorptions was increased by 5.7X, 8.8X and 17.6X at 10, 30 and 100 mg/kg, respectively; Mean post implantation losses were increased with the dose; Post implantation loss at 10, 30 and 100 mg/kg were 5.7X, 9.9X and 20X, respectively; Mean fetal body weight at 100 mg/kg was decreased by 22%; Fetal ano-genital distance was decreased in males relative to the control group by 11% and 20% at 30 and 100 mg/kg.
- There were no reported treatment related fetal malformations at all dose levels. An increase in skeletal variation was observed and were likely attributable to the decrease in fetal body weights observed at all dose levels. Bilateral ureter dilation was the only visceral anomaly reported at 100 mg/kg.
- Fetal ano-genital distance was decreased in males relative to the control group by 11% and 20% at 30 and 100 mg/kg, respectively.

11 Integrated Summary and Safety Evaluation

Abiraterone acetate (Zytiga®) was approved in 2011 for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel. The non-clinical study reports submitted with this supplemental NDA support the approval of abiraterone acetate for the new proposed indication.

See the EXECUTIVE SUMMARY for an overall summary of nonclinical findings.

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/s/

KIMBERLY R RINGGOLD
11/20/2012

TODD R PALMBY
11/20/2012

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 202379 **Applicant: Genetech** **Stamp Date: 14 June 2012**

Drug Name: Zytiga® **NDA/BLA Type: Priority** **PDUFA Date: 14 Dec 2012**
Abiraterone Acetate

On **initial** overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	X		
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	X		
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	X		
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	X		
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			NA
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	X		
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	X		
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X		

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?			This is a review issue.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			This is a review issue
11	Has the applicant addressed any abuse potential issues in the submission?			NA
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			NA

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? YES

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

Reviewing Pharmacologist Date

Team Leader/Supervisor Date

File name: 5_Pharmacology_Toxicology Filing Checklist for NDA_BLA or Supplement 010908

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

/s/

KIMBERLY R RINGGOLD
08/01/2012

TODD R PALMBY
08/02/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 202379/ S005

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA Serial Number:	NDA 202,379/ SE005
Drug Name:	ZYTIGA®
Indication(s):	(b) (4) patients with metastatic castration-resistant prostate cancer
Applicant:	Janssen Biotech Inc.
Date(s):	Submission Date: 14 June 2012
	PDUFA Due Date: 14 December 2012
Review Priority:	Priority
Biometrics Division:	Division of Biometrics 5 (HFD-711)
Statistical Reviewer:	Lijun Zhang, Ph.D.
Concurring Reviewers:	Shenghui Tang, Ph.D., Team Leader
	Rajeshwari Sridhara, Ph.D., Division Director
Medical Division:	Division of Oncology Products 1 (HFD-150)
Clinical Team:	Paul Kluetz, M.D.
	Virginia E. Maher , M.D., Team Leader
Project Manager:	Amy Tilley

Keywords: Progression-Free Survival, Overall Survival, Logrank Test, Randomization, Interim Analysis

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1. EXECUTIVE SUMMARY

Abiraterone Acetate (Zytiga™), a steroidal inhibitor of 17-alpha-hydroxylase, was approved for the treatment of metastatic castration-resistant prostate cancer (CRPC) in patients who have received prior chemotherapy containing a taxane. In this supplemental New Drug Application (sNDA), the applicant seeks the approval of abiraterone acetate for (b) (4) (b) (4)

The pivotal Phase 3 study COU-AA-302 was a multicenter, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of abiraterone acetate plus prednisone to placebo plus prednisone in asymptomatic or mildly symptomatic patients with chemotherapy-naïve metastatic CRPC. The co-primary efficacy endpoints included overall survival (OS) and radiographic progression-free survival (rPFS) per independent radiographic review (IRR).

The planned 3rd interim OS analysis conducted with 434 deaths (56% of the total deaths required for the planned final analysis) numerically favored the abiraterone arm, but the O'Brien-Fleming efficacy boundary (two-sided alpha = 0.0035) was not crossed. The Hazard Ratio (HR) was 0.79 (95 % CI: 0.66, 0.96) with a two-sided p-value of 0.015. The planned final analysis of OS will be conducted when 734 deaths occur.

The final analysis of rPFS per IRR assessment demonstrated a statistically significant improvement (HR = 0.43; 95% CI: 0.35, 0.52; $p < 0.0001$) of abiraterone acetate over placebo in all randomized patients. The median of rPFS was 8.3 months in the placebo arm and was not reached in the abiraterone arm.

Abiraterone acetate has also shown improvement over placebo in the pre-specified secondary endpoint measures of time to initiation of cytotoxic chemotherapy and time to opiate use for cancer pain. The median time to initiation of cytotoxic chemotherapy was 25.2 months in the abiraterone arm and 16.8 months in the placebo arm (HR=0.58; 95% CI: 0.49, 0.69; $p < 0.0001$). The time to opiate use for cancer pain was delayed for patients receiving abiraterone acetate when compared to those receiving placebo (HR=0.69; 95% CI: 0.57, 0.83; $p = 0.0001$). The result of time to opiate use was supported by a delay in patient reported pain progression.

Radiographic PFS as a stand-alone endpoint is not an established surrogate endpoint of overall survival, and has not been used to support a marketing approval in the disease setting of (b) (4) (b) (4). However, it is noted that abiraterone acetate has been approved based on OS improvement (study COU-AA-301) in a more refractory population. Therefore, the approvability of this sNDA should be considered based on the totality of the data shown in the study COU-AA-302 in the context of overall survival benefit of abiraterone acetate in a more refractory population. The judgment on the approvability is deferred to the clinical review team.

2. INTRODUCTION

2.1 Overview

Abiraterone acetate in combination with prednisone has been approved for the treatment of metastatic CRPC in patients who have received prior chemotherapy containing docetaxel in 2011

based on a significant overall survival improvement compared to the placebo arm. The current sNDA submission is based on a Phase 3 pivotal study (COU-AA-302) (Table 1), entitled "A phase 3, randomized double-blind, placebo-controlled study of abiraterone acetate plus prednisone vs. placebo plus prednisone in asymptomatic or mildly symptomatic patients with metastatic castration-resistant prostate cancer". The co-primary efficacy endpoints were OS and rPFS by IRR assessment. The key secondary endpoints included time to opiate use for cancer pain, time to initiation of cytotoxic chemotherapy, time to deterioration in ECOG Performance Score (PS) by ≥ 1 point, and time to Prostate Specific Antigen (PSA) progression based on Prostate Cancer Working Group 2 (PCWG2) criteria.

Table 1: Overview of the Pivotal Study COU-AA-302

Study design	**Treatment period**	**Follow-Up period**	**Treatment arms (number of randomized subjects)**	**Enrollment period** **Geographic region: n**
A randomized double-blind, placebo-controlled study of abiraterone acetate plus prednisone vs. placebo plus prednisone in asymptomatic or mildly symptomatic patients with metastatic castration-resistant prostate cancer	Treated until radiographic progression of disease and/or unequivocal clinical progression	Follow-up for survival, opiate use, ECOG PS, and subsequent therapy would be collected every 3 months for up to 5 years	Abiraterone Acetate + Prednisone (n=546) Placebo + Prednisone (n=542)	April 2009 – June 2010 151 sites in: North America: 73 (Canada: 12; United States: 61) Europe: 60 Australia: 18

The original protocol of Study COU-AA-302 was implemented on 11 February 2009 and amended three times thereafter. This study received a special protocol assessment (SPA) agreement in 2009. In the Amendment 1 (dated 23 April 2010), genetic analyses were expanded to include biomarkers other than TMPRSS2-ERG. Following the implementation of Amendment 2 (dated 7 June 2011), the timing of the interim OS analyses was adjusted, and a third interim analysis of OS at about 55% of the targeted total deaths was added.

Based on the 2nd interim OS analysis results, the independent data monitoring committee (IDMC) recommended unblinding of the study. Treatment assignments were then unblinded and patients currently receiving placebo were offered crossover therapy to abiraterone acetate in the Amendment 3 (dated 2 April 2012). The schedule of events for patients who were originally randomized to the abiraterone acetate treatment group would not change.

In this review, patients who were randomized to receive abiraterone acetate and prednisone are referred as the "abiraterone arm", whereas patients who were randomized to receive matching placebo and prednisone are referred as the "placebo arm". In the tables and figures, "AA" represents the abiraterone arm and "Placebo" represents the placebo arm.

2.2 Data Sources

Electronic submission including protocols, statistical analysis plan, study reports, and analysis datasets for this sNDA submission (clinical cutoff date: 20 December 2010 for the final rPFS analyses, 20 December 2011 for the second OS interim analysis and all secondary endpoints analyses) is located on network with network path: \\Cdsesub1\evsprod\NDA202379\0056\m5\. Results and datasets of the third OS interim analysis are located at \\Cdsesub1\evsprod\NDA202379\0064\m5\.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The data and analysis quality of the submission was acceptable for the reviewer to be able to perform the statistical review.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

3.2.1.1 Overall Study Design

Study COU-AA-302 was a multicenter, randomized, double-blind, placebo-controlled Phase 3 study to evaluate the efficacy and safety of abiraterone acetate plus prednisone compared to placebo plus prednisone in patients with chemotherapy-naïve metastatic CRPC who were asymptomatic or mildly symptomatic. Study randomization was stratified by ECOG performance status (0 vs. 1).

The study had two co-primary endpoints: OS and rPFS per IRR assessment. Three interim analyses were planned for the OS endpoint, after approximately 15% (in conjunction with the final rPFS analysis), 40%, and 55% of the total targeted OS events were observed. The final OS analysis was planned to occur with 773 deaths. Only one analysis was planned for rPFS, to occur after 378 rPFS events.

3.2.1.2 Schedule of Assessments

Based on modified Response Evaluation Criteria In Solid Tumors (RECIST) version 1.0 (MRI/CT scan) and PCWG2 criteria (bone scan), radiographic evaluation were assessed at screening, day 1 of cycles 3, 5, 7, and 10; every 3 cycles beyond cycle 10; and at treatment discontinuation, if applicable. All scans were reviewed at the site and by central IRR. The independent review data were used for the primary efficacy analysis. Following the protocol Amendment #3, patients on the placebo arm were offered crossover to receive abiraterone acetate treatment. The schedule of events for patients who were originally randomized to the abiraterone arm would not change.

Patients were to be maintained on study medication until radiographic or unequivocal clinical progression was documented. The reasons for unequivocal clinical progression included the need to discontinue due to cancer pain requiring immediate administration of chronic opiate analgesics, deterioration of ECOG PS to Grade 3 or higher, or immediate need to initiate cytotoxic chemotherapy or have either radiation therapy or surgical intervention for

complications due to tumor progression. If the patient had radiographic progression in the absence of unequivocal clinical progression, and alternate treatment was not indicated, the patient was allowed to continue on study medication based on the investigator's clinical judgment. After progression or study treatment discontinuation, patients continued to be followed for survival, opiate use, ECOG PS, and cytotoxic chemotherapy for prostate cancer at regular follow-up intervals (of 3 months) up to 5 years.

3.2.1.3 Efficacy Endpoints

Primary endpoints:

- OS
- Radiographic PFS as determined by IRR assessment

Major secondary endpoints:

- Time to opiate use for cancer pain
- Time to initiation of cytotoxic chemotherapy
- Time to clinical deterioration in ECOG PS by ≥ 1 grade
- Time to PSA progression

Other efficacy endpoints:

- PSA response rate
- Objective response rate
- Duration of response
- Time to analgesic progression
- Patient-reported outcomes

OS was defined as the time from randomization to death due to any cause.

Radiographic PFS, based on criteria adapted from PCWG2 criteria (bone scan) and modified RECIST (MRI/CT scan), was defined as the time from randomization to the occurrence of one of the following, whichever occurred first:

1. A patient was considered to have progressed by bone scan if one scan showed new lesions that were confirmed by further progression on a second bone scan as follows (as assessed by the independent radiographic review),

- The first bone scan with ≥ 2 new lesions compared with baseline was observed < 12 weeks from randomization and was confirmed by a second bone scan taken ≥ 6 weeks later showing ≥ 2 additional new lesions (≥ 4 new lesions compared with baseline);

- The first bone scan with ≥ 2 new lesions compared with baseline was observed ≥ 12 weeks from randomization, and the new lesions were verified on the next bone scan ≥ 6 weeks later (≥ 2 new lesions compared with baseline).

Confirmatory bone scans were required to avoid premature treatment discontinuation due to false positive progression resulting from tumor flare and other phenomena (e.g., trauma, arthritis, infection).

2. Progression of soft tissue lesions measured by CT or MRI as defined by modified RECIST criteria (as assessed by the independent radiographic review).

3. Death from any cause.

Time to opiate use for cancer pain was defined as the time interval from the date of randomization to the date of opiate use for cancer pain. Patients who had no opiate use at the time of analysis were censored at the last known date of no opiate use for cancer pain. Patients with no assessment were censored at the date of randomization.

Time to initiation of cytotoxic chemotherapy was defined as the time interval from the date of randomization to the date of initiation of cytotoxic chemotherapy for prostate cancer. Patients who had no cytotoxic chemotherapy administration at the time of analysis were censored at the last known date when no cytotoxic chemotherapy was administered. Patients with no assessment were censored at the date of randomization.

Time to clinical deterioration in ECOG PS by ≥ 1 grade was defined as the time interval from the date of randomization to the first date at which there was at least a 1 grade change (worsening) in the ECOG PS grade. Patients who had no deterioration in ECOG PS grade at the time of the analysis were censored at the last known date of no deterioration. Patients with no assessment were censored at the date of randomization.

Time to PSA progression was defined as the time interval from the date of randomization to the date of the PSA progression as defined in the PCWG2 criteria. Patients who had no PSA progression at the time of analysis were censored at the last known date of no progression. Patients with no on-study assessment or no baseline assessment were censored at the date of randomization.

PSA response rate was defined as the proportion of patients achieving a PSA decline ≥ 50% from baseline according to adapted PCWG2 criteria. For a PSA response to be confirmed, an additional central laboratory measurement obtained four or more weeks later had to show ≥ 50% decline from baseline.

Objective response rate was defined as the proportion of patients with measurable disease at baseline achieving a complete or partial response (CR or PR) according to RECIST criteria (baseline lymph node size was required to be ≥ 2 cm to be considered a target lesion). Duration of response was defined for the subset of patients who achieved a confirmed CR or PR, and was calculated as the time from the date of the first documented evidence of CR or PR until the date of either the first documented sign of progressive disease or death due to any cause. Patients who have neither died nor progressed were censored at the date of the last adequate radiologic assessment. Same censoring rules have been applied as the primary rPFS analysis.

Time to analgesic progression was defined as the time interval from randomization to first date of increase in analgesic usage score ≥ 30% from baseline observed at 2 consecutive evaluation ≥ 4 weeks apart. Analgesic scores were based on the World Health Organization (WHO) scale. Patients who have not experienced progression in analgesic use at the time of analysis were

censored on the last date patient was known to have not progressed. Patients with no on-study assessment or no baseline assessment were censored at date of randomization.

Patient reported outcomes (PRO) were based on data collected from two instruments, the Brief Pain Inventory-Short Form (BPI-SF) and the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire. The major PRO measures for analysis included the BPI-SF average pain intensity in the last 24 hours (average score of items 3, 4, 5, and 6), the BPI-SF worst pain intensity in the last 24 hours (item #3), the FACT-P Prostate Cancer Scale (PCS) and total score. The BPI-SF was collected at screening, day 1 of each cycle, and at the End-of-Treatment visit. FACT-P was collected at Cycles 1, 3, 5, 7, and 10 and was then collected every 3rd cycle beyond cycle 10 and the End-of-Treatment visit. No PRO assessments were planned after the End-of-Treatment visit.

Time to average pain intensity progression was defined as the time interval from randomization to the first date that a patient experienced an increase of ≥ 30% from baseline in the average of the BPI-SF pain intensity item scores (items 3, 4, 5, and 6) that was observed at 2 consecutive evaluations ≥ 4 weeks apart without a decrease in analgesic usage score.

Time to worst pain intensity progression was defined as the time interval from randomization to the first date a patient experienced an increase of ≥ 30% from baseline in the BPI-SF worst pain intensity item (item 3) observed at 2 consecutive evaluations ≥ 4 weeks apart without a decrease in analgesic usage score.

Time to degradation of FACT-P was defined as the time interval from randomization to the first date a patient experienced a decrease by more than the threshold of degradation as defined in Table 2.

Table 2. FACT-P Degradation Thresholds

Scale/Subscale	Minimum decrease from baseline required to meet definition of degradation
Physical Well-Being (PWB)	3
Social/Family Well-Being (SFWB)	3
Emotional Well-Being (EWB)	3
Functional Well-Being (FWB)	3
FACT-G (General) Scale	9
Prostate Cancer Subscale (PCS)	3
Trial Outcome Index (TOI)	9
FACT-P Total Score	10

[Source: PRO Analysis Plan Table FACT-P Degradation Outcome Thresholds, page 56]

Reviewer's Comments

- *There are no well-established thresholds for pain progression definition, as most of the PRO pain endpoints that have been used in the prior drug application have focused on pain palliation. The 30% increase threshold in average pain score and in worst pain score is questionable to define pain progression.*
- (b) (4)

[redacted] (b) (4)

3.2.1.4 Sample Size Determination

The overall significance level for the study was controlled at two-sided 0.05, which was allocated between the co-primary endpoints (0.04 for OS and 0.01 for rPFS). A total of 378 rPFS events were needed to detect a HR of 0.67 (corresponding to an increase from 4 to 6 months in median rPFS) with a 91% power at a 2-sided significance level of 0.01. Assuming a 22-month median survival for the placebo arm, 773 death events were needed (using a 4-look Lan-Demets group sequential design with O'Brien-Fleming type boundary) to detect an improvement of 5.5 months on median OS (corresponding to a HR of 0.80) at a 2-sided significance level of 0.04 with a power of 85%.

3.2.1.5 Interim Analyses

There was no interim analysis planned for rPFS. There were three interim analyses and one final analysis planned for OS. The first interim OS analysis was performed at the time of the final rPFS analysis. The second and third OS interim analyses and the final analysis were event driven and were planned to occur following 311, 425, and 773 deaths (corresponding to approximately 40%, 55%, and 100% of the total events), respectively. The O'Brien-Fleming boundaries as implemented by Lan-DeMets α-spending function were used for the efficacy boundary. The purpose of the planned interim analysis was to allow for the early termination of the study if superiority was demonstrated on OS. In the event of early termination for superiority, the collection of survival data was to continue.

3.2.2 Statistical Methodologies

3.2.2.1 Efficacy Analysis Population

The intent-to-treat (ITT) population included all patients randomized into the study. Patients were to be classified according to assigned treatment group, regardless of the actual treatment received. The ITT population was used for all efficacy analyses, and all analyses of disposition, demographic, and baseline disease characteristics.

3.2.2.2 Efficacy Analysis Methods

The primary analysis of OS was performed within the ITT population. OS was summarized using Kaplan-Meier survival curves, and compared between the two treatment arms using a stratified log-rank test (strata based ECOG PS as obtained through IWRS/IVRS). A stratified Cox proportional hazards model was used to estimate the hazard ratio of OS, along with a 95% confidence interval.

The primary analysis of rPFS was based on IRR assessments within the ITT population. Radiographic PFS was summarized using Kaplan-Meier survival curves, and compared between the two treatment arms using a stratified log-rank test (strata based ECOG PS as obtained through IWRS/IVRS). The hazard ratio with a two-sided 95% confidence interval was derived from a stratified Cox proportional hazards model.

In the analysis of rPFS, the following censoring rules were specified in the statistical analysis plan:

1. If the patient did not have a baseline scan or on-study scans, he was to be censored on the date of randomization.

2. If the patient did not show progression according to modified RECIST or bone scan, he was to be censored on the date of the last scheduled scan.

3. If the patient remains on study treatment and prior scans do not show radiographic progression, the patient will be censored on the date of the last scan showing no disease progression;

4. If the patient discontinues study treatment for any reason and progression was not observed in the scans prior to the discontinuation, the patient will be censored on the last scan showing no disease progression;

5. If the patient discontinues study treatment for any reason and additional new lesions were observed in the scan prior to the discontinuation, and there was no confirmatory scan, the patient will be censored on the date of the last scan that showed no disease progression;

6. Patients will also be censored on the date of the last scan that shows no disease progression if:

   a. the patient receives another therapy (ie, cytotoxic chemotherapy) known or intended for treatment of metastatic CRPC during the study;

   b. the patient misses ≥ 2 planned radiographic scans or has ≥ 2 consecutive unreadable scans;

   c. the patient has unequivocal progression of non-bone non-target lesions (eg, appearance of nonmeasurable visceral metastases or pathologically confirmed malignant effusions).

There were four major secondary efficacy endpoints: time to opiate use for cancer pain, time to initiation of cytotoxic chemotherapy, time to clinical deterioration in ECOG performance status ≥ 1 grade, and time to PSA progression. Each of the four major secondary endpoints was summarized using Kaplan-Meier survival curves, and compared between the two treatment arms using a stratified log-rank test. Comparisons between treatment groups were conducted according to Hochberg's procedure to control the overall type I error rate.

Time to deterioration in each PRO endpoint was compared between the two treatment arms in the ITT population using a stratified log-rank test.

Reviewer's Comments

- *The overall level of significance for this study was two-sided 0.05, which was allocated between the co-primary endpoints (0.01 for rPFS and 0.04 for OS). The type I error rate for the 4 major secondary endpoints comparison was planned to be controlled by using Hochberg's procedure at an overall 2-sided 0.05 level as pre-specified in the statistical analysis plan. In this sNDA submission, only rPFS benefit was demonstrated as statistically significant while OS results have not crossed the efficacy boundary; therefore, for the major secondary endpoints comparisons, the overall type I error rate should be controlled at an overall 2-sided 0.01 level instead of 0.05 level. There was no multiplicity adjustment for the*

analyses of other secondary endpoints and exploratory endpoints specified in the statistical analysis plan.

- *The censoring rule 6c specified in the statistical analysis plan was not applied in the primary analysis of rPFS. Patients who had unequivocal progression of non-bone non-target lesions were considered as an rPFS event in the primary analysis. The applicant clarified that this rule could not be programmatically determined and verified by the company because non-target lesions do not have physical measurements and are assessed qualitatively by the reviewing radiologist. The FDA statistical reviewer did a sensitivity analysis by including this censoring rule in the rPFS analysis in order to evaluate its impact. The results of this sensitivity analysis are summarized in Section 3.2.4 FDA sensitivity analysis 1.*

3.2.3. Patient Disposition, Demographic and Baseline Characteristics

3.2.3.1 Patients Disposition

From 28 April 2009 until 23 June 2010, a total of 1088 patients from 151 clinical sites in 12 countries were randomized to receive abiraterone acetate plus prednisone or placebo plus prednisone in a 1:1 randomization ratio. Four patients randomized to the abiraterone arm and two patients randomized to the placebo arm did not receive study treatment. As of the 20 December 2011 data cut-off date for the 2nd OS interim analysis, blinded treatment was ongoing for 252 patients (23%) while 830 patients (77%) had discontinued study treatment. Radiographic progression and unequivocal clinical progression were the two most common reasons for treatment discontinuation and was more frequent in the placebo arm, as shown in Table 3.

Table 3. Patient Disposition (Cutoff Date: 20 December 2011)

	Number (%) of Patients	
	AA (N=546)	**Placebo (N=542)**
Treated	542	540
Treatment status		
Discontinued study treatment	376 (69)	454 (84)
On study treatment	166 (31)	86 (16)
Primary reason for discontinuation of study treatment		
Discontinued per Protocol Section 6.6	283 (52)	351 (65)
Radiographic and Unequivocal Clinical Progression	57 (11)	53 (10)
Radiographic Progression Only	115 (21)	162 (30)
Unequivocal Clinical Progression Only	111 (21)	136 (25)
Patient withdrew consent	32 (6)	46 (9)
Adverse event(s)	40 (7)	29 (5)
Other	20 (4)	28 (5)
Lost to follow-up	1 (<1)	0

[Source: CSR Table 7]

3.2.3.2 Demographic and Baseline Characteristics

The demographic and baseline characteristics are presented in Tables 4 and 5. The median age of all randomized patients was 70 years old. Twenty-five percent of patients in the abiraterone arm were < 65 years of age, compared with 29% of patients in the placebo arm; 34% versus 30% of patients, respectively, were ≥ 75 years of age. Ninety-five percent were white, and only less than 3% were black. Forty-three percent (43%) of patients were enrolled in the United States. Twenty-six percent (26%) of patients had presented with metastatic disease (M1) at diagnosis. At initial diagnosis, 54% of patients in the abiraterone arm and 50% of patients in the placebo arm had a Gleason Score ≥ 8. Eighty-three percent (83%) of patients in the abiraterone arm and 80% of patients in the placebo arm had bone metastases at study entry. Twenty-four percent (24%) of patients had baseline ECOG performance score of 1 compared to 76% with score of 0. Sixty-six percent of patients had baseline BPI-SF worst pain score (item #3 in the questionnaire) in the last 24 hours of 0-1 (asymptomatic), and 26% with score of 2-3 (mildly symptomatic).

Table 4. Summary of Demographics Characteristics

	AA (N=546)	**Placebo (N=542)**	**All patients (N=1088)**
Age (years)			
n	546	542	1088
Median	71	70	70
Range	44, 95	44, 90	44, 95
Age category, n (%)			
<65	135 (25%)	155 (29%)	290 (27%)
65 - 74	226 (41%)	222 (41%)	448 (41%)
≥75	185 (34%)	165 (30%)	350 (32%)
Race, n (%)			
White	520 (95%)	510 (94%)	1030 (95%)
Asian	4 (<1%)	9 (2%)	13 (1%)
Black	15 (3%)	13 (2%)	28 (3%)
Native Hawaiian or other Pacific islander	0	2 (<1%)	2 (<1%)
Other	6 (1%)	6 (1%)	12 (1%)
Region, n (%)			
U.S.	234 (43%)	238 (44%)	472 (43%)
Non – U.S.	312 (57%)	304 (56%)	616 (57%)

[Source CSR Table 9]

Table 5. Summary of Baseline Disease Characteristics

	AA (N=546)	Placebo (N=542)	All Patients (N=1088)
Time From Initial Diagnosis to First Dose (years)			
n	542	540	1082
Mean (SD)	6.7 (4.85)	6.5 (4.77)	6.6 (4.81)
Median (Range)	5.5 (0, 28)	5.1 (0, 28)	5.3 (0, 28)
PSA at Initial Diagnosis (ng/mL)			
n	470	454	924
Mean (SD)	174.01 (540.433)	219.69 (888.783)	196.46 (732.545)
Median (Range)	22.30 (0.4, 5036.0)	21.00 (0.3, 9726.3)	22.00 (0.3, 9726.3)
Tumor Stage at Diagnosis			
n	542	540	1082
N0	218 (40%)	220 (41%)	438 (41%)
N1	61 (11%)	58 (11%)	119 (11%)
N2	16 (3%)	10 (2%)	26 (2%)
N3	8 (2%)	8 (2%)	16 (2%)
NX	118 (22%)	114 (21%)	232 (21%)
Unknown	117 (22%)	121 (22%)	238 (22%)
Not Applicable	4 (<1%)	9 (2%)	13 (1%)
Metastasis Stage at Diagnosis			
n	542	541	1083
M0	239 (44%)	230 (43%)	469 (43%)
M1, M1a, M1b, M1c	135 (25%)	142 (26%)	277 (26%)
MX	75 (14%)	88 (16%)	163 (15%)
Unknown	91 (17%)	75 (14%)	166 (15%)
Not Applicable	2 (<1%)	6 (1%)	8 (<1%)
Gleason Score at Initial Diagnosis			
n	488	508	996
< 7	65 (13%)	64 (13%)	129 (13%)
7	160 (33%)	190 (37%)	350 (35%)
2+5	0	1 (<1%)	1 (<1%)
3+4	81 (17%)	90 (18%)	171 (17%)
4+3	78 (16%)	98 (19%)	176 (18%)
≥ 8	263 (54%)	254 (50%)	517 (52%)
Extent of Disease at study entry			
n	544	542	1086
Bone	452 (83%)	432 (80%)	884 (81%)
Bone only	274 (50%)	267 (49%)	541 (50%)
Soft tissue or node	267 (49%)	271 (50%)	538 (50%)
Bone, soft tissue, or node	544 (100%)	542 (100%)	1086 (100%)
Other	4 (<1%)	7 (1%)	11 (1%)
ECOG PS			
n	546	542	1088
0	416 (76%)	414 (76%)	830 (76%)
1	130 (24%)	128 (24%)	258 (24%)
Baseline BPI-SF Pain Score (Worst pain in last 24 hours)			
n	539	534	1073
0	270 (50%)	260 (49%)	530 (49%)
1	100 (19%)	86 (16%)	186 (17%)
2	76 (14%)	86 (16%)	162 (15%)
3	53 (10%)	61 (11%)	114 (11%)
≥4	40 (7%)	41 (8%)	81 (8%)

[Source CSR Tables 10 and 12]

Reviewer's comments

- *The demographics and baseline disease characteristics were balanced between the two treatment arms.*
- *Racial minorities were under-represented in this study. African Americans make up only 3% of the ITT population. The incidence of prostate cancer in African Americans is 226 cases per 100,000, which is higher than the rate in whites which is 145 per 100,000 per CDC report.*
- *The primary efficacy analyses were stratified by IWRS-based ECOG PS data. Most patients had consistent baseline ECOG performance score per the IWRS system and the Case Report Form (CRF) collection, while entries for ECOG performance score were corrected for 24 (2%) patients in the CRF after randomization. The small number of patients with discrepancies on the stratification factor would not bias the estimate of treatment effect.*

3.2.3.3 Prior Anti-Cancer Therapy

Patients enrolled in this study were chemotherapy naïve. As shown in Table 6, fifty-two percent (52%) of patients in the abiraterone arm and 56% of patients in the placebo arm had prior prostate cancer radiotherapy; 47% and 45% of patients, respectively, had prior prostate cancer-related surgery. Twenty (4%) patients in the abiraterone arm and 24 (4%) patients in the placebo arm had an orchiectomy. Two patients in the abiraterone arm did not receive prior hormonal therapy and both were captured as protocol deviations.

Table 6. Summary of Prior Anti-Cancer Therapy

	AA (N=546) n (%)	Placebo (N=542) n (%)	All patients (N=1088) n (%)
Surgery	256 (47)	244 (45)	500 (46)
Radiotherapy	283 (52)	303 (56)	586 (54)
Hormonal	544 (99.6)	542 (100)	1086 (99.8)
Orchiectomy	20 (4)	24 (4)	44 (4)
Other	82 (15)	63 (12)	145 (13)

[Source CSR Table 13]

3.2.3.4 Post-Study Treatment Anti-Cancer Therapy

As of the clinical cut-off date for the second OS interim analysis (20 December 2011), fifty-nine percent (59%) of patients in the abiraterone arm and 74% in the placebo arm have received subsequent therapies. A summary of selected subsequent therapies for prostate cancer is provided in Table 7. Subsequent abiraterone acetate use was documented for 54 patients (10%) in the placebo arm. During reviewing this sNDA, the analysis results from the third OS interim analysis were submitted using a cutoff date of 22 May 2012, and the subsequent therapy information was updated as well (Table 7). At the time of third interim OS analysis, 7% and 14% of the patients in the abiraterone arm and placebo arm, respectively, received abiraterone acetate as a subsequent therapy.

Table 7. Summary of Subsequent Therapy

	AA (N=546) n (%)	Placebo (N=542) n (%)
Cutoff: 20 December 2011 (the 2nd OS interim analysis)		
Number of patients with selected subsequent therapy for prostate cancer	242 (44)	327 (60)
Docetaxel	207 (38)	287 (53)
Cabazitaxel	45 (8)	52 (10)
Ketoconazole	39 (7)	63 (12)
Provenge or Sipuleucel-T	27 (5)	24 (4)
Abiraterone acetate	26 (5)	54 (10)
Cutoff: 22 May 2012 (the 3rd OS interim analysis)		
Number of patients with selected subsequent therapy for prostate cancer	274 (50)	348 (64)
Docetaxel	239 (44)	304 (56)
Cabazitaxel	60 (11)	70 (13)
Ketoconazole	39 (7)	63 (12)
Provenge or Sipuleucel-T	33 (6)	28 (5)
Abiraterone acetate	38 (7)	78 (14)

[Source: CSR Tables 14, TEFF20, and OS-update Table 2]

Reviewer's comments

Following the protocol amendment #3, patients in the placebo arm were allowed to crossover to receive abiraterone acetate treatment. The crossover of the first patient through the protocol amendment #3 occurred on 7 May 2012. The cutoff of the 3rd interim analysis was 22 May 2012, which was two weeks after the first crossover under protocol Amendment #3. The small percentage of crossover, i.e., 14% of patient in the placebo receiving subsequent abiraterone acetate, would not have strong confounding impact on the randomized treatment effect on overall survival.

3.2.3.5 Protocol deviations

Twelve percent (12%) of patients in the abiraterone arm and 10% of patients in the placebo arm had major protocol deviations during the study (Table 8). Major protocol deviations were defined as: any protocol deviation that has the potential to impact or impacts patients' rights, safety, or well-being, or the integrity and/or results of the trial. Eligibility criteria not being met was the most common protocol deviation, followed by receiving prohibited concurrent medication.

Table 8. Major Protocol Deviations

	AA (N=546) n (%)	Placebo (N=542) n (%)	All patients (N=1088) n (%)
Total number of patients with a major deviation	67 (12)	55 (10)	122 (11)
Eligibility criteria not met	30 (6)	24 (4)	54 (5)
Prohibited concurrent medication	20 (4)	13 (2)	33 (3)
Treatment discontinuation criteria not followed	5 (< 1)	13 (2)	18 (2)
IP dosing error	6 (1)	3 (< 1)	9 (< 1)
Drug dispensing error	2 (< 1)	4 (< 1)	6 (< 1)
Assessment/visit/phone follow-up not done	2 (< 1)	2 (< 1)	4 (< 1)
Assessment not performed properly per protocol	0	1 (< 1)	1 (< 1)
Dose modification/toxicity management not followed	1 (< 1)	0	1 (< 1)
Other Deviation	3 (< 1)	1 (< 1)	4 (< 1)

[Source CSR Table 15]

Reviewer's comments

Sensitivity analyses have been performed on rPFS and OS by excluding patients with major protocol deviations. The results are consistent with the primary analysis results per ITT population, as summarized in section 3.2.4.

3.2.4 Results and Conclusions

3.2.4.1 Primary Efficacy Endpoints

Overall Survival

Overall survival was a co-primary efficacy endpoint of this pivotal study. The first interim OS analysis was conducted at the time of the final rPFS analysis, with 98 death events. The second and third interim OS analyses were conducted when 333 and 434 death events occurred, respectively. The efficacy boundaries, observed HRs, and p-values for the three interim analyses are summarized in Table 9. The efficacy boundaries were not crossed at any of the three interim analyses. The final OS analysis will be performed when 773 death events occur.

Table 9. Summary of OS Interim Analysis Results

Analysis	Planned cumulative OS events, n (% information)	Observed cumulative OS events, n (% information)	Alpha boundary *	Observed HR (p-value)
Interim 1	116 (15%)	98 (13%)	<0.0001	1.08 (0.69)
Interim 2	311 (40%)	333 (43%)	0.0008	0.75 (0.0097)
Interim 3	425 (55%)	434 (56%)	0.0035	0.79 (0.015)
Final	773 (100%)			

*per O'Brien-Fleming boundary

The cutoff date for the 2nd OS interim analysis was 20 December 2011. The IDMC met on 27 February 2012 to review the masked efficacy and safety outcomes for this pre-specified 2nd

interim analysis and unanimously recommended unblinding the treatment and allowing patients in the placebo group to receive abiraterone acetate. The company sent a letter to the sites with treatment assignments on 26 March 2012. The crossover of the first patient through amendment 3 of protocol COU-AA-302 occurred on 7 May 2012. The data cutoff date for the 3rd OS interim analysis was 22 May 2012. The detailed results from the 3rd interim analysis are presented in Table 10. The corresponding Kaplan-Meier curves at the 3rd interim analysis are given in Figure 1.

Table 10. Summary of the 3rd Interim Overall Survival Analysis

	AA (N=546)	Placebo (N=542)
Number of deaths, n (%)	200 (37%)	234 (43%)
Median (95% CI), in months	35.3(31.2, 35.3)	30.1 (27.3, 34.1)
Hazard ratio (95% CI) [a]	0.79 (0.66, 0.96)	
Stratified log rank p-value [b]	0.015	

[a] Hazard ratio was obtained from a Cox proportional hazards model stratified by IWRS-based ECOG PS
[b] P-value was obtained from a log-rank test stratified by IWRS-based ECOG PS
[Source: OS-update report Table 1]

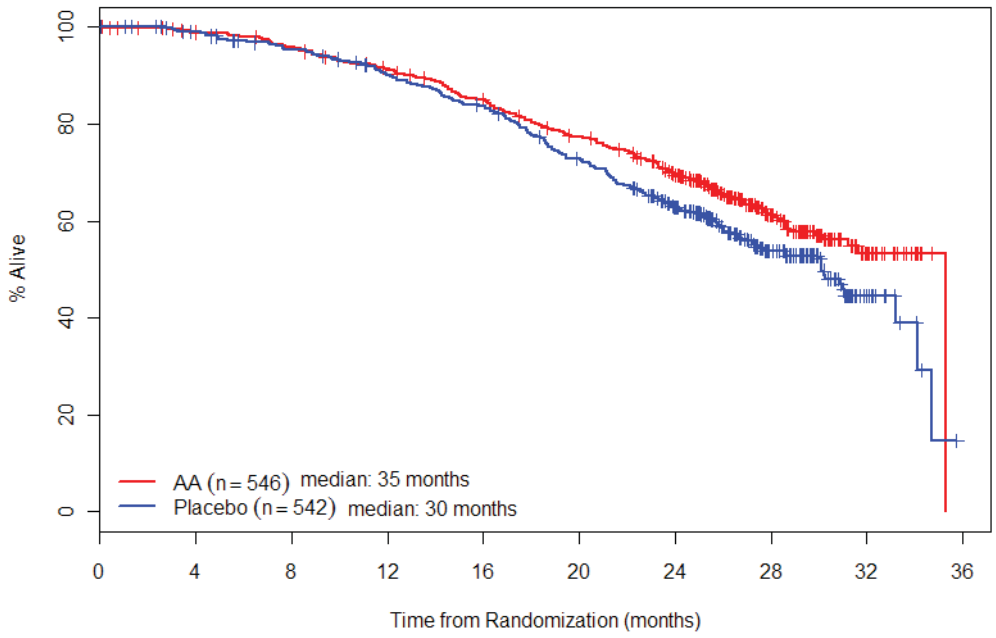

Figure 1. Kaplan-Meier Curves of the 3rd Interim Overall Survival Analysis
[Source: OS-update report Figure 1]

Reviewer's Comments

- *At the cutoff date for the 3rd interim OS analysis, 14% of patients in the placebo arm and 7% of patients in the abiraterone arm have received subsequent abiraterone acetate treatment. As the number of crossover was small, no strong confounding impact from crossover on OS results is expected. The Applicant performed three sensitivity analyses to address crossover*

effect, i.e.,1) excluding placebo patients who received subsequent abiraterone acetate, 2) using iterative parameter estimate, 3) using rank preserving failure time. The results were similar to the primary analysis.

- *The median estimates of OS are not robust, especially in the abiraterone arm, as it was driven by one event which occurred late.*
- *Using a non-stratified analysis, the HR estimate of the 3rd interim OS analysis was 0.79 (95% CI: 0.66, 0.96), which was consistent to the HR estimated in the primary stratified analysis.*
- *If excluding patients with major protocol deviation from the 3rd interim OS analysis, the HR was 0.76 (95% CI: 0.62, 0.93), which was consistent to the primary findings in the ITT population.*

Radiographic PFS – Primary Efficacy Analysis

The other co-primary endpoint of this pivotal study was rPFS. The primary analysis of rPFS was based on the IRR assessment with a cutoff date of 20 December 2010 in the ITT population, using a stratified log-rank test. A statistically significant improvement in rPFS was observed in the abiraterone arm compared with the placebo arm. The median rPFS was 8.28 months in the placebo arm and was not reached in the abiraterone arm, with a corresponding HR of 0.43 (95% CI: 0.35, 0.52) under adjustment of the stratification factor, as presented in Table 11. The Kaplan-Meier curves are shown in Figure 2.

Table 11. Radiographic Progression-Free Survival per IRR (Cutoff: 20 December 2010)

	AA (N=546)	Placebo (N=542)
Patient Classification, n (%)		
rPFS Events	150 (28)	251 (46)
Progression by bone scan only	57 (10)	79 (15)
Progression by CT/MRI only	66 (12)	115 (21)
Progression by both bone scan and CT/MRI	18 (3)	46 (9)
Death without progression	9 (2)	11 (2)
Censored	396 (72)	291 (54)
Median (95% CI), in months	NE (11.66, NE)	8.28 (8.12, 8.54)
Hazard ratio (95% CI) [a]	0.43 (0.35, 0.52)	
Stratified log rank p-value [b]	<0.0001	

[a] Hazard ratio was obtained from a Cox proportional hazards model stratified by ECOG performance status
[b] P-value was obtained from a log rank test stratified by ECOG performance status.
NE=Not estimable *[Source CSR Table 21]*

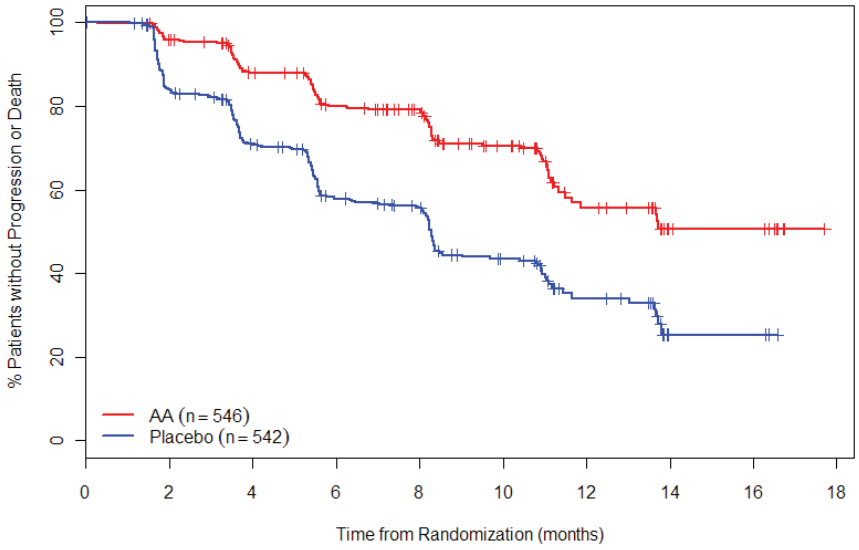

Figure 2. Kaplan-Meier Curves of Radiographic Progression-Free Survival per IRR

[Source: Adapted from CSR Figure 3]

Reviewer's Comments

- *The FDA clinical and statistical review team has re-evaluated each patient's radiographic progression status based on the raw lesion data per independent radiographic assessment following the modified RECIST 1.0 criteria (CT/MRI scan) and PCWG2 criteria (bone scan. A total of 12 patients (6 patients in each arm) have been identified with different rPFS event type and/or time compared to the IRR rPFS data submitted. The median and HR estimates from the FDA rPFS analysis are the same as the primary findings from the Applicant's primary rPFS analysis.*
- *The median follow-up time for rPFS in the ITT population was 8 months in both arms using the inverse Kaplan-Meier method based on the IRR assessment.*

Radiographic PFS Supportive Analysis -- per Investigator Assessment

The primary rPFS analysis was based on the IRR assessment. To evaluate consistency between the independent and investigator radiographic reviews, a supportive analysis of rPFS based on the investigator (INV) assessment was conducted. At the time of the final rPFS analysis (cutoff date of 20 December 2010), there were 435 rPFS events documented per INV assessment. The estimated median of INV-based rPFS was 13.73 months in the abiraterone arm and was 8.25 months in the placebo arm, with a HR of 0.49 (95% CI: 0.41, 0.60) and a p-value < 0.0001 (Table 12). Kaplan-Meier curves of rPFS per INV are illustrated in Figure 3.

Table 12. Radiographic Progression-Free Survival per INV

	AA (N=546)	Placebo (N=542)
Patient Classification, n (%)		
Events	174 (32)	261 (48)
Censored	372 (68)	281 (52)
Median (95% CI), in months	13.73 (11.33, 16.26)	8.25 (7.92, 9.69)
Hazard ratio (95% CI) [a]	0.49 (0.41, 0.60)	
Stratified log rank p-value [b]	<0.0001	

[a] Hazard ratio was obtained from a Cox proportional hazards model stratified by ECOG PS
[b] P-value was obtained from a log-rank test stratified by ECOG PS
[Source CSR Table 22]

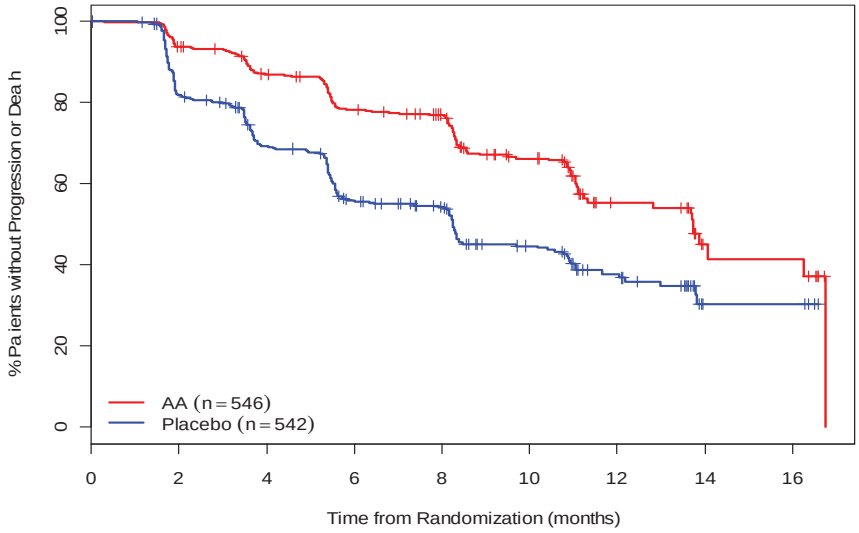

Figure 3. Kaplan-Meier Curves of Radiographic Progression-Free Survival per INV

[Source: CSR Figure 5]

Reviewer's Comments:

- *The rPFS analysis results per investigator assessment were consistent with those per independent radiographic review assessment.*
- *An un-planned rPFS update per INV post the final rPFS analysis was performed at the time of the second OS interim analysis. As shown in Table 13, the results were consistent with those of the primary analysis.*

Table 13. Unplanned Update on Radiographic Progression-Free Survival per INV

	AA (N=546)	Placebo (N=542)
Patient Classification, n (%)		
Events	271 (50)	336 (62)
Censored	275 (50)	206 (38)
Median (95% CI), in months	16.46 (13.80, 16.79)	8.25 (8.05, 9.43)
Hazard ratio (95% CI) [a]	0.53 (0.45, 0.62)	

[a] Hazard ratio was obtained from a Cox proportional hazards model stratified by ECOG PS
Cutoff date: 20 December 2011
[Source CSR Table 23]

Censoring Reasons for rPFS

The censoring reasons for rPFS based on IRR and INV assessment are summarized in Table 14. For patients who were censored permanently, the major censoring reason was 'new anti-cancer therapy added'. In IRR-based rPFS analysis, there were a total of 111 patients (44 in the abiraterone arm and 67 in the placebo arm) censored due to new anti-cancer therapy added, of whom, 50 patients had documented disease progression per investigator assessment.

Table 14. Summary of Censoring Reasons for rPFS per IRR and INV

	IRR		INV	
	AA (N=546) n (%)	Placebo (N=542) n (%)	AA (N=546) n (%)	Placebo (N=542) n (%)
Censored patients	396 (72)	291 (54)	372 (68)	281 (52)
Still at risk	327 (60)	197 (36)	314 (58)	200 (37)
On treatment and no event by cutoff	287 (53)	151 (28)	281 (51)	159 (29)
Off treatment and alive in follow-up by cutoff	40 (7)	46 (9)	33 (6)	41 (8)
Permanently censored	69 (13)	94 (17)	58 (11)	81 (15)
No baseline and post-line assessments	10 (2)	11 (2)	2 (<1)	0
No post baseline assessments	0	3 (<1)	8 (1)	14 (3)
New anti-cancer therapy added	44 (8)	67 (12)	34 (6)	54 (10)
Events after ≥ 2 missing tumor assessments	6 (1)	4 (<1)	4 (<1)	5 (<1)
Withdrew consent to remain on study	9 (2)	9 (2)	10 (2)	8 (1)

[Source: CSR Table 11-15]

Reviewer's Comment

- *Of patients censored due to "new anti-cancer therapy added" in the IRR-based rPFS analysis, a large proportion was expected to be close to disease progression per IRR, which might contribute to informative censoring. To address this potential informative censoring, a sensitivity analysis was performed. The results are summarized in the section 3.2.4.*
- *Per the study protocol, radiographic disease assessment was planned to be conducted until the end of study treatment. Therefore, patients who were off study treatment and still alive in follow-up by the cutoff date would not have any further radiographic disease assessment.*

Comparison of Independent and Investigator Assessment of Progression

The discordance rate between IRR and INV assessment in terms of rPFS event type (event vs. censored) was 21% in the abiraterone arm and 24% in the placebo arm as presented in Table 15.

Table 15. Comparison of Progression based on INV and IRR

	AA (N=546)	Placebo (N=542)
Overall discordance rate, n (%)	116 (21)	128 (24)
PFS event by IRR, n (%)	150 (27)	251 (46)
PFS event by Investigator, n (%)	104 (19)	192 (35)
Censored by Investigator, n (%)	46 (8)	59 (11)
Censored by IRR, n (%)	396 (73)	291 (54)
Censored by Investigator, n (%)	326 (60)	222 (41)
PFS event by Investigator, n (%)	70 (13)	69 (13)

[Source: CSR Table 11-9]

Reviewer's Comments

- *If considering the time of censoring/event as well, the discordance rate was 36% in the abiraterone arm and 44% in the placebo arm (Table 16). The median of difference on censoring/event time between IRR and INV was 58 days among patients with different rPFS time but same event type. Despite the discordance rate, the analysis results were consistent based on IRR and INV assessment.*

Table 16. Discordance between INV and IRR, including rPFS Event Type and Time

AA			Placebo		
Type	**Timing**	**Total**	**Type**	**Timing**	**Total**
21%	15%	36%	24%	20%	44%

- *The event type discordance rate per MRI/CT scan alone was 15% for the abirateron arm and 18% for the placebo arm; while the event type discordance rate per bone scan alone was 13% in the abiraterone arm and 18% in the placebo arm.*

Sensitivity Analyses of rPFS

Sensitivity analyses for rPFS performed by the applicant are summarized in Table 17.

Table 17. Overview of Applicant's Sensitivity Analyses of rPFS per IRR assessment

Sensitivity Analysis	AA	Placebo	Hazard Ratio [a]
	Median rPFS (months)		(95% CI)
Unstratified Cox model	NE	8.28	0.43 (0.35, 0.52)
Including the initiation of cytotoxic chemotherapy as an event	11.86	7.03	0.42 (0.35, 0.51)
Excluding patients with major protocol deviations [b]	NE	8.25	0.41 (0.33, 0.50)
Including unconfirmed bone progression as an event	11.0	5.5	0.57 (0.49, 0.68)
Including the unequivocal clinical progression as an event	11.99	7.92	0.42 (0.35, 0.51)

[a] Hazard ratio was obtained from a non-stratified Cox proportional hazards model. Hazard ratio < 1 favors Abiraterone arm
[b] This is a post-hoc analysis
NE= Not Estimable
[Source CSR Tables TEFF01B, TEFF01D, TEFF01F, and TEFF01H]

This reviewer performed additional sensitivity analyses to evaluate the robustness of the primary findings of rPFS per IRR assessment. The results are summarized in Table 18.

FDA Sensitivity Analysis 1: Censoring patients whose radiographic progression was based on non-target lesions only at the last non-progression assessment time.

FDA Sensitivity Analyis 2: Considering patients who were censored due to receiving a new anti-cancer therapy as having disease progression at the next scheduled tumor assessment.

FDA Sensitivity Analysis 3: Using the earlier time of IRR and INV to define rPFS events. If rPFS event types (event vs. censoring) were same between IRR and INV assessment, the shortest rPFS time was used. For discrepant cases (i.e. cases that have been deemed failure according to one source and censored observation according to the other source), patients were considered as failures and failure time was used.

FDA Sensitivity Analysis 4: To address potential bias by informative censoring in the rPFS analysis based on IRR assessment, a sensitivity analysis was performed by applying the rules following:

- For patients in the abiraterone arm, who were censored due to "new anti-cancer therapy added" per IRR and were assessed as rPFS events per investigator, rPFS events were imputed and the corresponding rPFS time was extended by 8 weeks from the last non-progression assessment visit, assuming they would have progressed at the next tumor assessment.
- For patients in the placebo arm, there was no imputation rule applied and patients who were censored for new anti-cancer therapy were not imputed to have an event.

Table 18. Overview of FDA's Sensitivity Analyses of rPFS per IRR Assessment

Sensitivity Analysis	AA	Placebo	Hazard Ratio [a]
	Median rPFS (months)		(95% CI)
FDA Sensitivity Analysis 1	NE	8.4	0.43 (0.35, 0.53)
FDA Sensitivity Analysis 2	12.1	7.1	0.44 (0.36, 0.52)
FDA Sensitivity Analysis 3	11.1	5.6	0.48 (0.40, 0.57)
FDA Sensitivity Analysis 4	13.7	8.3	0.48 (0.40, 0.59)

[a] Hazard ratio was obtained from a non-stratified Cox proportional hazards model. Hazard ratio < 1 favors Abiraterone arm
NE= Not Estimable

The results of sensitivity analyses support the robustness of the primary rPFS findings.

FDA Exploratory Analyses: Evaluation of Time to Tumor Assessment

To evaluate whether the assessment time influenced rPFS outcome, an exploratory analysis comparing time to tumor assessment between the two treatment arms was performed. Time from randomization to each assessment (including unscheduled visits) was calculated. When a patient missed a scheduled visit, his/her next visit time was used to calculate the time to the current assessment. Log-rank test was used to test if cumulative percentages (survival curves) were equal in the two treatment arms. Medians and test results for MRI/CT scans and bone scans are presented in Tables 19 and 20, respectively. The log-rank test showed that there was no significant difference between the two treatment arms on time to assessment.

Table 19. Median of Time to Tumor Assessment (MRI/CT scan) and Log-rank Test

Time from randomization to the	Median (n), in weeks		Log-rank Test
	AA (N=546)	Placebo (N=542)	Nominal P-value*
1st assessment	7.7 (532)	7.7 (526)	0.58
2nd assessment	15.7 (507)	15.7 (463)	0.38
3rd assessment	23.7 (471)	23.9 (375)	0.30
4th assessment	35.7 (384)	35.6 (265)	0.19
5th assessment	47.7 (190)	47.6 (122)	0.08
6th assessment	59.6 (59)	59.6 (49)	0.95
7th assessment	71.1 (15)	71.2 (6)	0.70

* Not adjusted for multiplicity

Table 20. Median of Time to Tumor Assessment (bone scan) and Log-rank Test

Time from randomization to the	Median (n), in weeks		Log-rank Test
	AA (N=546)	Placebo (N=542)	Nominal P-value*
1st assessment	7.7 (533)	7.7 (527)	0.27
2nd assessment	15.7 (507)	15.7 (473)	0.86
3rd assessment	23.7 (472)	23.7 (380)	0.70
4th assessment	35.7 (385)	35.6 (270)	0.68
5th assessment	47.7 (189)	47.6 (126)	0.12
6th assessment	59.6 (61)	59.6 (51)	0.21
7th assessment	71.1 (15)	71.1 (7)	0.72

* Not adjusted for multiplicity

3.2.4.2 Major Secondary Endpoints

This pivotal study had 4 pre-specified major secondary efficacy endpoints with the overall alpha controlled by the Hochberg procedure.

Time to opiate use for cancer pain

Opiate use for cancer pain was documented for 34% of patients in the abiraterone arm and 43% of patients in the placebo arm. A statistically significant improvement in time to opiate use for cancer pain was observed in the abiraterone arm compared with the placebo arm. The median was 23.66 months in the placebo arm and was not reached in the abiraterone arm, with a corresponding HR of 0.69 (95% CI: 0.57, 0.83) and a p-value of 0.0001, as presented in Table 21. The Kaplan-Meier curves are shown in Figure 4.

Table 21. Time to Opiate Use for Cancer Pain

	AA (N=546)	Placebo (N=542)
Events, n (%)	183 (34%)	235 (43%)
Median (95% CI), in months	NE (28.25, NE)	23.66 (20.24, NE)
Hazard ratio (95% CI) [a]	0.69 (0.57, 0.83)	
Stratified log rank p-value [b]	0.0001	

Note: NE=not estimable

[a] Hazard ratio was obtained from a Cox proportional hazards model stratified by ECOG PS

[b] P-value was obtained from a log-rank test stratified by ECOG PS

[Source: CSR Table 29]

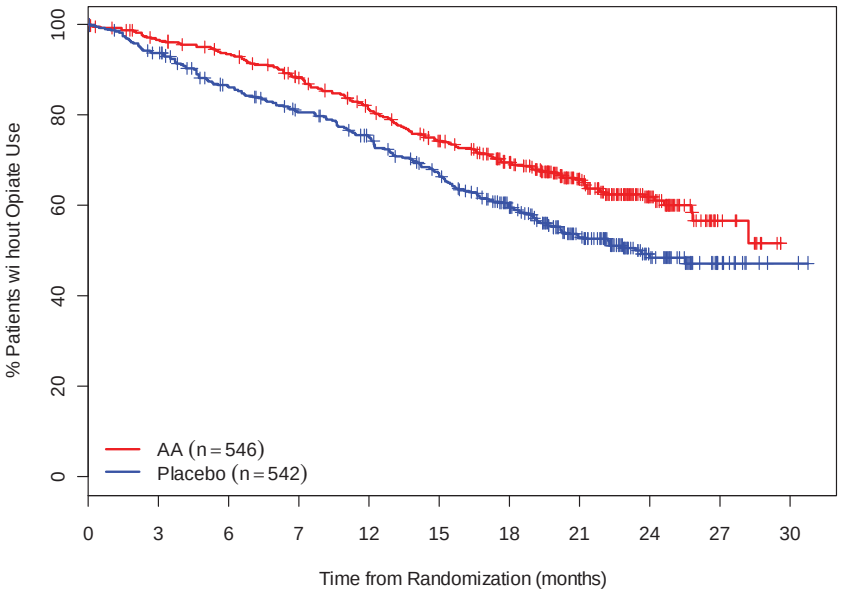

Figure 4. Kaplan-Meier Curves of Time to Opiate Use for Cancer Pain

[Source: CSR Figure 13]

Reviewer's Comments

- *The time to opiate use analysis was based on the attribution of the opiate use to cancer pain which may introduce some subjectivity into the endpoint. Results of a sensitivity analysis for time to opiate use regardless of indication favored the abiraterone arm (Table 22).*

Table 22. Time to Opiate Use Regardless of Indication

	AA (N=546)	Placebo (N=542)
Events, n (%)	281 (51%)	321 (59%)
Median (95% CI), months	20.11 (16.79, 22.08)	15.24 (13.54, 16.89)
HR (95% CI) [a]	0.76 (0.65, 0.90)	
P-value [b]	0.001	

[a] Hazard ratio was obtained from a Cox proportional hazards model stratified by ECOG PS
[b] P-value was obtained from a log-rank test stratified by ECOG PS

- *The collection of data in the on-study case report forms for time to opiate use was not optimal. Rather than a yes/no question (i.e. "Did you take any of the following medicines for cancer pain since your last visit"), this analysis relied on a review of collected concomitant medications records. It was unclear whether the lack of an opiate use was a true negative (patient did not take an opiate) or was missing data (patient forgot to include it on the list). Therefore, an information request was sent to the applicant:*

  FDA Information Request 8/23/2012:
  We have a concern regarding the collection of concomitant medications supporting your key secondary endpoints: time to cytotoxic chemotherapy and time to first opiate use. We noted that for the long term quarterly follow-up visits (CRF "FU"), there are specific

questions asked for opiate use (yes/no/unknown) and cytotoxic chemotherapy or any other prostate cancer therapies (yes/no/unknown) since last follow-up visit. However, no such questions were found for the on-study treatment visits. Without specifically asking these questions, we rely on the lack of reporting of these medications in an overall concomitant medication list. As such, it is unclear if the lack of opiate or cytotoxic during the prior period was a true negative or missing data.

The applicant considers that a lack of opiates on the concomitant medication list was "true negatives" for the following reasons:

- *Extensive site monitoring to ensure source documentation captured in CRF*
- *Cross validation was performed to verify that the appropriate medications were entered in the Concomitant Medication Form by checking data from multiple locations within CRFs including:*
    - *Treatment Discontinuation Reason (Unequivocal Clinical Progression by cytotoxic chemotherapy or chronic opiate pain medication use)*
    - *Adverse event for pain*
    - *Analgesic Use Form (0- no analgesic, 1- non-opioid analgesic, 2- opioid for mod pain, 3- opioid for severe pain)*
    - *BPI-SF Form (Queried on Question #7: "What treatments or medications are you receiving for your pain? (Please record treatments or medications on Concomitant Medication Form)"*

Per FDA's request, the applicant performed a sensitivity analysis by censoring patients who had at least 2 consecutive missing visits to the last visit with no event. The result favored the abiraterone arm with a HR of 0.69 (95% CI; 0.57, 0.83).

The lack of a single yes/no answer for each on-study visit with respect to whether a patient had taken an opiate pain medication is a limitation potentially weakening the results. However; the duplication and cross-validation of opiate use data throughout multiple case report forms mitigates the potential for missing opiate use data from the concomitant medications CRF. Furthermore, additional trial results including time to analgesic score progression and patient reported outcomes for pain as discussed later in the efficacy review support an improvement in the time to opiate use.

Time to initiation of cytotoxic chemotherapy

Initiation of cytotoxic chemotherapy was documented for 40% of patients in the abiraterone arm and 55% of patients in the placebo arm. A statistically significant improvement in time to initiation of cytotoxic chemotherapy was observed in the abiraterone arm compared with the placebo arm. The median was 25.17 months in the abiraterone arm and was 16.82 months in the placebo arm, with a corresponding HR of 0.58 (95% CI: 0.49, 0.69) and a p-value less than 0.0001, as presented in Table 23. The Kaplan-Meier curves are shown in Figure 5.

Table 23. Time to Initiation of Cytotoxic Chemotherapy

	AA (N=546)	Placebo (N=542)
Events, n (%)	220 (40%)	298 (55%)
Median (95% CI), in months	25.17 (23.26, NE)	16.82 (14.55, 19.38)
Hazard ratio (95% CI) [a]	0.58 (0.49, 0.69)	
Stratified log rank p-value [b]	<0.0001	

[a] Hazard ratio was obtained from a Cox proportional hazards model stratified by ECOG PS
[b] P-value was obtained from a log-rank test stratified by ECOG PS
NE=not estimable
[Source: CSR Table 30]

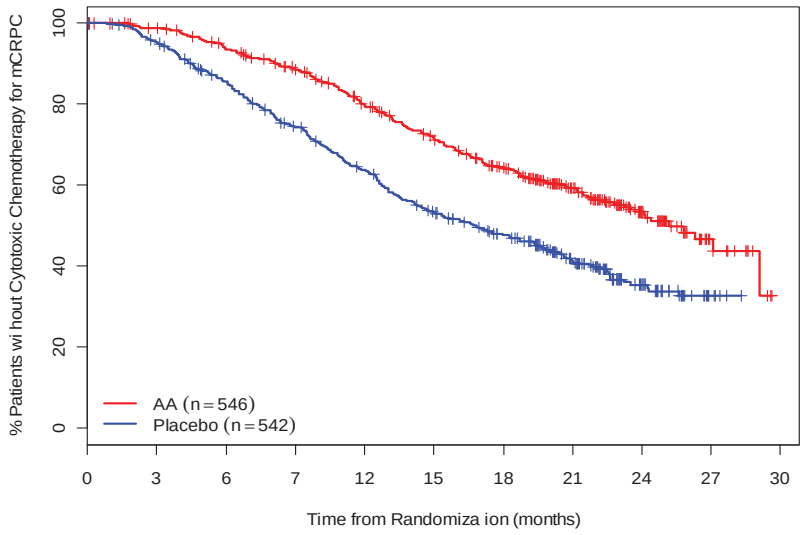

Figure 5. Kaplan-Meier Curves of Time to Initiation of Cytotoxic Chemotherapy
[Source: CSR Figure 14]

Reviewer's Comments

- *The applicant did not pre-specify the type of cytotoxic chemotherapy in the statistical analysis plan, but provided the list in the dataset definition file. The following cytotoxic chemotherapies were included in the applicant's analysis: alkylating agents, plant alkyloids and other natural products, cytotoxic antibiotics and related substances, antimetabolites, platinum compounds, combinations of antineoplastic agents, and other antineoplastic agents.*
- *The clinical reviewer reviewed the concomitant medications dataset and identified all medications that were consistent with cytotoxic agents. This dataset was then re-analyzed by the statistical reviewer and the results continued to favor the abiraterone arm (Table 24).*

Table 24: Time to Initiation of Cytotoxic Chemotherapy (FDA Analysis)

	AA (N=546)	Placebo (N=542)
Events, n (%)	220 (40%)	301 (56%)
Median (95% CI), months	25.17 (23.26, NE)	16.62 (14.29, 19.32)
HR (95% CI) [a]	0.57 (0.48, 0.68)	
P-value [b]	<0.0001	

[a] Hazard ratio was obtained from a Cox proportional hazards model stratified by ECOG PS
[b] P-value was obtained from a log-rank test stratified by ECOG PS
NE=not estimable

- *The review team also performed an exploratory analysis on time to cytotoxic chemotherapy or other prostate cancer-related procedure. The clinical reviewer reviewed a list of on-study procedures from SDTM dataset [YB]. This was done blinded to treatment arm and those procedures likely related to treatment for prostate cancer or prostate cancer related morbidity were flagged and included in the analysis. Some of the more common procedures included: nephrostomy tube insertion (revisions/replacements not included), ureteral stenting, radiation therapy, orthopedic procedures, TURP and suprapubic catheter insertion.*

  The time to chemotherapy or prostate-cancer related procedures favored the abiraterone arm with a HR of 0.62 (Table 25).

Table 25: Time to Cytotoxic Chemotherapy OR Prostate Cancer-Related Procedure

	AA (N=546)	Placebo (N=542)
Events, n (%)	280 (51%)	353 (65%)
Median (95% CI) in months	20.07 (17.71, 21.91)	13.21 (12.19, 14.55)
HR (95% CI) [a]	0.62 (0.53, 0.72)	
P-value [b]	<0.0001	

[a] Hazard ratio was obtained from a Cox proportional hazards model stratified by ECOG PS
[b] P-value was obtained from a log-rank test stratified by ECOG PS

- *Results the FDA's analyses are consistent to the primary finding of the time to cytotoxic chemotherapy. Although the endpoint, time to cytotoxic chemotherapy, had the same problem of data collection methods as the time to opiate use endpoint, by cross-checking related CRF entries the applicant claimed that there was no on-treatment missing data. It is also acknowledged by the medical reviewer that it would be much less likely for a patient to inadvertently forget to list cytotoxic chemotherapy as a concomitant medication.*

Time to ECOG performance status deterioration

Deterioration in ECOG performance status grade by ≥ 1 grade was observed in 71% of patients in the abiraterone arm and 76% of patients in the placebo arm. A statistically significant time to deterioration in ECOG performance status grade by ≥ 1 grade was observed in the abiraterone arm compared with the placebo arm. The median was 10.87 months in the placebo arm and was 12.29 months in the abiraterone arm, with a corresponding HR of 0.82 (95% CI: 0.71, 0.94) and a p-value of 0.005, as presented in Table 26.

A post-hoc analysis was performed with the requirement of confirmation of deterioration at the next visit. The detailed results are presented in Table 26.

Table 26. Time to Deterioration in ECOG PS Grade ≥ 1 Point

	Abiraterone (N=546)	Placebo (N=542)
Pre-specified analysis with no requirement of confirmation		
Events, n (%)	390 (71%)	411 (76%)
Median (95% CI), in months	12.29 (11.33, 14.29)	10.87 (9.49, 11.76)
Hazard ratio (95% CI) [a]	0.82 (0.71, 0.94)	
P-value [b]	0.005	
Post-hoc analysis with the requirement of confirmation		
Events, n (%)	268 (49%)	306 (57%)
Median (95% CI), in months	19.58 (17.74, 23.85)	15.51 (13.83, 16.92)
Hazard ratio (95% CI) [a]	0.75 (0.64, 0.89)	
P-value [b]	0.0007	

[a] Hazard ratio was obtained from a Cox proportional hazards model stratified by baseline ECOG PS
[b] P-value was obtained from a log-rank test stratified by baseline ECOG PS
[Source: CSR Tables 31 and 32]

Reviewer's Comments

- *To evaluate the robustness of the findings in time to ECOG PS deterioration analysis, the FDA has requested the applicant to conduct a sensitivity analysis using the following censoring rules.*

  Censoring patients on the date of the last visit with no deterioration

  (1) if the patient received subsequent anti-cancer therapy before deterioration

  (2) if the patient missed ≥ 2 consecutive visits for ECOG status evaluation

  The sensitivity analysis results showed that for the time to ECOG PS deterioration without requirement of confirmation, the HR was 0.81 (95% CI: 0.69, 0.95) with a p-value of 0.0103, which is slightly greater than the significance level of 0.01. The results indicate that the findings of time to ECOG deterioration are not robust.

- [redacted] (b) (4)

Time to PSA progression

PSA progression was documented for 62% of patients in the abiraterone arm and 70% of patients in the placebo arm. A statistically significant time to PSA progression was observed in the abiraterone arm compared with the placebo arm. The median was 5.55 months in the placebo arm and was 11.07 months in the abiraterone arm, with a corresponding HR of 0.49 (95% CI: 0.42, 0.57) and a p-value less than 0.0001, as presented in Table 27.

Table 27. Time to PSA Progression

	AA (N=546)	Placebo (N=542)
Events, n (%)	339 (62%)	381 (70%)
Median (95% CI), in months	11.07 (8.51, 11.24)	5.55 (5.39, 5.59)
Hazard ratio (95% CI) [a]	0.49 (0.42, 0.57)	
P-value [b]	<0.0001	

[a] Hazard ratio was obtained from a Cox proportional hazards model stratified by baseline ECOG PS
[b] P-value was obtained from a log-rank test stratified by baseline ECOG PS
[Source: CSR Table 32]

3.2.4.3 Other Secondary Endpoints

Objective Response

Per IRR assessment with a cutoff date of 20 December 2010, the objective response rate according to RECIST criteria was 36% in the abiraterone arm and 16% in the placebo arm, among patients with measurable disease at baseline. The response duration was 10 months in the abiraterone arm responders and 8.6 months in the placebo arm responders. The median of time to response was 3.5 months in both arms.

PSA Response

The rate of confirmed PSA response was 62% in the abiraterone arm and 24% in the placebo arm, and the median of time to PSA response was 1.9 months in both arms. If including the unconfirmed PSA response as well, the response rate was 69% in the arbiaterone arm and was 29% in the placebo arm.

Time to Analgesic Progression

Analgesic progression was documented for 23% of patients in the abiraterone arm and 25% of patients in the placebo arm, with a HR of 0.69 (95% CI: 0.54, 0.88). The median time to analgesic progression was not reached in either arm (Table 28).

Table 28. Time to Analgesic Progression

	AA (N=546)	Placebo (N=542)
Events, n (%)	127 (23%)	134 (25%)
Median (95% CI), in months	NE	NE
Hazard ratio (95% CI) [a]	0.69 (0.54, 0.88)	

Note: NE=not estimable; cutoff date: 20 December 2011
[a] Hazard ratio was obtained from a Cox proportional hazards model stratified by baseline ECOG PS

Patient Report Outcomes

PRO data were collected from the BPI-SF and the FACT-P questionnaires. Across both treatment arms, the cumulative compliance rate for completion of the BPI-SF and the FACT-P instruments was 95% or higher at any given point during treatment.

Time to average pain intensity progression

Time to average pain intensity progression was documented for 36% of patients in the abiraterone arm and 35% of patients in the placebo arm. The median was 18.40 months in the placebo arm and was 26.74 months in the abiraterone arm, with a corresponding HR of 0.82 (95% CI: 0.67, 1.00), as presented in Table 29. The Kaplan-Meier curves are shown in Figure 6.

Table 29. Time to Pain Progression (Average BPI-SF items 3, 4, 5 and 6)

	AA (N=546)	Placebo (N=542)
Events, n (%)	199 (36%)	188 (35%)
Median (95% CI), in months	26.74 (19.29, NE)	18.40 (14.88, NE)
Hazard ratio (95% CI) [a]	0.82 (0.67, 1.00)	

[a] Hazard ratio was obtained from a Cox proportional hazards model stratified by baseline ECOG PS
NE=not estimable

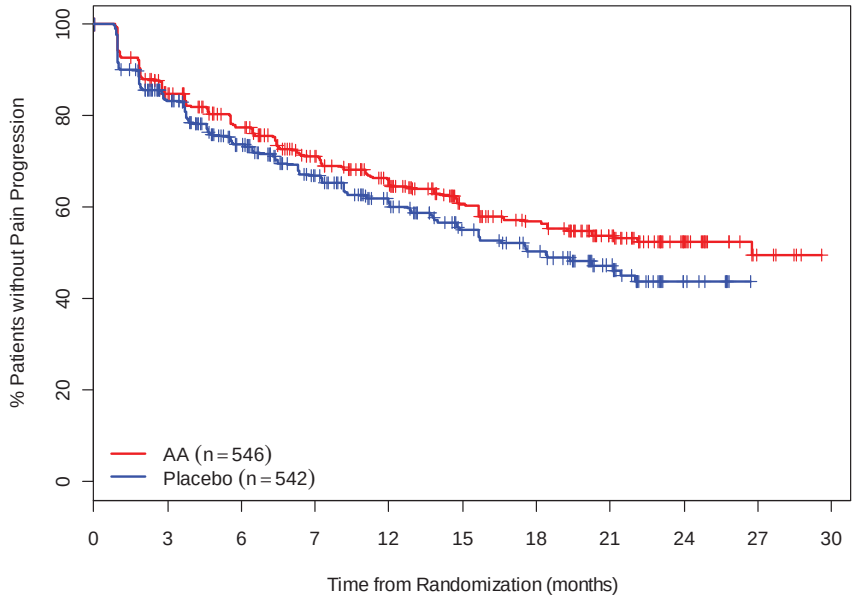

Figure 6. Kaplan-Meier Curves of Time to Average Pain Intensity Progression
[Source: CSR Figure 19]

Time to worst pain intensity progression

The pre-specified worst pain intensity progression was based on an increase by ≥ 30% from baseline observed at 2 consecutive evaluations ≥ 4 weeks apart without a decrease in analgesic usage score. The median time to worst pain intensity progression was 19.4 months in the placebo arm and was 26.7 months in the abiraterone arm, with a corresponding HR of 0.85 (95% CI: 0.69, 1.04), as presented in Table 30. The Kaplan-Meier curves are shown in Figure 7.

A post-hoc worst pain intensity progression was based on a 2-point increase from baseline observed at 2 consecutive evaluations ≥ 4 weeks apart without a decrease in analgesic usage

score. The median was not reached in either arm, with a HR of 0.78 (95% CI: 0.61, 1.00), as presented in Table 30.

Table 30. Time to BPI-SF Worst Pain Intensity Progression

	AA (N=546)	Placebo (N=542)
Pre-specified analysis per 30% threshold		
Events, n (%)	194 (36%)	177 (33%)
Median (95% CI), in months	26.74 (19.38, NE)	19.38 (16.59, NE)
Hazard ratio (95% CI) [a]	0.85 (0.69, 1.04)	
Post-hoc analysis per 2-point threshold		
Events, n (%)	131 (24%)	126 (23%)
Median (95% CI), in months	NE (NE, NE)	NE (22.01, NE)
Hazard ratio (95% CI) [a]	0.78 (0.61, 0.995)	

Note: NE=not estimable

[a] Hazard ratio was obtained from a Cox proportional hazards model stratified by baseline ECOG PS

[Source: CSR Tables TEFF33A and 38]

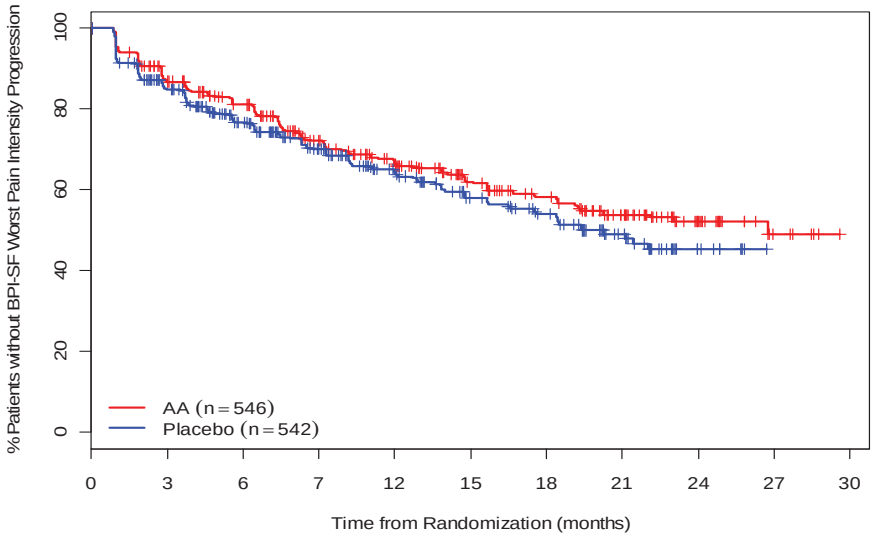

Figure 7. Kaplan-Meier Curves of Time to Worst Pain Intensity Progression (Using 30% Threshold)

[Source: CSR Figure FREF31A]

Time to Degradation of FACT-P

Results of time to degradation of FACT-P scales/subscales are summarized in Table 31. There was an improvement favoring the abiraterone arm noted in the time to progression for all FACT-P subscales with the exception of Social/Family Well Being.

Table 31. Summary of FACT-P Subscale Results

FACT-P Subscale	Median (95% CI) Time to Progression (months)		HR of AA/Placebo (95% CI)
	AA	Placebo	
FACT-P (Total Score)	12.65 (11.07, 14.00)	8.31 (7.39, 10.61)	0.78 (0.66, 0.92)
PCS	11.10 (8.64, 13.80)	5.78 (5.49, 8.31)	0.70 (0.60, 0.83)
TOI	13.86 (11.99, 16.49)	9.26 (8.31, 11.07)	0.75 (0.63, 0.88)
FACT-G	16.56 (13.86, 19.35)	11.07 (8.51, 14.75)	0.76 (0.63, 0.91)
PWB	14.78 (13.63, 16.82)	11.07 (9.10, 13.80)	0.76 (0.64, 0.90)
SFWB	18.40 (13.83, NE)	16.59 (11.07, NE)	0.94 (0.78, 1.14)
EWB	22.11 (17.35, NE)	14.16 (13.34, 19.45)	0.71 (0.59, 0.87)
FWB	13.34 (11.01, 15.74)	8.35 (7.39, 10.12)	0.76 (0.64, 0.90)

PCS=Prostate cancer scale; TOI=Total outcome index; PWB=Physical well being; SFWB=Social/Family well being; EWB=Emotional well being; FWB=Functional well being
NE=Not estimable
Cutoff: 20 December 2011
[Source: CSR Table 39]

Reviewer's Comments

- *There was no multiplicity adjustment for all of the other secondary endpoint analyses.*
- *Time to pain progression results overall were supportive of the benefit of abiraterone acetate. However, there is no widely agreed definition for pain progression (average pain score vs. worst pain score, 30% increase vs. 1-point increase vs. 2-point increase), because most of the PRO pain endpoints that have been used in the prior drug application have focused on pain palliation. With that deficiency, the magnitude of the improvement cannot be well justified, although overall the PRO pain results favored the abiraterone arm.*
- *Time to degradation of FACT-P favored the abiraterone arm, which was consistent with the findings of the major secondary endpoints and PRO pain endpoints. However,* (b) (4) *results of this endpoint can only be considered as exploratory, and cannot support disease related quality of life for registration, labeling or promotional claims in this population*

3.2.5 Conclusions for Efficacy

The pivotal study COU-AA-302 has demonstrated a statistically significant benefit of abiraterone acetate over placebo on rPFS by showing a hazard ratio of 0.43 (95% CI: 0.35, 0.52; p-value < 0.0001) per IRR assessment and an improvement on OS (HR=0.79, 95% CI: 0.66, 0.96; p-value=0.015) which numerically favored the abiraterone arm but did not cross the statistical efficacy boundary at the pre-specified interim analysis. The median rPFS time was 8.28 months in the placebo arm and has not been reached in the abiraterone arm. The median OS was 30.1 months in the placebo arm and was 35.3 months in the abiraterone arm. Subgroup and sensitivity analyses for rPFS and OS were consistent with the overall results of the primary analyses. The final OS analysis will be conducted when 773 death events occur. In addition, the abiraterone arm showed statistically significant improvements in the pre-specified major secondary endpoints, including time to initiation of cytotoxic chemotherapy and time to opiate

use for cancer pain, although each endpoint had its own limitations. Exploratory PRO analysis results overall favored the abiraterone arm. Please refer to the SEALD review of this application for more comments on the following endpoints: time to opiate use for cancer pain, time to initiation of cytotoxic chemotherapy, [redacted] (b) (4)

3.3 Evaluation of Safety

Please refer to the clinical evaluations of this application for safety results and conclusions for safety.

3.4 Benefit-Risk Assessment

Please refer to clinical evaluations of this application for a benefit-risk evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Tables 32 and 33 summarize OS and rPFS results by age, race and geographic region. Subgroup analysis by gender for this male-only study is not applicable. The subgroup analyses by age, race, and geographic region showed that the effect of abiraterone acetate on OS and rPFS was consistent cross the subgroups, except for black patients. However, the HR estimates for black patient subpopulation was not robust due to a small sample size (n=28). All OS analyses were based on the 3rd interim analysis data, and all rPFS analyses were based on IRR assessment.

Table 32. OS Subgroup Analyses by Age, Race, and Region

	N	AA		Placebo		Hazard Ratio[a] (95% CI)
		# event/n (%)	Median (months)	# event/n (%)	Median (months)	
Age						
< 65 years	290	48/135 (36)	35.3	60/155 (39)	34.1	0.82 (0.56, 1.20)
≥ 65 years	798	152/411 (37)	NE	174/387 (45)	30.1	0.78 (0.63, 0.97)
Race						
White	1030	190/520 (37)	35.3	220/510 (43)	30.1	0.79 (0.65, 0.96)
Black	28	6/15 (40)	NE	4/13 (31)	NE	1.32 (0.37, 4.69)
Other	27	3/10 (30)	NE	9/17 (50)	25.2	0.50 (0.13, 1.85)
Region						
U.S.	472	81/234 (35)	35.3	107/238 (45)	30.1	0.69 (0.52, 0.93)
Non – U.S.	616	119/312 (38)	NE	127/304 (42)	30.3	0.88 (0.68, 1.12)

[a] Hazard ratios were estimated from unstratified Cox proportional hazards models. A hazard ratio < 1 indicates a lower risk with abiraterone compared to placebo
NE=Not estimable

Table 33. Radiographic PFS Subgroup Analyses (per IRR) by Age, Race, and Region

	N	AA		Placebo		Hazard Ratio[a] (95% CI)
		# event/n (%)	Median (months)	# event/n (%)	Median (months)	
Age						
< 65 years	290	45/135 (33)	13.7	84/155 (54)	5.6	0.36 (0.25, 0.53)
≥ 65 years	798	105/411 (26)	NE	167/387 (43)	9.7	0.45 (0.36, 0.58)
Race						
White	1030	142/520 (27)	NE	234/510 (46)	8.3	0.42 (0.34, 0.52)
Black	28	5/15 (33)	11.1	7/13 (54)	8.4	0.72 (0.22, 2.43)
Other	27	3/10 (30)	NE	9/17 (53)	5.4	0.35 (0.09, 1.31)
Region						
U.S.	472	56/234 (24)	NE	121/238 (51)	8.2	0.32 (0.23, 0.44)
Non – U.S.	616	94/312 (30)	11.3	130/304 (43)	8.3	0.53 (0.41, 0.69)

[a] Hazard ratios were estimated from unstratified Cox proportional hazards models. A hazard ratio <1 indicates a lower risk with abiraterone compared to placebo
NE=Not estimable

4.2 Other Special/Subgroup Populations

Exploratory analyses of OS and rPFS by baseline ECOG PS level, BPI worst pain score, bone metastasis status, PSA, LDH, and ALK level are presented in Tables 34 and 35. All OS analyses were based on the 3rd interim analysis data, and all rPFS analyses were based on IRR assessment.

Table 34. Additional OS Subgroup Analyses

	N	AA		Placebo		Hazard Ratio [a] (95% CI)
		# event/n (%)	Median (months)	# event/n (%)	Median (months)	
ECOG PS (IWRS)						
0	830	139/416 (33)	35.3	171/414 (41)	30.3	0.76 (0.61, 0.95)
1	258	61/130 (47)	28.3	63/128 (49)	26.4	0.89 (0.62, 1.26)
Baseline BPI						
0-1	716	117/370 (32)	35.3	136/346 (39)	31.1	0.74 (0.58, 0.94)
2-3	276	65/129 (50)	26.5	78/147 (53)	27.0	0.95 (0.68, 1.31)
Bone metastasis only at entry						
Yes	479	72/238 (30)	35.3	93/241 (39)	31.0	0.70 (0.51, 0.95)
No	609	128/308 (42)	30.2	141/301 (47)	30.0	0.86 (0.68, 1.10)
Gleason Score at initial diagnosis						
<= 7	479	77/225 (34)	NE	108/254 (43)	31.1	0.72 (0.54, 0.97)
>7	517	109/263 (41)	31.6	116/254 (46)	30.0	0.83 (0.64, 1.08)
Baseline PSA above median						
Yes	542	124/282 (44)	28.6	140/260 (54)	25.7	0.78 (0.61, 0.99)
No	546	76/264 (29)	35.3	94/282 (33)	33.2	0.78 (0.58, 1.06)
Baseline LDH above median						
Yes	537	114/278 (41)	NE	139/259 (54)	24.3	0.68 (0.53, 0.87)
No	551	86/268 (32)	35.3	95/283 (34)	34.7	0.93 (0.69, 1.24)
Baseline ALK-p above median						
Yes	535	127/279 (46)	27.8	128/256 (50)	26.6	0.86 (0.67, 1.10)
No	553	73/267 (27)	NE	106/286 (37)	31.1	0.67 (0.50, 0.91)

[a] Hazard ratios obtained using unstratified Cox proportional hazards models. A hazard ratio <1 indicates a lower risk with abiraterone compared to placebo
NE=Not estimable

Table 35. Additional rPFS Subgroup Analyses

	N	AA		Placebo		Hazard Ratio [a] (95% CI)
		# event/n (%)	Median (months)	# event/n (%)	Median (months)	
ECOG PS (IWRS)						
0	830	115/416 (28)	13.7	185/414 (45)	8.3	0.45 (0.36, 0.57)
1	258	35/130 (27)	NE	66/128 (52)	7.4	0.35 (0.23, 0.54)
Baseline BPI						
0-1	716	96/370 (26)	NE	155/346 (45)	8.4	0.42 (0.32, 0.54)
2-3	276	44/129 (34)	11.1	68/147 (46)	8.2	0.51 (0.35, 0.75)
Bone metastasis only at entry						
Yes	479	52/238 (22)	NE	83/241 (34)	13.7	0.49 (0.34, 0.69)
No	609	98/310 (32)	11.3	168/301 (56)	5.6	0.38 (0.30, 0.49)
Gleason Score at initial diagnosis						
<= 7	479	55/225 (24)	NE	118/254 (46)	8.3	0.37 (0.27, 0.51)
> 7	617	87/263 (33)	11.3	125/254 (49)	8.3	0.46 (0.35, 0.61)
Baseline PSA above median						
Yes	542	86/282 (30)	11.9	126/260 (48)	8.0	0.44 (0.33, 0.58)
No	546	64/264 (24)	NE	125/282 (44)	8.5	0.40 (0.29, 0.54)
Baseline LDH above median						
Yes	537	77/278 (28)	NE	128/259 (49)	5.6	0.37 (0.28, 0.49)
No	551	73/268 (27)	NE	123/283 (43)	9.0	0.48 (0.36, 0.65)
Baseline ALK-p above median						
Yes	535	90/279 (32)	11.5	117/256 (46)	8.2	0.50 (0.38, 0.66)
No	553	60/267 (22)	NE	134/286 (47)	8.3	0.34 (0.25, 0.47)

[a] Hazard ratios obtained using unstratified Cox proportional hazards models. A hazard ratio <1 indicates a lower risk with abiraterone compared to placebo

NE=Not Estimable

FDA Exploratory Subgroup Analyses

1. Efficacy results in patients with visceral metastatic disease

Patients with visceral metastatic disease were excluded from the pivotal trial. However, there were 21 patients with baseline visceral metastatic disease to the liver, lung, and adrenal glands or pancreas. The efficacy of abiraterone acetate was explored in this small subgroup of patients as the proposed indication includes this group of patients. As presented in Table 36, there were 3 patients with an objective response in the abiraterone arm and 1 responder in the placebo arm.

Table 36. Efficacy Results in the Patients with Visceral Metastatic disease

	AA (N=12)		**Placebo (N=9)**
rPFS per IRR (20 December 2010)			
# of rPFS events	3 (25%)		6 (67%)
Median (95% CI) in months	NE		3.7 (1.5, 11.2)
HR (95% CI)		0.25 (0.06, 1.00)	
rPFS per INV (20 December 2010)			
# of rPFS events	2 (17%)		5 (56%)
Median (95% CI) in months	NE		1.9 (1.5, NE)
HR (95% CI)		0.22 (0.04, 1.12)	
OS (3rd interim, 22 May 2012)			
# of OS events	6 (50%)		7 (78%)
Median (95% CI) in months	NE (13.1, NE)		17.8 (8.7, NE)
HR (95% CI)		0.43 (0.15, 1.3)	
# of objective responders (IRR)*	3 (25%)		1 (11%)
# of confirmed PSA responders	9 (75%)		2 (22%)
# of confirmed and un-confirmed PSA responders	9 (75%)		4 (45%)

*All 4 responders are Partial Responders. Time to response: 59, 164, 246 days for the 3 responders in the AA arm, and 53 for the responder in the Placebo arm.
NE=Not estimable

2. Efficacy results in patients with moderate to severe pain at baseline (BPI-SF #3 ≥ 4)

The pivotal study was designed to enroll only patients who were asymptomatic or mildly symptomatic from prostate cancer, as defined by a score of 0 or 1 (asymptomatic) or 2-3 (mildly symptomatic) on the BPI-SF Question #3. However, there were 81 patients enrolled with moderate to severe pain (BPI-SF question #3 score ≥ 4). The efficacy results for this sub-population are summarized in Table 37.

Table 37. Efficacy Results in the Patients with Moderate to Severe Pain

	AA (N=40)	Placebo (N=41)
rPFS per IRR (20 December 2010)		
# of rPFS events	10 (25%)	23 (56%)
Median (95% CI) in months	NE (11.1, NE)	7.0 (3.5, 8.3)
HR (95% CI)	0.30 (0.14, 0.63)	
rPFS per INV (20 December 2010)		
# of rPFS events	11 (25%)	22 (54%)
Median (95% CI) in months	10.9 (10.8, NE)	5.2 (3.3, NE)
HR (95% CI)	0.36 (0.18, 0.75)	
OS (3rd interim, 22 May 2012)		
# of OS events	17 (43%)	19 (46%)
Median (95% CI) in months	27.8 (22.1, NE)	25.5 (21.3, 34.7)
HR (95% CI)	0.87 (0.45, 1.68)	
# of objective responders (IRR)	7 (18%)	3 (7%)
# of confirmed PSA responders	24 (60%)	6 (15%)
# of confirmed and un-confirmed PSA responders	27 (68%)	10 (25%)

NE=Not estimable

Reviewer's Comments

- *The OS and rPFS improvements in the abiraterone arm were held across various subgroups except in the small subgroup of black patient population which had only 28 patients.*
- *All the subgroup analyses presented in this section are considered exploratory or hypothesis generating and no formal inference may be drawn.*
- *Although the pivotal study was designed to enroll only patients being asymptomatic or mildly symptomatic and without visceral metastatic disease, abiraterone acetate has shown some anti-cancer activity in small subgroups of patients with visceral metastases or with moderate to severe pain.*

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

In the metastatic CRPC patient population under evaluation, rPFS is not an established surrogate endpoint of OS, and it has not been used to support a marketing approval. Therefore, rPFS alone can not support efficacy claim. Instead, the totality of the data should be considered, which

includes overall survival, rPFS, other measures representing clinical benefit such as opiate pain use and cytotoxic chemotherapy use, and patient report outcomes. The major statistical issue of this submission was data collection in time to opiate use for cancer pain and time to cytotoxic chemotherapy use. However, this review concluded that this issue does not have impact on the efficacy conclusions.

The collection of data in the on-study case report forms for time to opiate use and time to cytotoxic chemotherapy was not optimal. Rather than a yes/no question (i.e. "Did you take any of the following medicines for cancer pain since your last visit", "Did you take any of the following cytotoxic chemotherapies since your last visit"), this analysis relied on a review of collected concomitant medications records. It was unclear whether the lack of an opiate use or cytotoxic chemotherapy use on the concomitant medication list was a true negative (patient did not take an opiate/cytotoxic chemotherapy) or was missing data (patient forgot to include it on the list). Therefore, an information request was sent to the applicant for this true negative vs. missing data issue.

The applicant considers that a lack of opiates/cytotoxic chemotherapies on the concomitant medication list was "true negatives" for the following reasons:

- Extensive site monitoring to ensure source documentation captured in CRF
- Cross validation was performed to verify that the appropriate medications were entered in the Concomitant Medication Form by checking data from multiple locations within CRFs including:
    - Treatment Discontinuation Reason (Unequivocal Clinical Progression by cytotoxic chemotherapy or chronic opiate pain medication use)
    - Adverse event for pain
    - Analgesic Use Form (0- no analgesic, 1- non-opioid analgesic, 2- opioid for mod pain, 3- opioid for severe pain)
    - BPI-SF Form (Queried on Question #7: "What treatments or medications are you receiving for your pain? (Please record treatments or medications on Concomitant Medication Form)"

For the time to opiate use endpoint, per FDA's request, the applicant performed a sensitivity analysis by censoring patients who had at least 2 consecutive missing visits to the last visit with no event. The result favored the abiraterone arm with a HR of 0.69 (95% CI; 0.57, 0.83). No such sensitivity analysis was performed for the time to cytotoxic chemotherapy endpoint, as there was no patient with at least 2 consecutive missing visits for this endpoint assessment.

The lack of a single yes/no answer for each on-study visit with respect to whether a patient had taken an opiate pain medication/cytotoxic chemotherapy is a limitation potentially weakening the results. However, the duplication and cross-validation of opiate/cytotoxic chemotherapy use data throughout multiple case report forms mitigate the potential for missing opiate/cytotoxic chemotherapy use data from the concomitant medications CRF. Additional trial results including time to analgesic progression, and patient reported outcomes for pain support an improvement in the time to opiate use. The FDA medical reviewer also acknowledged that it would be less likely for a patient to inadvertently forget to list cytotoxic chemotherapy as a concomitant medication.

Furthermore, as the true blindness could have been maintained for this study due to no outstanding safety issues related to abiraterone acetate, missing would have occurred randomly in the two arms if there are some. Overall, this reviewer concluded that results from these two secondary endpoints favor the abiraterone arm and support the primary findings.

5.2 Collective Evidences

In the pivotal study, COU-AA-302, results of overall survival numerically favored the abiraterone arm with a hazard ratio of 0.79 (95% CI: 0.66, 0.96; p-value = 0.015) but did not cross the statistical efficacy boundary at the 3rd pre-specified interim analysis (56% information). The median was 30.1 months in the placebo arm and was 35.3 months in the abiraterone arm. Per the independent radiographic review, the abiraterone arm showed a statistically significant radiographic progression-free survival improvement over the placebo arm, with a hazard ratio of 0.43 (95% CI: 0.35, 0.52; p-value < 0.0001). The rPFS median was 8.3 months in the placebo arm and has not been reached in the abiraterone arm. Abiraterone acetate has also shown efficacy over placebo in the pre-specified major secondary endpoints. The median time to initiation of cytotoxic chemotherapy was 16.8 months in the placebo arm and 25.2 months in the abiraterone arm with a hazard ratio of 0.58 (95% CI: 0.49, 0.69, p-value < 0.0001). The median time to opiate use for prostate cancer pain was 23.7 months in the placebo arm and was not reached in the abiraterone arm with a hazard ratio of 0.69 (95% CI: 0.57, 0.83, p-value = 0.0001). The time to opiate use result was supported by a delay in patient reported pain progression favoring the abiraterone arm. In addition, abiraterone acetate has been approved based on an OS improvement (HR=0.65, 95% CI: 0.54, 0.77; p-value < 0.0001) for the treatment of metastatic CRPC in patients who have received prior chemotherapy containing docetaxel.

5.3 Conclusions and Recommendations

The applicant submitted results from a multicenter, phase 3, randomized, double-blind, placebo-controlled clinical study (Study COU-AA-302) comparing abiraterone acetate plus prednisone to placebo plus prednisone in the treatment of patients with metastatic CRPC who were asymptomatic or mildly symptomatic after failure of androgen deprivation therapy. The abiraterone arm showed a statistically significant improvement over placebo in rPFS as assessed by independent radiographic review. The overall survival results were not mature at this time, with the 3rd interim analysis results numerically but not statistically favoring the abiraterone arm. The abiraterone arm has also demonstrated benefit over the placebo arm in the pre-specified major secondary endpoints, i.e., time to initiation of cytotoxic chemotherapy use, and time to opiate use for cancer pain. In addition, the patient reported data of delaying pain progression supported the time to opiate use for cancer pain. In this disease setting, because rPFS is not an established surrogate endpoint of overall survival, and has not been used to support a marketing approval, the approvability of this supplemental NDA should be considered based on the totality of the data in the pivotal trial (including overall survival, rPFS, other measures representing clinical benefit such as opiate pain use and cytotoxic chemotherapy use, and patient report outcomes) in the context of overall survival benefit of abiraterone acetate demonstrated in a more refractory population. The judgment on the approvability is deferred to the clinical review team.

5.4 Labeling Recommendations

We recommend that the labeling includes results of the third interim OS analysis, the final rPFS analysis, the time to initiation of cytotoxic chemotherapy analysis, and the time to opiate use for cancer pain analysis. The benefit of abiraterone acetate on delaying pain progression was also observed, however, due to the lack of widely agreed definition on pain progression, no statistics of the improvement on delaying pain progression will be included in the label, but a general statement will be used: the time to opiate use result was supported by a delay in patient reported pain progression favoring the abiraterone arm.

SIGNATURES/DISTRIBUTION LIST

Primary Statistical Reviewer: Lijun Zhang, Ph.D.
Date: November 20th, 2012

Concurring Reviewer(s)

Statistical Team Leader: Shenghui Tang, Ph.D.

Biometrics Division Director: Rajeshwari Sridhara, Ph.D.

cc:
Project Manager: Amy Tilley
Medical Officer: Paul Kluetz, M.D.
Medical Team Leader: Virginia E Maher, M.D.
Primary Statistical Reviewer: Lijun Zhang, Ph.D.
Statistical Team Leader: Shenghui Tang, Ph.D.
Biometrics Division Director: Rajeshwari Sridhara, Ph.D.
Lillian Patrician

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

/s/

LIJUN ZHANG
11/20/2012

SHENGHUI TANG
11/20/2012

RAJESHWARI SRIDHARA
11/20/2012

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 202379 **Applicant: Janssen Research & Development** **Stamp Date: 06/14/2012**

Drug Name: Zytiga **NDA/BLA Type: Efficacy Supplement 005**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			No ISE as only one study used for efficacy assessment
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			Gender not applicable (all males)
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	X			
Appropriate references for novel statistical methodology (if present) are included.			X	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

Lijun Zhang 7/15/2012

Reviewing Statistician Date

Shenghui Tang

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Supervisor/Team Leader Date

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

/s/

LIJUN ZHANG
07/25/2012

SHENGHUI TANG
07/25/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 202379/ S005

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA	202379
Submission Date:	14th June 2012
Brand Name:	Zytiga®
Generic Name:	Abiraterone Acetate
Formulation:	Immediate release 250 mg tablets
OCP Reviewer:	Elimika Pfuma, Pharm.D. / Ph.D.
OCP Team Leader:	Qi Liu, Ph.D.
OCP Division:	Division of Clinical Pharmacology V
ORM Division:	Division of Drug Oncology Products 1
Sponsor:	Janssen Research
Submission Type; Code:	sNDA;202379/145
Dosing regimen:	ZYTIGA 1,000 mg (four 250 mg tablets) administered orally once daily in combination with prednisone 5 mg administered orally twice daily.
Indication:	**Current**: For the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel. **Newly Proposed**: the treatment of patients with metastatic castration-resistant prostate cancer (b) (4) (b) (4) (b) (4).

Abiraterone (active metabolite of abiraterone acetate [Zytiga®]) is a selective steroidal inhibitor of 17α hydroxylase/C17, 20-lyase (**CYP17**), an enzyme that is required for androgen biosynthesis. Abiraterone acetate is indicated for use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) who have received prior chemotherapy containing docetaxel. It is approved at a dose of 1000 mg once daily in combination with 5 mg twice daily of oral prednisone. The current submission (SDN# 145) is an efficacy supplement for an indication for the treatment of patients with mCRPC (b) (4) (b) (4). The same dosing regimen is proposed for the new indication.

Trial COU-AA-302 (N=1088) in support of this indication, was a double-blind, placebo-controlled study of 1000 mg daily abiraterone acetate plus 5 mg twice daily prednisone compared with placebo plus prednisone in men with asymptomatic or mildly symptomatic mCRPC. The co-primary efficacy endpoints were radiographic progression-free survival (rPFS) and overall survival (OS). At the first interim analysis for OS and the final analysis of rPFS, the risk of rPFS was decreased by 58% compared with placebo plus prednisone (HR=0.425; $p<0.0001$). At the second OS analysis, the IDMC recommended that patients on placebo be allowed to cross over to the abiraterone acetate arm based on rPFS (40% of total events; cutoff date 12/20/11). The overall survival was longer for the abiraterone acetate group (HR=0.752,

p=0.0097), but had not crossed the pre-specified boundary for statistical significance. The adverse event profile were similar to that previously seen in patients with mCRPC after prior docetaxel including fluid retention/edema (28%), hypokalemia (17%) and hypertension (22%). The incidence of LFT abnormalities (ALT and AST increases) was higher in pivotal trial COU-AA-302 than previously observed (18% versus the previously seen 11%).

Pharmacometrics Division was consulted regarding the submitted population PK model/data. However, population PK analysis was not performed for the current review as no new labeling claims were added based on population PK and the population PK model was one that was previously submitted with the original NDA and updated by adding the current patient population.

1.2 RECOMMENDATIONS

This submission is acceptable from a clinical pharmacology perspective. Based on recommendations from SEALD, we recommended a change to the title of Section 5.4 of the Warnings and Precautions section of label. We changed the title from (b) (4) to "Increased Zytiga Exposures with Food".

Signatures

Elimika Pfuma, Pharm.D./ Ph.D.	Qi Liu, Ph.D.
Reviewer	Team Leader
Division of Clinical Pharmacology 5	Division of Clinical Pharmacology 5

CC: DDOP: CSO – A Tilley; MTL – E Maher; MO - P Kluetz
DCP-5: Reviewer - E Pfuma; TL - Q Liu; DDD - B Booth; DD - A Rahman

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/s/

ELIMIKA PFUMA
11/13/2012

QI LIU
11/13/2012

CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR NDA # 202-379

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**202-379**	**Brand Name**	**Zytiga®**
OCP Division (I, II, III, IV, V)	**V**	**Generic Name**	**Abiraterone Acetate**
Medical Division	**Oncology**	**Drug Class**	**Androgen biosynthesis inhibitor**
OCP Reviewer	**Elimika Pfuma, Pharm.D., Ph D.**	**Indication(s)**	**Approved:** The treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel **Newly Proposed:** The treatment of patients with metastatic castration-resistant prostate cancer (b) (4) (b) (4)
OCP Team Leader	**Qi Liu, Ph.D.**	**Dosage Form**	250 mg tablets
Date of Submission	**14-June-2012**	**Dosing Regimen**	1 gram of oral abiraterone acetate administered once daily in combination with prednisone 5 mg twice daily
Estimated Due Date of OCP Review			
Medical Division Due Date		**Route of Administration**	**Oral**
PDUFA Due Date		**Sponsor**	**Janssen**
		Priority Classification	
	"X" if included at filing		

STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**1**		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics -	**X**			**Pivotal phase 3 Trial COU-AA-302**
Healthy Volunteers-				
single dose:				
multiple dose:				

Patients-	**X**			
single dose:				
multiple dose:	**X**	**6**		**The pivotal phase 3 trial COU-AA-302, the supportive efficacy trials COU-AA-001, COU-AA-001EXT, COU-AA-002 and COU-AA-301 and a BE trial COU-AA-BE. The supportive trials and BE trial were also previously submitted with the original NDA**
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD - QT Study:				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	**X**	**1**		**Sparse PK from the pivotal phase 3 Trial COU-AA-302. A total of six samples were obtained in the patients with PK sampling (N=210 with 103 patients on the abiraterone acetate arm): 2 samples each on Day 1 of each Cycle 1, 2 and 5.**
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	**X**			**BE trial compares the capsule formulation and the tablet formulation. The capsule formulation was used in the earlier trials such as the submitted phase1/2 supportive efficacy trials**
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				

Pediatric development plan				
Literature References				
Total Number of Studies				
		8		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	Cross referenced original NDA
2	Has the applicant provided metabolism and drug-drug interaction information?			X	Cross referenced original NDA
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	Cross referenced original NDA
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		X		
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		X		Exposure response analyses for efficacy were performed in the original NDA submission

15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Applicant is applying for waiver
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

Elimika Pfuma, Pharm.D., Ph.D. 02-July-12

Clinical Pharmacology Reviewer Date

Qi Liu, Ph.D 02-July-12

Clinical Pharmacology Team Leader Date

Clinical Pharmacology - sNDA Filing Memo

NDA: 202-379 **IND:** 71023
Compound: Abiraterone acetate 250 mg tablets
Sponsor: Janssen
Filing Date: July 17, 2012
Clinical Pharmacology Reviewer: Elimika Pfuma, Pharm.D., Ph.D.

Mechanism of Action and Proposed Indication

- Abiraterone acetate is an acetyl ester of abiraterone that is converted *in vivo* to abiraterone.
- Abiraterone is an androgen biosynthesis inhibitor that selectively inhibits the enzyme 17α-hydroxylase/C17,20-lyase (CYP17).
- It is currently approved for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel.
- It is proposed for the treatment of patients with metastatic castration-resistant prostate cancer (b) (4)

Pivotal Trial (COU-AA-302)

The pivotal trial in this submission is a Phase 3, randomized, double-blind, placebo-controlled study of abiraterone acetate (1000 mg daily) plus prednisone (5 mg twice a day) compared with placebo plus prednisone in 1088 asymptomatic or mildly symptomatic subjects with mCRPC who have not received previous cytotoxic chemotherapy (Trial # COU-AA-302). The co-primary efficacy endpoints were radiographic progression-free survival (rPFS) and overall survival (OS). At the first interim analysis for OS and the final analysis of rPFS, the risk of rPFS was decreased by 58% compared with placebo plus prednisone (HR=0.425; $p<0.0001$). At the second OS analysis, the IDMC recommended that patients on placebo be allowed to cross over to the abiraterone acetate arm based on rPFS. The overall survival was longer for the abiraterone acetate group (HR=0.752, p=0.0097), but had not crossed the pre-specified boundary for statistical significance. The adverse event profile were similar to that previously seen in patients with mCRPC after prior docetaxel including fluid retention/edema (28%), hypokalemia (17%) and hypertension (22%). The incidence of LFT abnormalities (ALT and AST increases) was higher in pivotal trial COU-AA-302 than previously observed.

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/s/

ELIMIKA PFUMA
08/23/2012

QI LIU
08/28/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 202379/ S005

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	November 20, 2012
To:	Robert Justice, MD Director **Division of Oncology Products 1 (DOP1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling Team **Division of Medical Policy Programs**
From:	Latonia M. Ford, RN, BSN, MBA Patient Labeling Reviewer **Division of Medical Policy Programs**
Subject:	DMPP Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	ZYTIGA (abiraterone acetate)
Dosage Form and Route:	Tablets For Oral Administration
Application Type/Number/Supplement:	NDA 202-379/S-005
Applicant:	Janssen Research & Development, LLC.

1 INTRODUCTION

On June 13, 2012 Janssen Research & Development, LLC submitted Supplemental New Drug Application (NDA) 202-379/S-005 for ZYTIGA (abiraterone acetate) Tablets. This submission seeks approval of ZYTIGA (abiraterone acetate) Tablets, in combination with prednisone, for the treatment of patients with metastatic castration-resistant prostate cancer (b) (4) (b) (4). On July 16, 2012, Janssen Research & Development, LLC submitted an amendment to pending Supplement 005 for ZYTIGA (abiraterone acetate) Tablets. The amendment was submitted in response to an Agency approval letter received by the Applicant on July 3, 2012, for Supplement 003 which requested that the Applicant amend all pending supplemental applications for this NDA with the labeling changes approved in the final Supplement 003 application.

ZYTIGA (abiraterone acetate) Tablets were originally approved on April 28, 2011 for use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel.

On August 13, 2012, the Division of Drug Oncology Products 1 (DOP1) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for ZYTIGA (abiraterone acetate) Tablets.

This review is written in response to a request by the Division of Oncology Products (DOP1) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Patient Package Insert (PPI) for ZYTIGA (abiraterone acetate) Tablets.

2 MATERIAL REVIEWED

- Draft ZYTIGA (abiraterone acetate) Tablets Patient Package Insert (PPI) received on July 16, 2012 and received by DMPP on November 9, 2012.
- Draft ZYTIGA (abiraterone acetate) Tablets Prescribing Information (PI) received on July 16, 2012 revised by the Review Division throughout the current review cycle and received by DMPP on November 9, 2012.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI, the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with are recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the PPI are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

LATONIA M FORD
11/20/2012

BARBARA A FULLER
11/20/2012

LASHAWN M GRIFFITHS
11/20/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Consumer Drug Promotion

******Pre-decisional Agency Information******

Memorandum

Date: November 20, 2012

To: Amy Tilley – Regulatory Project Manager
Division of Oncology Products 1 (DOP 1)
Office of Hematology and Oncology Products

From: Michelle Safarik, PA-C – Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)
Office of Prescription Drug Promotion

Subject: DCDP comments on draft Patient Product Labeling (PPI)
ZYTIGA (abiraterone acetate) Tablets (Zytiga)
NDA 202379/S-005

As requested in your consult dated August 28, 2012, DCDP has reviewed the draft PPI for Zytiga. S-005 provides for the treatment of patients with metastatic castration-resistant prostate cancer (b) (4) (b) (4).

Comments on the proposed package insert (PI) were provided on November 15, 2012.

DCDP's comments are based on the proposed, marked-up, substantially complete version of the PI sent to the sponsor and obtained via the DOP 1 shared drive on November 13, 2012, and the Division of Medical Policy Program's (DMPP) review of the proposed PPI dated November 20, 2012.

DCDP agrees with DMPP's comments and recommendations, and has the following additional comments below.

Thank you for your consult.

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/s/

MICHELLE L SAFARIK
11/20/2012

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
Division of Prescription Drug Promotion (DPDP)

****Pre-decisional Agency Information****

Memorandum

Date: November 15, 2012

To: Amy Tilley, Regulatory Project Manager
Division of Oncology Products 1 (DOP1)
Office of Hematology Oncology Products (OHOP)

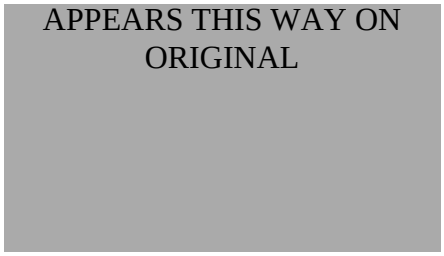
From: Marybeth Toscano, PharmD, Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
OPDP

Subject: OPDP comments on draft product labeling for Zytiga (abiraterone acetate) tablets
NDA 202379/S-005

In response to your consult request dated August 28, 2012, OPDP has reviewed the draft labeling (Package Insert [PI]), for Zytiga tablets. OPDP's comments are based on the proposed, substantially complete version of the PI sent to OPDP via email on November 9, 2012, available in the EDR at \\CDSESUB1\EVSPROD\NDA202379\202379.enx.

If you have any questions about OPDP's comments on the PI, please contact Marybeth Toscano at 6-2617 or at Marybeth.Toscano@fda.hhs.gov.

Section	Statement from draft	Comment
• **14 Clinical Studies**	The median time to opiate use for prostate cancer pain was not reached for patients receiving ZYTIGA and was 23.7 months for patients receiving placebo (HR=0.686; 95% CI: [0.566, 0.833], p=0.0001). The time to opiate use result was supported by **a delay in patient reported pain progression favoring the ZYTIGA arm.**	We recommend qualifying the bolded statement with data about time to pain progression in each arm. As currently worded, the statement is vague and could be used misleadingly in promotion.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/s/

MARYBETH TOSCANO
11/15/2012

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Provision of Pharmacovigilance Data

Date:	10/12/2012
Reviewer(s):	Katherine Coyle, Pharm.D., BCOP Safety Evaluator, Division of Pharmacovigilance II
Team Leader(s):	Robert Pratt, Pharm.D. Team Leader, Division of Pharmacovigilance II
Product Name(s):	Zytiga (Abiraterone)
Subject:	Multiple Adverse Events
Applicant/Sponsor:	JANSSEN BIOTECH
NDA:	202379
Submission Number:	005
RCM Number:	2012-2184

1 INTRODUCTION

The Division of Pharmacovigilance (DPV) received a request from the Division of Oncology Products 1 (DOP1) to provide a general Empirica safety signal analysis and to review the FAERS database for crude counts[a] and the number of fatal outcomes for the following adverse events associated with abiraterone: liver toxicity, diarrhea, pulmonary toxicity, cardiac failure, and specific skin disorders including severe rash, DRESS and Stevens Johnson Syndrome.

Abiraterone is a CYP17 inhibitor (an enzyme required for androgen biosynthesis) approved on April 28, 2011 for use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel[b]. DOP1 is currently reviewing Submission 005 for the indication of the treatment of patients with metastatic castration-resistant prostate cancer (b) (4) (b) (4).

2 METHODS AND MATERIALS

The FDA Adverse Event Reporting System (FAERS) was searched with the strategy described in Table 1.[c]

Table 1. FAERS Search Strategy	
Date of search	September 28, 2012
Time period of search	1/1/1969* - 9/28/2012
Report	Product/Manufacturer Adverse Event Reporting Summary
Active ingredient	Abiraterone, abiraterone acetate
Product name	Zytiga
FAERS Quick Query Terms	▪ Any event
	Outcome of death with each of the following queries: ▪ Hepatic failure, fibrosis and cirrhosis and other liver damage related conditions (SMQ broad) ▪ Cardiac failure (SMQ) ▪ Respiratory, thoracic, and mediastinal disorders (SOC) ▪ Diarrhea (PT)

* FAERS data range

The Empirica Signal database was searched with the strategy described in Table 2.[d]

[a] Crude counts may include duplicates and the reported adverse event may not be causally related to the associated drug.
[b] Abiraterone package insert. Accessed: http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202379s004lbl.pdf on 10/9/12.
[c] FAERS is a database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. FAERS data do have limitations (e.g., variable quality and quantity of information provided, cannot determine causality, voluntary reporting system, reporting biases). Additionally, FAERS cannot be used to calculate the incidence of an adverse event in the U.S. population.
[d] OSE uses Empirica Signal software, which uses the Multi-item Gamma Poisson Shrinker (MGPS) data mining algorithm, to perform analyses on FAERS data and identify patterns of associations or unexpected occurrences (i.e., "potential signals") in large databases. MGPS analyzes the records in FAERS and then quantifies reported drug-event associations by producing a set of values or scores that indicate varying strengths of reporting relationships between drugs and events. These scores, denoted as Empirical Bayes Geometric Mean (EBGM) values, provide a stable estimate of the relative reporting of an event for a particular drug relative to all other drugs and events in AERS. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95, respectively. Because EBGM scores are based on FAERS data, limitations relating to FAERS data also apply to data mining-derived data.

Table 2. Empirica Data Mining Search Strategy	
Data Refresh Date	10/2/2012
Product Terms	Abiraterone
Empirica Signal Run Name	Generic (S)
EB05	> 1.0

3 DATA

3.1 FAERS CRUDE COUNTS ON ALL ABIRATERONE REPORTS

Table 3 contains crude count numbers of abiraterone reports received to the FAERS database from 1/1/1969 - 9/28/2012 categorized by country and outcome.

Table 3. FAERS Reports of Abiraterone by Country and Outcome

Country	Total Reports	Expedited (15-Day)	Non-Serious	Serious	DE	HO	LT	DS	OT
USA	349	228	29	320	56	146	21	5	158
FOREIGN	424	328	6	418	90	258	44	20	176
NULL	1	1	0	1	0	1	0	0	0
Total	774	557	35	739	146	405	65	25	334

[a] Crude counts may include duplicates and the reported adverse event may not be causally related to the associated drug.
DE – Death; DS – Disability; HO – Hospitalization; LT - Life-Threatening; OT - Other Serious/Medically Important

Table 4 contains the top 25 reported MedDRA Preferred Terms ranked by crude count for reports received to the FAERS database from 1/1/1969 - 9/28/2012. Reports in Table 4 may have reported multiple Preferred Terms.

Table 4. Abiraterone Most Frequently Reported MedDRA Preferred Terms (PTs) in Reports – Top 25[a]

Event-Preferred Terms (PTs)	Total Reports	Percent of Total
PROSTATIC SPECIFIC ANTIGEN INCREASED	49	11.75
DEATH	43	10.31
DYSPNOEA	42	10.07
OEDEMA PERIPHERAL	40	9.59
FATIGUE	39	9.35
ANAEMIA	35	8.39
PAIN	33	7.91
DRUG INEFFECTIVE	27	6.47
NAUSEA	27	6.47
HYPOKALAEMIA	26	6.24
PULMONARY EMBOLISM	26	6.24
DECREASED APPETITE	25	6
VOMITING	24	5.76
ASTHENIA	23	5.52
CONFUSIONAL STATE	23	5.52
BLOOD ALKALINE PHOSPHATASE	21	5.04
PROSTATE CANCER	21	5.04
THROMBOCYTOPENIA	21	5.04

DISEASE PROGRESSION	19	4.56
PYREXIA	19	4.56
PROSTATE CANCER METASTATIC	18	4.32
RENAL FAILURE	18	4.32
RENAL FAILURE ACUTE	18	4.32
DIARRHOEA	17	4.08
WEIGHT DECREASED	17	4.08

[a] Crude counts may include duplicates and the reported adverse event may not be causally related to the associated drug.

3.2 EMPIRICA SIGNAL SCORES – ALL ABIRATERONE REPORTS

Table 5 shows the rank order of MedDRA PTs associated with abiraterone FAERS reports that have an EB05 score > 1.0.

Table 5. Empirica Generic (S) Signal Run for Abiraterone with EB05 > 1.0

PT	EB05
Prostatic specific antigen increased	24.447
Prostate cancer metastatic	17.269
Hypokalaemia	5.854
Blood alkaline phosphatase increased	5.073
Prostate cancer	3.394
Pulmonary embolism	2.81
Bone pain	2.629
Oedema peripheral	2.211
Fluid retention	2.004
Disease progression	1.957
Urinary tract infection	1.95
Spinal cord compression	1.898
Liver function test abnormal	1.822
Inappropriate schedule of drug administration	1.779
Anaemia	1.773
Adverse event	1.724
Alanine aminotransferase increased	1.696
Haematuria	1.687
Metastases to liver	1.655
Confusional state	1.655
Oedema	1.627
Thrombocytopenia	1.615
Metastases to central nervous system	1.554
Pleural effusion	1.483
Decreased appetite	1.465
Lower respiratory tract infection	1.395
Hepatotoxicity	1.378
Ejection fraction decreased	1.316
Cauda equina syndrome	1.295
Hepatic enzyme increased	1.271
Muscular weakness	1.24
Fatigue	1.206
Drug administration error	1.2
Cancer pain	1.196
Sepsis	1.189

Vomiting	1.156
Hypokinesia	1.134
General physical health deterioration	1.133
Aspartate aminotransferase increased	1.106
Dyspnoea	1.092
Supraventricular tachycardia	1.092
Gastroenteritis	1.085
Failure to thrive	1.071
Dehydration	1.066
Transaminases increased	1.057
Gastric disorder	1.051
Arrhythmia	1.043
Hyponatraemia	1.042
Hepatic failure	1.036
Lymphoedema	1.035
Pain	1.021
Thrombotic thrombocytopenic purpura	1.012

3.3 FAERS CRUDE COUNTS OF ABIRETARONE - CONSULT SPECIFIC ADVERSE EVENTS

Table 6 shows crude count numbers of abiraterone reports, percent of total abiraterone reports, and the number of reports with an outcome of death for specified PTs, received to the FAERS database from 1/1/1969 - 9/28/2012. Preferred Terms are categorized by System Organ Class (SOC) and may appear in multiple SOCs. Each report may have reported multiple PTs.

Table 6. Abiraterone Most Frequently Reported MedDRA PTs with N ≥ 5 in Selected SOCs - Crude Counts [a] (Total Number of reports = 744)

Preferred Term(PT)	Total Reports	Percent of Total	Outcome of Death	High Level Term
SOC: HEPATOBILIARY DISORDERS				
HEPATIC FAILURE	7	0.9	5	HEPATIC FAILURE AND ASSOCIATED DISORDERS
METASTASES TO LIVER	7	0.9	6	MALIGNANT HEPATOBILIARY NEOPLASMS
HEPATOTOXICITY	6	0.78	3	HEPATOCELLULAR DAMAGE AND HEPATITIS NEC
JAUNDICE	5	0.65	2	CHOLESTASIS AND JAUNDICE
SOC: CARDIAC DISORDERS				
DYSPNOEA	42	5.43	5	DYSPNOEAS
OEDEMA PERIPHERAL	40	5.17	3	HEART FAILURE SIGNS AND SYMPTOMS
DIZZINESS	16	2.07	0	CARDIAC SIGNS AND SYMPTOMS NEC
CARDIAC FAILURE	11	1.42	3	HEART FAILURES NEC
ATRIAL FIBRILLATION	10	1.29	0	SUPRAVENTRICULAR ARRHYTHMIAS
CARDIAC DISORDER	8	1.03	1	CARDIAC DISORDERS NEC
SYNCOPE	8	1.03	1	CARDIAC SIGNS AND SYMPTOMS NEC
TACHYCARDIA	7	0.9	3	RATE AND RHYTHM DISORDERS NEC
PULMONARY OEDEMA	6	0.78	3	LEFT VENTRICULAR FAILURES
CARDIAC ARREST	5	0.65	4	VENTRICULAR ARRHYTHMIAS AND CARDIAC ARREST

MYOCARDIAL ISCHAEMIA	5	0.65	1	ISCHAEMIC CORONARY ARTERY DISORDERS
SOC: RESPIRATORY, THORACIC AND MEDIASTINA				
DYSPNOEA	42	5.43	5	BREATHING ABNORMALITIES
PULMONARY EMBOLISM	26	3.36	3	PULMONARY THROMBOTIC AND EMBOLIC CONDITIONS
PNEUMONIA	16	2.07	7	LOWER RESPIRATORY TRACT INFECTIONS NEC
PLEURAL EFFUSION	15	1.94	6	PNEUMOTHORAX AND PLEURAL EFFUSIONS NEC
LOWER RESPIRATORY TRACT INFECTION	10	1.29	0	LOWER RESPIRATORY TRACT INFECTIONS NEC
RESPIRATORY FAILURE	7	0.9	7	RESPIRATORY FAILURES (EXCL NEONATAL)
PULMONARY OEDEMA	6	0.78	3	PULMONARY OEDEMAS
COUGH	5	0.65	1	COUGHING AND ASSOCIATED SYMPTOMS
SOC: GASTROINTESTINAL DISORDERS				
NAUSEA	27	3.49	6	NAUSEA AND VOMITING SYMPTOMS
VOMITING	24	3.1	4	NAUSEA AND VOMITING SYMPTOMS
DIARRHOEA	17	2.2	7	DIARRHOEA (EXCL INFECTIVE)
CONSTIPATION	7	0.9	1	GASTROINTESTINAL ATONIC AND HYPOMOTILITY DISORDER
RECTAL HAEMORRHAGE	7	0.9	3	INTESTINAL HAEMORRHAGES
DYSPHAGIA	6	0.78	2	GASTROINTESTINAL SIGNS AND SYMPTOMS NEC
GASTRIC DISORDER	6	0.78	1	GASTROINTESTINAL DISORDERS NEC
GASTROENTERITIS	5	0.65	1	GASTRIC AND GASTROENTERIC INFECTIONS
SOC: SKIN AND SUBCUTANEOUS TISSUE DISORDER				
RASH	6	0.78	0	RASHES, ERUPTIONS AND EXANTHEMS NEC
JAUNDICE	5	0.65	2	DERMAL AND EPIDERMAL CONDITIONS NEC
SOC: SKIN AND SUBCUTANEOUS TISSUE DISORDER **Skin PTs with N < 5**				
DRUG RASH WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS	2	0.26	0	DERMATITIS ASCRIBED TO SPECIFIC AGENT
ERYTHEMA MULTIFORME	1	0.13	0	BULLOUS CONDITIONS
STEVENS JOHNSON SYNDROME	0	0	0	BULLOUS CONDITIONS

[a] Crude counts may include duplicates and the reported adverse event may not be causally related to the associated drug.

3.4 LINE LISTING FOR REPORTS OF DEATH ASSOCIATED WITH ABIRERATONE - - CONSULT SPECIFIC ADVERSE EVENTS

Tables 7-10 list reports of abiraterone with an outcome of death categorized by specific MedDRA search terms. Reports may appear multiple times in Tables 7-10 under different SMQ or MedDRA search strategies.

Table 7. Abiraterone Reports with Outcome of Death for SMQ Hepatic failure, fibrosis and cirrhosis and other liver damage related conditions

Case #	MFR Ctrl #	FDA Recd Date	All Suspects	PTs	Country	Age (Yrs)	Sex
8093403	AT-JNJFOC-20110800360	2/24/2012	ABIRATERONE ACETATE; PREDNISONE	RENAL FAILURE ACUTE;HEPATIC FAILURE;ANAEMIA;HYPERBILIRUBINAEMIA;THROMBOCYTOPENIA	AUT	63	M
8165296	US-JNJFOC-20110910885	11/29/2011	ZYTIGA; SOMATOSTATIN; EVEROL MUS	ASCITES;COMA;HEPATIC FAILURE;METASTASES TO PLEURA;LIVER FUNCTION TEST ABNORMAL;HEPATIC ENZYME NCREASED;MALIGNANT PLEURAL EFFUSION	USA	59	M
8235869	DE-JNJFOC-20111101852	12/22/2011	ABIRATERONE ACETATE	ACUTE HEPATIC FA LURE;CARDIOVASCULAR NSUFFICIENCY;METASTASES TO LIVER	DEU	79	M
8355957	GB-JNJFOC-20120108156	6/1/2012	ZYTIGA	ASCITES;PROSTATE CANCER METASTATIC	GBR	66	M
8373363	CH-JNJFOC-20120111694	5/18/2012	ZYTIGA; ASP RIN	HEPATOTOXICITY;METASTASES TO LIVER	CHE	82	M
8481489	ES-JNJFOC-20120309306	7/9/2012	ZYTIGA	DISEASE PROGRESSION;THROMBOCYTOPENIA;LIVER DISORDER INFECTION BONE MARROW DISORDER COAGULATION FACTOR DECREASED	ESP	80	M
8529954	BR-JNJFOC-20120410310	4/25/2012	ZYTIGA; KETOCONAZOLE	HEPATOTOXICITY	BRA	70	M
8533694	DE-JNJFOC-20120307241	5/16/2012	ZYTIGA	CHOLECYSTITIS ACUTE;JAUNDICE;PROSTATE CANCER METASTATIC;TRANSAM NASES INCREASED;BLOOD BILIRUBIN NCREASED;ASCITES	DEU	74	M
8582767	GB-JNJFOC-20120507036	5/29/2012	ZYTIGA	PULMONARY EMBOLISM;HAEMOGLOBIN DECREASED;STAPHYLOCOCCAL INFECTION;HEPATOTOXICITY;BLOOD ALKALINE PHOSPHATASE INCREASED	GBR	UNK	M
8708524		7/26/2012	ABIRATERONE	ACUTE HEPATIC FAILURE INTERNATIONAL NORMALISED RATIO INCREASED	USA	72	M
8765678	US-JNJFOC-20120815090	9/4/2012	ZYTIGA	ADVERSE DRUG REACTION;DISEASE PROGRESSION;DRUG NEFFECTIVE;HEPATIC FAILURE	USA	54	M

Table 8. Abiraterone Reports with Outcome of Death for SMQ Cardiac Failure

Case #	MFR Ctrl #	FDA Recd Date	All Suspects	PTs	Country	Age (Yrs)	Sex
7941534	IL-JNJFOC-20110503870	5/15/2012	ABIRATERONE ACETATE;PREDNISONE	ACUTE MYOCARDIAL INFARCTION DEATH OEDEMA PLEURAL EFFUSION CARDIAC FAILURE CONGESTIVE	ISR	76	M
7968206	FR-JNJFOC-20110510582	4/3/2012	ABIRATERONE ACETATE	LYMPHANGITIS;DRUG NEFFECTIVE;PROSTATE CANCER;DYSPNOEA;OEDEMA;RENAL FA LURE	FRA	UNK	M
8084629	FR-JNJFOC-20110802436	4/17/2012	ABIRATERONE ACETATE;PREDNISONE	CARDIAC FA LURE;MYOCARDIAL ISCHAEMIA;LUNG DISORDER;SP NAL CORD COMPRESSION;PULMONARY OEDEMA	FRA	77	M
8232555	US-JNJFOC-20111101774	11/7/2011	ZYTIGA	HYPOKALAEMIA;SP NAL CORD COMPRESSION;MOBILITY DECREASED;MUSCULAR WEAKNESS;HYPOAESTHESIA;BACK PAIN;ABDOM NAL PAIN LOWER;FAILURE TO THRIVE;OEDEMA PERIPHERAL;PROSTATE CANCER;THROMBOCYTOPENIA;WEIGHT DECREASED;DECREASED APPETITE	USA	84	M
8306893	FR-JNJFOC-20111201025	12/22/2011	ABIRATERONE ACETATE	PROSTATE CANCER;DRUG NEFFECTIVE;OEDEMA PER PHERAL;PAIN	FRA	67	M
8474446	PT-JNJFOC-20120308361	5/22/2012	ZYTIGA	PAIN;LOCALISED OEDEMA;DISEASE PROGRESSION;HAEMOGLOBIN DECREASED;OEDEMA	PRT	65	M
8555779	FR-JNJFOC-20120508122	6/6/2012	ZYTIGA;DURAGESIC	RESP RATORY FA LURE;ACUTE PULMONARY OEDEMA;CARDIAC FA LURE ACUTE;SOMNOLENCE;NAUSEA	FRA	73	M
8591062	KR-JNJFOC-20120518067	6/1/2012	ABIRATERONE ACETATE;PREDNISOLONE	OEDEMA PERIPHERAL;PLEURAL EFFUSION;DISEASE PROGRESSION	KOR	81	M
8691031	US-JNJFOC-20120712605	9/14/2012	ZYTIGA	DEATH;PULMONARY OEDEMA	USA	64	M

Table 9. Abiraterone Reports with Outcome of Death for SOC Respiratory, Thoracic, and Mediastinal disorders

Case #	MFR Ctrl #	FDA Recd Date	All Suspects	PTs	Country	Age (Yrs)
7941534	IL-JNJFOC-20110503870	5/15/2012	ABIRATERONE ACETATE;PREDNISONE	ACUTE MYOCARDIAL INFARCTION;DEATH;OEDEMA;PLEURAL EFFUSION;CARDIAC FA LURE CONGESTIVE	ISR	76
7968206	FR-JNJFOC-20110510582	4/3/2012	ABIRATERONE ACETATE	LYMPHANGITIS;DRUG NEFFECTIVE;PROSTATE CANCER;DYSPNOEA;OEDEMA;RENAL FA LURE	FRA	UNK
7985989	FR-JNJFOC-20110602381	8/12/2011	ABIRATERONE ACETATE;PREDNISOLONE	PULMONARY ARTERIAL HYPERTENSION;RESPIRATORY DISTRESS;HYPOXIA;BLOOD ALKAL NE PHOSPHATASE NCREASED;OXYGEN SATURATION DECREASED;THROMBOCYTOPENIA	FRA	54
7995378	US-JNJFOC-20110603596	9/2/2011	ZYTIGA;JEVTANA	BLOOD BIL RUBIN INCREASED;PLEURAL EFFUSION;ALANINE AMINOTRANSFERASE INCREASED;ANAEMIA;URINARY TRACT INFECTION;PROSTATE CANCER;BLOOD ALKAL NE PHOSPHATASE DECREASED;ASPARTATE AMINOTRANSFERASE INCREASED;PANCYTOPENIA	USA	62
8084629	FR-JNJFOC-20110802436	4/17/2012	ABIRATERONE ACETATE;PREDNISONE	CARDIAC FA LURE;MYOCARDIAL ISCHAEMIA;LUNG DISORDER;SP NAL CORD COMPRESSION;PULMONARY OEDEMA	FRA	77
8092150	GB-JNJFOC-20110408939	8/16/2011	ABIRATERONE ACETATE;PREDNISOLONE	RESP RATORY FAILURE;PNEUMONIA	GBR	81
8108440	US-JNJFOC-20110811296	8/26/2011	ZYTIGA	DEATH;COUGH	USA	UNK
8119433	IT-JNJFOC-20110813267	2/23/2012	ABIRATERONE ACETATE;PREDNISONE	RESPIRATORY FAILURE	ITA	77
8130164	AU-JNJFOC-20110805068	3/2/2012	ABIRATERONE ACETATE;PREDNISONE	LUNG NFECTION;SP NAL FRACTURE;DISEASE PROGRESSION	AUS	49
8133463	US-JNJFOC-20110904118	11/7/2011	ZYTIGA	PROSTATE CANCER METASTATIC;KIDNEY ENLARGEMENT;DYSPNOEA;SPEECH DISORDER;DECREASED APPETITE;UR NARY RETENTION;MALAISE;WEIGHT DECREASED;ASTHENIA;ABASIA;PULMONARY EMBOLISM	USA	79
8152806	GR-TEVA-301086ISR	9/22/2011	PREDNISOLONE;ABIRATERONE ACETATE	RESP RATORY TRACT INFECTION;RESPIRATORY FAILURE	GRC	72
8165296	US-JNJFOC-20110910885	11/29/2011	ZYTIGA;SOMATOSTATIN;EVEROLIMUS	ASCITES;COMA;HEPATIC FAILURE;METASTASES TO PLEURA;LIVER FUNCTION TEST ABNORMAL;HEPATIC ENZYME INCREASED;MALIGNANT PLEURAL EFFUSION	USA	59

8236400 8282279 8216134	US-PFIZER INC-2011261687; US-JNJFOC-20111203064; US-JNJFOC-20111012463	1/12/2012	SUNITINIB MALATE;AB RATERONE ACETATE;PREDNISONE	PNEUMONIA	USA	76
8240580	DE-JNJFOC-20111100782	1/5/2012	ZYTIGA	PROSTATE CANCER METASTATIC;MYOCARDIAL INFARCTION;PNEUMONIA	DEU	71
8337703	ES-JNJFOC-20120103734	2/13/2012	ABIRATERONE ACETATE;PREDNISONE	DYSPNOEA	ESP	77
8350870	FR-JNJFOC-20120108439	4/10/2012	ZYTIGA	DEATH;PULMONARY EMBOLISM;BLOOD PRESSURE DECREASED	FRA	85
8361636	US-JNJFOC-20120111031	1/31/2012	ABIRATERONE ACETATE;DASAT NIB	PNEUMONITIS	USA	UNK
8378214	IT-JNJFOC-20120112648	1/31/2012	ABIRATERONE ACETATE	HYPONATRAEMIA;SEPSIS;RESPIRATORY FAILURE;SOMNOLENCE;ABDOM NAL PAIN;HYPOTENSION;TACHYCARDIA	ITA	78
8429845	BR-JNJFOC-20120209440	8/21/2012	ABIRATERONE ACETATE;PREDNISONE	DEEP VE N THROMBOSIS;PNEUMONIA	BRA	75
8552007	BR-JNJFOC-20120504354	5/8/2012	ZYTIGA	RESPIRATORY FAILURE;TRANSAMINASES ABNORMAL;METASTASES TO LIVER;JAUNDICE;RESPIRATORY DISORDER	BRA	UNK
8555779	FR-JNJFOC-20120508122	6/6/2012	ZYTIGA;DURAGESIC	RESP RATORY FA LURE;ACUTE PULMONARY OEDEMA;CARDIAC FAILURE ACUTE;SOMNOLENCE;NAUSEA	FRA	73
8582767	GB-JNJFOC-20120507036	5/29/2012	ZYTIGA	PULMONARY EMBOLISM;HAEMOGLOBIN DECREASED;STAPHYLOCOCCAL NFECTION;HEPATOTOXICITY;BLOOD ALKALINE PHOSPHATASE NCREASED	GBR	UNK
8586565		5/22/2012	ZYTIGA	DYSSTASIA;DIARRHOEA;RESP RATORY ARREST;FAECALOMA;RESPIRATORY TRACT CONGESTION;MOVEMENT DISORDER;METASTASES TO LIVER;PYREXIA;ABDOM NAL DISTENSION;SPEECH DISORDER;BLOOD PRESSURE DECREASED;ASTHENIA;OXYGEN SATURATION DECREASED	USA	76
8591062	KR-JNJFOC-20120518067	6/1/2012	ABIRATERONE ACETATE;PREDNISOLONE	OEDEMA PERIPHERAL;PLEURAL EFFUSION;DISEASE PROGRESSION	KOR	81
8641201	US-JNJFOC-20120613678	8/13/2012	ZYTIGA	ADVERSE EVENT;DRUG NEFFECTIVE;DYSPNOEA;FATIGUE;PNEUMONIA	USA	84
8646920	TW-JNJFOC-20120606230	7/30/2012	ABIRATERONE ACETATE;PREDNISOLONE	ACUTE RESPIRATORY FAILURE HYPOKALAEMIA RENAL FAILURE ACUTE	TWN	77
8691031	US-JNJFOC-20120712605	9/14/2012	ZYTIGA	DEATH;PULMONARY OEDEMA	USA	64
8713007	RO-JNJFOC-20120610357	8/21/2012	ABIRATERONE ACETATE;PREDNISONE	CARDIO-RESPIRATORY ARREST;DEHYDRATION;ANAEMIA	ROM	66

Table 10. Abiraterone Reports with Outcome of Death for PT Diarrhea

Case #	MFR Ctrl #	FDA Recd Date	All Suspects	PTs	Country	Age (Yrs)	Sex
8008712	GB-JNJFOC-20110603204	2/1/2012	ABIRATERONE ACETATE	BREAST CANCER METASTATIC;DRUG DOSE OMISSION;GASTROENTERITIS VIRAL;HAEMOGLOB N DECREASED;DISEASE PROGRESSION;HYPOKALAEMIA;VOMIT NG;DIARRHOEA	GBR	58	F
8335418	FR-JNJFOC-20120103365	6/29/2012	ZYTIGA	SEPTIC SHOCK;DIARRHOEA;DISSEMINATED INTRAVASCULAR COAGULATION;RENAL FA LURE ACUTE	FRA	75	M
8458100	FR-JNJFOC-20100302650	3/14/2012	ABIRATERONE ACETATE;PREDNISOLONE	GASTROINTESTINAL NECROSIS;ASTHENIA;INTESTINAL INFARCTION;WOUND COMPLICATION;SHOCK;DIARRHOEA;PROCEDURAL PAIN;GASTROINTESTINAL PERFORATION;INFECTIOUS PERITONITIS;INTESTINAL ISCHAEMIA;INGUINAL HERNIA STRANGULATED;SMALL INTESTINAL OBSTRUCTION;RENAL FAILURE ACUTE;LIVEDO RETICULARIS TACHYCARDIA HYPOTENSION DECREASED APPETITE;FOOD INTOLERANCE;VOMITING	FRA	83	M
8586565		5/22/2012	ZYTIGA	DYSSTASIA DIARRHOEA RESPIRATORY ARREST;FAECALOMA;RESPIRATORY TRACT CONGESTION;MOVEMENT DISORDER;METASTASES TO LIVER;PYREXIA;ABDOMINAL DISTENSION;SPEECH DISORDER;BLOOD PRESSURE DECREASED;ASTHENIA;OXYGEN SATURATION DECREASED	USA	76	M
8643197	BR-JNJFOC-20120613332	8/21/2012	ABIRATERONE ACETATE;PREDNISONE	DIARRHOEA	BRA	52	M
8652742	US-JNJFOC-20120701746	7/6/2012	ZYTIGA	DEATH;ASTHENIA;DIARRHOEA;OXYGEN SATURATION DECREASED;HYPOTENSION	USA	UNK	M
8726052	AU-JNJFOC-20120610977	9/6/2012	ABIRATERONE ACETATE;PREDNISONE	DIARRHOEA;MULTI-ORGAN FAILURE;SEPSIS	AUS	79	M

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/s/

KATHERINE M COYLE
10/12/2012

ROBERT G PRATT
10/12/2012

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE:	October 5, 2012
TO:	Amy Tilley, Regulatory Project Manager Paul Kluetz, M.D., Clinical Reviewer Division of Oncology Products 1
FROM	John Lee, M.D., Medical Officer Good Clinical Practice Assessment Branch Division of Good Clinical Practice Compliance Office of Scientific Investigations
THROUGH:	Janice Pohlman, M.D., M.P.H., Team Leader Good Clinical Practice Assessment Branch Division of Good Clinical Practice Compliance Office of Scientific Investigations
	Susan D. Thompson, M.D., Acting Branch Chief Good Clinical Practice Assessment Branch Division of Good Clinical Practice Compliance Office of Scientific Investigations
SUBJECT:	Evaluation of Clinical Inspections
APPLICATION:	NDA 202-379 S-005
APPLICANT:	Janssen Biotech, Inc.
DRUG:	Zytiga® (abiraterone acetate)
NME:	No
INDICATION:	Treatment of patients with metastatic castration-resistant prostate cancer [redacted] (b) (4)

REVIEW CLASSIFICATION:	Priority
CONSULTATION REQUEST DATE:	June 28, 2012
INSPECTION SUMMARY GOAL DATE:	October 31, 2012
DOP-1 ACTION GOAL DATE:	December 14, 2012
PDUFA DUE DATE:	December 14, 2012

I. Background

Extragonadal androgen synthesis can support prostate cancer progression, and prostate cancer itself may produce androgens to support self-growth. Following primary (medical or surgical) androgen deprivation therapy (**ADT**), biochemical strategies that further reduce androgen synthesis, in normal and neoplastic tissue, may be effective in managing castration-resistant prostate cancer (**CRPC**), including metastatic CRPC (**mCRPC**). Currently, optimal management of CRPC remains poorly defined, particularly in asymptomatic or mildly symptomatic disease.

Abiraterone acetate (Zytiga®) inhibits an enzyme essential for androgen synthesis in the testes, adrenals, and prostatic neoplasms, including adenocarcinoma. In a phase 2 study (COU-AA-301), the use of abiraterone acetate was associated with prolonged survival in mCRPC without treatment-limiting toxicities. Study COU-AA-302 was designed as a phase 3 study to show that the use of abiraterone acetate in chemotherapy-naive mCRPC slows disease progression, increases survival, and delays the need for chemotherapy and/or opiate therapy.

Study COU-AA-302

This randomized, double-blind, placebo-controlled study was conducted over 14 months (April 2009 - June 2010) in 1088 subjects at 151 study sites (United States, Europe, Australia, and Canada) to compare abiraterone acetate with placebo in treating asymptomatic (or mildly symptomatic) chemotherapy-naive mCRPC. Subjects were stratified according to the Eastern Cooperative Oncology Group (**ECOG**) performance status (Grade 0 versus Grade 1) and were randomized in equal ratio to receive either abiraterone acetate (plus prednisone) or placebo (plus prednisone).

The study consisted of three phases: (1) *Screening and Randomization*, 14 days before first dose; (2) *Treatment*, first dose through End-of-Study Treatment Visit; and (3) *Follow-up*, survival status assessed every 3 months up to five years. Treatment, monitored in 28-day cycles, consisted of oral abiraterone acetate 1.0 g once daily plus prednisone 5 mg twice daily, or matching placebo plus prednisone. Subjects received treatment until disease progression was observed radiographically or clinically based on cancer pain and/or deterioration of ECOG performance status ($\geq$ 1 Grade).

Efficacy assessments included sequential imaging (radiographic disease progression), concomitant medication use (need for opiates for cancer pain), time to chemotherapy, history and physical (ECOG performance status), and serum prostate-specific antigen (biochemical disease progression). Safety assessments included history, vital signs, physical examinations, laboratory testing, serial electrocardiograms (**EKGs**), and adverse event (**AE**) monitoring. Left ventricular ejection fraction (**LVEF**) was measured at baseline only using multiple gated acquisition scan (**MUGA**) or echocardiogram (if MUGA unavailable).

In NDA 202-379 S-005, the sponsor claims that the results of Study COU-AA-302 demonstrate the efficacy and safety of abiraterone acetate in treating mCRPC: (1) the use of a treatment regimen consisting of abiraterone acetate plus prednisone resulted in a more favorable clinical outcome than treatment with prednisone alone, as evidenced by a substantial delay in disease progression, improved overall survival, and equally well-preserved quality of life; (2) the safety profile of abiraterone acetate plus prednisone in chemotherapy naive mCRPC was similar to the safety profile of the treatment regimen in the post-docetaxel setting, and (3) AEs did not interfere with treatment. Major features of the protocol for Study COU-AA-302 are outlined below.

Clinical Trial Outline:

- Primary Objective: Compare the clinical benefit of abiraterone acetate plus prednisone to placebo plus prednisone in asymptomatic or mildly symptomatic men with chemotherapy-naive mCRPC
- Secondary Objectives:
  - Establish additional clinically relevant improvements in prostate cancer subjects treated with abiraterone acetate in comparison with placebo
  - Characterize the safety profile of abiraterone acetate in this subject population, and the pharmacokinetic profile of abiraterone acetate when administered with prednisone
- Inclusion Criteria:
  - Men (18 years of age or older) with adenocarcinoma of the prostate, confirmed by tissue biopsy histology and/or tissue aspirate cytology
  - Laboratory evidence of ongoing androgen deprivation (serum testosterone <50 ng/dL) and an ECOG performance status Grade 0 or 1
  - Progression of prostate cancer, as evidenced by progressively rising levels of the prostate-specific antigen (**PSA**) that meet adapted Prostate Cancer Working Group 2 (**PCWG2**) criteria, or radiographic progression according to modified Response Evaluation Criteria in Solid Tumors (**RECIST**) criteria
- Exclusion Criteria:
  - Serious or uncontrolled co-existent non-malignant disease (including uncontrolled infection)
  - Prior cytotoxic chemotherapy or biologic therapy for CRPC
  - Liver, visceral organ, or brain metastasis
  - Use of opiate analgesics for cancer-related pain within 4 weeks of Cycle 1 Day 1
  - Abnormal aspartate or alanine aminotransferase $\geq$ 2.5 times upper limit of normal
- Study Groups and Treatment Regimen:
  - Test Group: Oral abiraterone acetate 1.0 g once daily plus prednisone 5 mg twice daily
  - Control Group: Matching placebo plus prednisone
- Co-Primary Efficacy Endpoints:
  - Radiographic progression-free survival (**rPFS**)
  - Overall survival (**OS**)
- Major Secondary Endpoints (Times to):
  - Opiate use for cancer-related pain
  - Initiation of chemotherapy
  - Clinical deterioration as assessed by ECOG performance status
  - Biochemical disease progression as assessed by prostate-specific antigen
- Safety Monitoring:
  - General: history, vital signs, physical examinations, laboratory testing, and AE monitoring
  - Cardiac: LVEF (baseline only using MUGA or echocardiogram) and serial EKGs

II. GCP Inspections

The pivotal study supporting this NDA supplement (Study COU-AA-302) enrolled 1088 subjects at 151 clinical study sites worldwide. No single site accounted for more than four percent of total subject enrollment. The overall efficacy results indicated a statistically significant improvement in the co-primary efficacy endpoints, rPFS and OS.

For the pivotal Study COU-AA-302, four sites in the United States and Spain were selected for good clinical practice (**GCP**) inspections based on: large subject enrollment, high reporting rate of major protocol violations and adverse events (**AE**) including serious adverse events (**SAE**), and relatively large site-specific efficacy margin of the investigational treatment regimen over the control.

	Clinical Investigator	Site & Subjects	Inspection Dates	Outcome Classification
1	Charles Ryan, MD UCSF Medical Center 1600 Divisadero Street, Box 1711 San Francisco, California 94115	Site 157 40 subjects	Aug 9 - 21, 2012	Pending Preliminary NAI
2	Dana E. Rathkopf, MD Memorial Sloan Kettering Hospital 1275 York Avenue New York, NY 10065	Site 160 41 subjects	Aug 21 - 24, 2012	NAI
3	Joan Carles, M.D. Hospital Universitari Vall d´Hebron Servicio Oncologia Passeig Vall d'Hebron, 119-129 Barcelona, 08035 Spain	Site 812 15 subjects	Sep 17 - 24, 2012	Pending Preliminary NAI
4	Jose P. Rodriguez, M.D. Institut Catala d'Oncologia L'Hospitalet Servicio Oncologia Avda Gran Via de l'Hospitalet, 199-203 Barcelona, 08907 Spain	Site 814 18 subjects	Sep 25 - 28, 2012	Pending Preliminary VAI

NAI = no action indicated, no deviation from regulations; VAI = voluntary action indicated, deviation from regulations; OAI = official action indicated, significant deviation from regulations and/or data unreliable

Pending: This preliminary classification is based on information on Form FDA 483 and communication with the field investigator; final inspection report has not been received from the field office and OSI's complete review of the report remains pending as of this clinical inspection summary.

1. Charles Ryan, M.D. (Site 157)

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring and IRB oversight, AE monitoring and reporting, and adherence to the study protocol and applicable GCP regulations
- Data verification: co-primary (rPFS and OS) and major secondary endpoints, AEs, subject randomization, protocol violations, and subject discontinuations
- Subjects: 51 subjects were screened, 40 were enrolled, 17 completed treatment, and three were receiving treatment at time of inspection. Subject records for all 40 enrolled subjects were reviewed, including detailed review of 14 records to include informed consent, randomization, AE monitoring and reporting, and evaluation of efficacy.

b. General observations and comments:

- No significant deficiencies were observed and a Form FDA 483 was not issued. IRB oversight and study monitoring appeared to be adequate.
- Endpoint data were verifiable: data matched among source records, case report forms (**CRFs**), and data listings in the NDA. Underreporting of AEs was not observed.
- All subjects at this site appeared to have been consented properly. Source records appeared factual and complete, and matched corresponding CRFs. Drug accountability was well documented. No significant objectionable conditions were observed.

c. Assessment of data integrity: Data from this study site appear reliable.

Note: Observations noted above for this Site 157 of Study COU-AA-302 are based on preliminary communications with the field investigator. An addendum to this clinical inspection summary (**CIS**) will be forwarded to DOP-1 if conclusions change upon receipt and review of the final establishment inspection report (**EIR**).

2. Dana E. Rathkopf, M.D. (Site 160)

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring and IRB oversight, AE monitoring and reporting, and adherence to the study protocol and applicable GCP regulations
- Data verification: co-primary (rPFS and OS) and major secondary endpoints, AEs, subject randomization, protocol violations, and subject discontinuations
- Subjects: 46 subjects were screened, 41 were enrolled, and 34 completed treatment. At time of inspection, seven subjects were still receiving treatment, 18 (of 34 completing treatment) died (disease progression), and 16 (of 34 completing treatment) were still being followed. Subject records for all 41 enrolled subjects were reviewed. For 14 enrolled subjects (12 active, two placebo), the records were completely reviewed. For the remaining 27 subjects, the records were reviewed for informed consent, randomization, AE monitoring and reporting, and evaluation of efficacy.

b. General observations and comments:

- No significant deficiencies were observed and a Form FDA 483 was not issued. Study oversight by the Memorial Sloan Kettering Cancer Center Institutional Review Board (MSKCC-IRB) appeared to be adequate, as did study monitoring by the contract research organization (CRO) Cougar Biotechnology, Inc.
- Endpoint data were verifiable: data matched among source records, CRFs, and data listings in the NDA. Underreporting of AEs was not observed.
- All subjects at this site appeared to have been consented properly. Source records appeared factual and complete, and matched corresponding CRFs. Drug accountability was well documented. No significant objectionable conditions were observed.

c. Assessment of data integrity: Data from this study site appear reliable.

3. Joan Carles, M.D. (Site 812)

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring and IRB oversight, AE monitoring and reporting, and adherence to the study protocol and applicable GCP regulations
- Data verification: co-primary (rPFS and OS) and major secondary endpoints, AEs, subject randomization, protocol violations, and subject discontinuations
- Subjects: 23 subjects were screened, 15 were enrolled, 10 completed treatment, and five were receiving treatment at time of inspection. Subject records for all enrolled subjects were reviewed, including detailed review for four subjects to include informed consent, randomization, AE monitoring and reporting, and evaluation of efficacy.

b. General observations and comments:

- No significant deficiencies were observed and a Form FDA 483 was not issued. IRB oversight and study monitoring appeared to be adequate.
- Endpoint data were verifiable: data matched among source records, CRFs, and data listings in the NDA. Underreporting of AEs was not observed.
- All subjects at this site appeared to have been consented properly. Source records appeared factual and complete, and matched corresponding CRFs. Drug accountability was well documented. No significant objectionable conditions were observed.

c. Assessment of data integrity: Data from this study site appear reliable.

Note: Observations noted above for this Site 812 of Study COU-AA-302 are based on preliminary communications with the field investigator. An addendum to this CIS will be forwarded to DOP-1 if conclusions change upon receipt and review of the final EIR.

4. Jose P. Rodriguez, M.D. (Site 814)

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, study monitoring and IRB oversight, AE monitoring and reporting, and adherence to the study protocol and applicable GCP regulations

- Data verification: co-primary (rPFS and OS) and major secondary endpoints, AEs, subject randomization, protocol violations, and subject discontinuations
- Subjects: 31 subjects were screened, 18 were enrolled, 15 completed treatment, and three were receiving treatment at time of inspection. Subject records for all enrolled subjects were reviewed, including detailed review for five subjects to include informed consent, randomization, AE monitoring and reporting, and evaluation of efficacy.

b. General observations and comments:

- A Form FDA 483 was issued for the following deficiencies:
  - Four subjects were enrolled despite not meeting subject selection criteria: (1) androgen receptor inhibitor (bicalutimide) had not been discontinued $\geq$ six weeks before treatment initiation (Subject 2006, one month; Subject 2012, eight days), and (2) subjects were not excluded based on prior radiation therapy for mCRCP (Subjects 2020 and 2030).

    Review Comment: The protocol violations for Subjects 2012 (abiraterone acetate), 2020 (placebo), and 2030 (placebo) are reported in the sNDA. The protocol violation for Subject 2006 (placebo) is not reported in the sNDA.
  - Subjects 2001, 2008, and 2014: Testosterone level results were not obtained from the protocol-specified central laboratory and/or obtained and reviewed in a timely manner (inadequate documentation).
  - Subjects 2012 and 2029: Not all laboratory test results (other than testosterone levels) were obtained from the protocol-specified central laboratory, or were obtained and reviewed in a timely manner (inadequate documentation).
  - Subject 2029: Parts of the study questionnaires (for assessing pain or quality of life) appeared to have been filled out by someone other than the subject (inconsistent handwriting and/or ink color) without appropriate explanatory documentation.
- Endpoint data were verifiable: data matched among source records, CRFs, and data listings in the NDA. Underreporting of AEs was not observed.
- All subjects at this site appeared to have been consented properly. Source records appeared factual and complete, and matched corresponding CRFs. Drug accountability appeared to be well documented. IRB oversight and study monitoring appeared to be adequate.

c. Assessment of data integrity:

The subject eligibility violations for Subjects 2012, 2020, and 2030 are reported in the sNDA for evaluation of their significance by DOP-1. The subject eligibility violation for Subject 2006 (bicalutimide wash-out of one month, not $\geq$ six weeks) is not reported in the sNDA; however, the actual and protocol-specified time intervals are similar, and this violation appears to be an isolated sNDA-unreported finding of minor significance. The other remaining deficiency observations (about laboratory tests and study questionnaires) also appear to be minor in significance. Data from this study site appear reliable.

Note: Observations noted above for this Site 814 of Study COU-AA-302 are based on preliminary communications with the field investigator. An addendum to this CIS will be forwarded to DOP-1 if conclusions change upon receipt and review of the final EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

This efficacy supplement application has been assigned Priority Review Status based on prospective use in a patient population with limited available therapy options. For the pivotal Study COU-AA-302, four clinical study sites in the United States and Spain were selected for GCP inspections. At three of four study sites inspected, no significant deficiencies were observed and a Form FDA 483 was not issued.

At Site 814, a Form FDA 483 was issued for minor deficiencies in adhering to the study protocol regarding subject eligibility determination, laboratory testing, and subjects' completion of study questionnaires. The most significant of these, subject eligibility violations for Subjects 2012, 2020, and 2030 are reported in the sNDA for evaluation of their significance by DOP-1. Subject eligibility violation for Subject 2006 and other deficiencies (about laboratory testing and study questionnaires, five subjects) appear minor and isolated, and are not expected to impact subject safety or the study outcome. This site otherwise conducted the study in accordance with the study protocol and applicable GCP regulations. The study data from four inspected sites appear reliable as reported in the NDA supplement.

Note: For Sites 157 (Ryan), 812 (Carles), and 814 (Rodriguez), the EIRs have not been received from the field office and the final classification of the inspection outcome remains pending. The observations noted above are based on preliminary communications with the field investigator. An addendum to this CIS will be forwarded to DOP-1 if the classification of the inspection outcome changes or if additional observations of clinical or regulatory significance are discovered after completing the review of the EIRs.

{See appended electronic signature page}

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/s/

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10/05/2012

JANICE K POHLMAN
10/09/2012

SUSAN D THOMPSON
10/09/2012

STUDY ENDPOINT REVIEW

SEALD ACTION TRACK NUMBER	AT 2012-081
APPLICATION NUMBER	**NDA 202379 Supplement 005**
LETTER DATE/SUBMISSION NUMBER	**SD 145 eCTD 0056**
PDUFA GOAL DATE	December 14, 2012
DATE OF CONSULT REQUEST	July 13, 2012
REVIEW DIVISION	Division of Oncology Products 1
MEDICAL REVIEWER	**Paul Kluetz (TL: Virginia E. Maher)**
REVIEW DIVISION PM	Amy Tilley
SEALD REVIEWER(S)	**Jessica Voqui**
REVIEW COMPLETION DATE	**October 3, 2012**
ESTABLISHED NAME	abiraterone acetate
TRADE NAME	Zytiga
APPLICANT	Janssen/Cougar
ENDPOINT(S) CONCEPT(S)	**"clinical benefit";** [redacted] **time to disease progression**
MEASURE(S)	BPI-SF; time to opiate use; [redacted] time to initiation of cytotoxic chemotherapy
CLINICAL OUTCOME ASSESSMENT TYPE	**PRO: BPI-SF** **ClinRO: time to opiate use;** [redacted] **time to initiation of cytotoxic chemotherapy**
INDICATION	Treatment of patients with metastatic castration-resistant prostate cancer [redacted]
INTENDED POPULATION(S)	[redacted] medically or surgically castrated male patients who have shown tumor progression [redacted]

A. EXECUTIVE SUMMARY

This Study Endpoints and Labeling Development (SEALD) review is provided as a response to a request for consultation by the Division of Oncology Products 1 regarding NDA 202379, Efficacy Supplement 005. The applicant proposed the endpoints: 1) time to opiate use, 2) time to initiation of cytotoxic chemotherapy, and 3) (b) (4) as secondary endpoints to support a labeling claim for clinical benefit. Additionally the Brief Pain Inventory scores were also used to assess pain severity throughout the study treatment period, although it was not analyzed as a primary or secondary endpoint. (b) (4)

(b) (4)

It is plausible that results from time to opiate use (b) (4) may be used to support labeling statements of treatment benefit in this context.

B. STUDY ENDPOINT REVIEW

Regulatory Background:

Abiraterone acetate was initially approved in 2011 for use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who received prior chemotherapy containing docetaxel based upon improvement in overall survival. The applicant submitted a Phase 3 multinational, multicenter, randomized, double-blind, placebo-controlled study, stratified by ECOG PS score 0 versus 1. This study was intended to support an NDA Efficacy supplement to include an additional indication for patients with metastatic castration-resistant prostate cancer (b) (4)

(b) (4) Co-primary endpoints include radiographic progression free survival (rPFS) and overall survival. The rPFS endpoint was statistically superior at the second interim analysis with a strong OS trend (HR 0.752), which did not meet pre-specified statistical O'Brien-Fleming boundary (P=0.0097, required 0.0008). The independent data monitoring committee (IDMC) reviewed the efficacy and safety data from the interim analysis of OS (43% of death events) and concluded that all of the data demonstrated a significant advantage for patients in one arm of the study compared with the other arm. The IDMC unanimously recommended stopping the study, unblinding, and allowing crossover from the placebo arm to active therapy.

This application intends to seek approval based on a surrogate endpoint for which there is no regulatory precedence in this setting (rPFS in prostate cancer), and it will be a topic of an oncology drug advisory committee meeting scheduled for early November 2012. The division requested SEALD input regarding the robustness of (b) (4) time to opiate use in the consult request. In a separate email, the primary medical reviewer requested that the review also include comments regarding (b) (4) time to initiation of cytotoxic chemotherapy.

1 CLINICAL OUTCOME ASSESSMENT MEASURE(S)

The applicant measured the following secondary endpoints: time to opiate use for cancer pain, time to initiation of cytotoxic therapy, and time to deterioration in ECOG performance score by ≥ 1 point. Additionally, the applicant measured the following exploratory endpoints: pain progression as measured by the Brief Pain Inventory short form (BPI-SF) and the FACT-P Quality of Life Questionnaire. SEALD does not generally review exploratory endpoints, which are not included in the endpoint model that illustrates the hierarchy of endpoints and for which multiplicity adjustment is not performed. However, (b) (4) there will be brief comments regarding these instruments.

Reviewer's comments: Since several endpoints discussed here are time-to-event endpoints, there are some general comments regarding this type of endpoint. A time-to-event (e.g., opiate use or cytotoxic chemotherapy initiation) outcome requires more rigorous data collection methods in order to ensure accurate detection of the first clinically meaningful change. The event of interest must be clearly defined and if it is based on clinical judgment, then the criteria for this decision should also be standard and defined if possible. Additionally, the data points should be prospectively collected at a frequency that is high enough to capture this information as accurately as possible.

1.A. Time to opiate use

Time to opiate use for cancer-related pain was determined by initiation of any opiate use documented in the case report forms (CRF): concomitant medication list, analgesic use form, and BPI-SF form #7 ("What treatments or medications are you receiving for your pain?"). This

information was collected on Day 1 of each treatment cycle, i.e., every 28 days. SEALD has not reviewed any information regarding using this endpoint in the context of metastatic prostate cancer. The only rationale provided was "these endpoints were developed in consultation with Health Authorities and selected because they are clearly defined, verifiable, and supportive of the primary endpoint of delaying rPFS."

Reviewer's comments: While time to opiate use may reflect a delay in progression of pain, there is no evidence provided to demonstrate that relationship unless the pain experience is more fully characterized. In Clinical Study COU-AA-302, the BPI-SF was measured and analyzed as an exploratory endpoint, not a secondary endpoint. Concurrent measurement of pain intensity (e.g. using Question 3 of the BPI-SF) would better characterize the patient's pain experience. A statistical analysis conducted to demonstrate the relationship between the time to opiate use and BPI-SF Question 3 may provide more information regarding the relationship between time to opiate use and pain progression. It is also important to note that "opiate use" was not clearly defined, i.e., there was no list of specific drugs or drug classes in the clinical study protocol.

In the study submitted, opiate use was collected using patient self-report of concomitant medications every 4 weeks. Self-report of medication use is not generally reliable because there is a great concern regarding recall errors. Since the investigators can access source documents such as patient medical records and charts, it may be possible to use this information to support the use of data collected from the concomitant medication reports. For future reference, we generally recommend utilization of pain diaries that also document both pain intensity and analgesic use, both opioid and non-opioid medications, to measure pain.

It is also important to note the potential for other factors that could influence or confound this endpoint (e.g. history of opiate tolerance or abuse, pain management for comorbid conditions, opioid allergy, etc.), which make the results difficult to interpret if not controlled for in the analysis. While randomization usually balances these baseline factors across treatment arms, it is important to ensure that this balance was achieved.

1.B. Time to initiation of cytotoxic chemotherapy

Time to initiation of cytotoxic chemotherapy was determined by documentation of concomitant or subsequent medication. Also note that it was used to define "unequivocal clinical progression" if there was an immediate need to initiate cytotoxic chemotherapy. SEALD has not reviewed any information regarding using this endpoint in the context of metastatic prostate cancer. The only rationale provided was "these endpoints were developed in consultation with Health Authorities and selected because they are clearly defined, verifiable, and supportive of the primary endpoint of delaying rPFS."

Reviewer's comments: Time to cytotoxic chemotherapy initiation may be able to reflect delay of clinical progression (i.e. clinical benefit). However, there are similar issues as with the time to

opiate use. The criteria for initiation of cytotoxic chemotherapy should be clearly outlined and standardized in the study protocol. The criteria for "unequivocal clinical progression" also include initiation of radiation therapy and surgical intervention. We recommend that this endpoint also include all interventions that are initiated as a result of complications due to disease progression.

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(b) (4)

[redacted]

2 ENDPOINT MODEL

- Co-primary endpoints:
    - Overall survival (OS): defined as the time from randomization to date of death from any cause
    - Radiographic progression-free survival (rPFS): based on parameters suggested by PCWG2 and modified RECIST as the time from randomization to the occurrence of one of the following:
        1. A patient is considered to have progressed by bone scan if:
            a. The first bone scan with ≥ 2 lesions compared to baseline is observed and confirmed by a second bone scan (time cut-offs discussed in clinical study protocol).
        2. Progression of soft tissue lesions measured by CT or MRI as defined in modified RECIST criteria.
        3. Death from any cause.

- Secondary endpoints
    1. Time to opiate use for cancer pain: the time interval from the date of randomization to the date of opiate use for cancer pain.
        a. Censoring: Subjects who have no opiate use at the time of analysis were censored at the last known date of no opiate use for cancer pain. Subjects with no assessment were censored at the date of randomization.
    2. Time to initiation of cytotoxic chemotherapy: time interval from the date of randomization to the date of initiation of cytotoxic chemotherapy for prostate cancer.
        a. Censoring: subjects who had no cytotoxic chemotherapy administration at the time of analysis were censored at the last known date when no cytotoxic chemotherapy was administered. Subjects with no assessment were censored at the date of randomization.

3. Time to deterioration in ECOG performance score by ≥ 1 point: time interval from the date of randomization to the date of initiation of cytotoxic chemotherapy for prostate cancer.
    a. Censoring: Subjects who had no cytotoxic chemotherapy administration at the time of analysis were censored at the last known date when no cytotoxic chemotherapy was administered. Subjects with no assessment were censored at the date of randomization.
4. Time-to-PSA progression based on PCWG2 criteria: time interval from the date of randomization to the date of PSA progression as defined in the protocol-specific PCWG2 criteria (Protocol, Appendix 3).
    a. Censoring: Subjects who had no PSA progression at the time of the analysis were censored at the last known date of no PSA progression. Subjects with no on-study PSA assessment or no baseline PSA assessment were censored at the date of randomization.

- Exploratory endpoints (We consider any endpoints that are not part of the prespecified hierarchy of primary and secondary endpoints to be exploratory.)
    - PSA response rate
    - Objective response rate in patients with measurable disease
    - Duration of response in patients with measurable disease
    - QoL total score and each subscale score as assessed by FACT-P
    - Time to pain progression
        - Time to average pain intensity progression: BPI-SF increase by ≥ 30% in average of BPI-SF items #3, 4, 5, and 6 observed at 2 consecutive evaluations ≥ 4 weeks apart with no increase in WHO analgesic usage score.
        - Time to worst pain intensity progression: BPI-SF increase by ≥ 30% in BPI-SF item #3 observed at 2 consecutive evaluations ≥ 4 weeks apart with no increase in WHO analgesic usage score.
        - Time to worst pain intensity progression using 2-point increase threshold (post-hoc exploratory): BPI-SF item #3 increase by 2 points in 2 consecutive evaluations ≥ 4 weeks apart with no increase in WHO analgesic usage score.
    - Time to analgesic progression

3 CONCEPTUAL FRAMEWORK

- There was no conceptual framework described. In the reviewer's interpretation of the study protocol, the concepts that were intended to be measured were clinical benefit or delay to disease progression.

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(b) (4)

5 OTHER MEASUREMENT PROPERTIES (RELIABILITY, CONSTRUCT VALIDITY, ABILITY TO DETECT CHANGE)

- No other measurement properties were evaluated for any of the proposed endpoints. However, the content validity should be established before these measurement properties are evaluated.

6 INTERPRETATION OF SCORES

- Not applicable.

7 LANGUAGE TRANSLATION AND CULTURAL ADAPTATION

- No details regarding language translation and cultural adaptation plans were provided. However, we recommend that any instrument used in multinational trials as the basis to support labeling claims be translated using an appropriate process (e.g., the ISPOR Task Force Report: Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures).

8 REFORMATTING FOR NEW METHOD OR MODE OF ADMINISTRATION

- Not applicable.

9 PROTOCOL AND ANALYSIS PLAN

The clinical trial submitted for this NDA was a Phase 3, randomized, double-blind, placebo-controlled study of abiraterone acetate (Zytiga) plus prednisone in asymptomatic or mildly symptomatic patients with metastatic castration-resistant prostate cancer.

Primary Objective:

- To compare the clinical benefit of abiraterone acetate plus prednisone versus placebo plus prednisone in patients with chemotherapy-naïve castration-resistant prostate cancer (CRPC) who are asymptomatic or mildly symptomatic

Secondary Objectives:

- To establish additional clinically relevant improvements in prostate cancer patients treated with abiraterone acetate in comparison to placebo
- To characterize the safety profile of abiraterone acetate in this patient population

- To characterize the pharmacokinetics of abiraterone acetate when administered concurrently with prednisone

Study Design:

This study is a multinational, multicenter, randomized double-blind placebo-controlled study with a randomization allocation ratio of 1:1 between the abiraterone acetate group and the placebo group. Abiraterone acetate and placebo tablets will be referred to as study drug in a blinded fashion. Patients randomized to the abiraterone acetate group will receive a dose of 1000 mg daily (QD). Study drug will be administered as 4 x 250-mg abiraterone acetate tablets or 4 placebo tablets. Prednisone will be administered as 5 mg orally twice a day (bid) for both groups. Randomization will be stratified according to the following: ECOG performance status: 0 versus 1.

Study Population:

Approximately 1,000 medically or surgically castrated male patients with metastatic CRPC who have shown tumor progression and are non- or mildly-symptomatic will be enrolled from approximately 150 global study sites.

Duration of Treatment:

Patients will have a screening period of up to 14 days prior to randomization on Cycle 1 Day 1. Each cycle consists of 28 days. Patients will be treated until disease progression as defined in the protocol. After discontinuing study treatment, patients will be contacted once every three months up to 60 months (5 years) for survival follow-up. In addition to overall survival, opiate use, ECOG performance status, and next therapy for prostate cancer (including dose and treatment duration of cytotoxic chemotherapy) will also be collected.

Efficacy Assessment:
The primary efficacy endpoints are Overall Survival (OS) and Radiographic Progression-Free Survival (rPFS) (co-primary).

- Efficacy assessment in rPFS will utilize sequential imaging studies as defined by PCWG2 and modified RECIST criteria.
- Survival data will be collected throughout the study treatment phase and during follow-up.

Secondary efficacy assessments:

- Time to opiate use for cancer-related pain and time to administration of cytotoxic chemotherapy for metastatic prostate cancer will be prospectively assessed.
- ECOG performance status will be evaluated throughout the study to assess time to first deterioration.

PSA values will be collected throughout the study to assess time to PSA progression.

Assessment Schedule:

Table of Scheduled Events

		Treatment Phase						Follow-Up Phase
Evaluation	Screening Day -14 to 1	[1]Day 1 of Cycle 1	Day 15 of Cycle 1	[2]Day 1 of Cycles 2, 4, 6, 8, 9, 11, 12…	Day 15 of Cycles 2 and 3	[2]Day 1 of Cycles 3, 5, 7, 10…, and at Treatment Discontinuation[3]	End of Study Treatment Visit[4]	Q3 Months up to Month 60
Procedures								
Signed consent form	X[17]							
Medical history, demographics, prior prostate therapies	X							
QOL - FACT-P		X				X	X	
BPI-SF, analgesic usage	X	X		X		X	X	
Physical exam and Weight[5]	X		X	X		X	X	
Vital signs[6]	X	X	X	X		X	X	
ECOG	X	X	X	X		X	X	
12 Lead ECG[7]	X					X	X	
MUGA Scan or Cardiac ECHO[8]	X							
Dosing compliance			X	X		X	X	
Concomitant medications	X	X	X	X		X	X	
Adverse events	X[9]	X	X	X		X	X[10]	
Laboratory Assessments								
Hematology	X	X		X		X	X	
Coagulation Factors- PT/PTT (INR)	X		X					
Serum chemistry, electrolytes	X	X	X	X		X	X	
Fasting Glucose	X					X	X	
Serum Lipids	X					X	X	

Table of Scheduled Events

		Treatment Phase						Follow-Up Phase
Evaluation	Screening Day -14 to 1	[1]Day 1 of Cycle 1	Day 15 of Cycle 1	[2]Day 1 of Cycles 2, 4, 6, 8, 9, 11, 12…	Day 15 of Cycles 2 and 3	[2]Day 1 of Cycles 3, 5, 7, 10…, and at Treatment Discontinuation[3]	End of Study Treatment Visit[4]	Q3 Months up to Month 60
Liver function tests[16]					X[16]			
PSA[11]	X	X				X	X	
Serum testosterone	X							
Urinalysis (dipstick)	X							
Tumor Assessments								
CT / MRI /other imaging procedure	X[12]					X		
Bone Scan	X[12]					X[13]		
Disease progression assessment						X		
TMPRSS2-ERG and other biomarkers (at selected study centers)	X[18]							
PK[14] Sampling at Select Study Centers								
Pre-dose PK		X[14]		X[14]		X[14]		
In Clinic Dosing of Study Treatment for PK		X[14]		X[14]		X[14]		
Post-dose 12-Lead ECG		X[14]		X[14]		X[14]		
Post–dose PK		X[14]		X[14]		X[14]		
Follow-Up Period Assessments								
Follow-Up Assessments[15]								X[15]

1 The Cycle 1 Day 1 visit may occur on the same day as the Screening Visit provided that all screening assessments have been completed and results reviewed prior to the commencement of Cycle 1 Day1 assessments.

2 If patients continue on study without disease progression or discontinuation of treatment beyond Cycle 12, they should receive visit assessments as follows:

- At Cycle 13 and every third cycle thereafter (i.e. Cycles 13, 16, 19, 22…), patients should receive the same assessments as indicated for Cycles 3, 5, 7, and 10.
- At all other cycles (i.e. Cycles 14, 15, 17, 18, 20, 21…) they should receive the same assessments as indicated for Cycles 2, 4, 6, 8, 9, 11, and 12.

3 Treatment Discontinuation Visit can occur at any scheduled or unscheduled visit when applicable. At this visit, documentation to confirm progressive disease is required.

4 End of Study Treatment Visit should be scheduled to collect safety assessments between 15 to 28 days after the patient stops treatment. Patients will enter Follow up Phase at that time.

5 Weight will be recorded at every indicated visit. Height will be measured at Screening visit only.

6 Vitals include upright blood pressure, heart rate, respiratory rate, and oral or aural body temperature.

7 ECGs should not be obtained when serum potassium is < 3.5mg/mL. Hypokalemia should be corrected prior to ECG collection.

8 A MUGA scan should be obtained at baseline (up to 28 days prior to Cycle 1 Day 1). A cardiac ECHO can be used if MUGA is not available or when ECHO is standard of care at the study site.

9 Pre-Treatment SAEs should be reported from time patient signs a consent form up to Cycle 1 Day 1 treatment administration.

10 Adverse event follow-up is 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 exists. Follow-up could be conducted by sites via telephone attempts and must be documented in source notes.

11 If patient undergoes a digital rectal exam (DRE), PSA must be sampled prior to the DRE

12 Scans (CT, MRI, and Bone) performed up to 28 days prior to Cycle 1 Day 1 can be used for baseline assessments.

13 If disease progression is observed on the bone scan, confirmatory bone scan is required at least 6 weeks later. Study treatment should be continued in the interim unless there is unequivocal clinical progression as defined in Section 6.6. If the confirmatory scan is negative (does not confirm PD), then the patient should be seen again at the next scheduled study visit as specified in the protocol.

14 Selected Study Centers Only: PK blood samples collected pre and post dose at the following visits: Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 5 Day 1. Patients will be asked to withhold their daily dose and take study treatment following pre-dose PK collection.

15 Follow-up assessments may be collected by telephone interview or chart review. Information will be collected on overall survival, opiate use, ECOG performance status, next therapy for prostate cancer (including dose and treatment duration of cytotoxic chemotherapy), and study treatment related SAEs.

16 Liver function tests include: ALK-P, ALT (SGPT), AST (SGOT), LDH, and direct and total bilirubin

17 Informed consent may be obtained prior to Day -14, as long as it is obtained before any study-specific procedures are completed.

18 Shipment of samples to the central laboratory for biomarker analysis can be completed at any point after Screening.

10 KEY REFERENCES FOR MEASURE

1. Cleeland CS. The measurement of pain by subjective report. In: CR chapman & JD Loeser (eds), Advance of pain research and therapy, Vol 12: Issues in pain measurement. New York:Raven Press; 1989, p39-403.

2. Cleeland CS, Ryan KM. (1994) Pain assessment: Global use of the Brief Pain Inventory. Ann Academic Medicine 23(2):129-138.

3. Farrar JT, Young JP, LaMoreaux L, Werth JL, Poole RM. (2001) Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 94:149-58.

4. Dworkin RH, Turk DC, Wyrwich KW, Beaton D, Cleeland CS, Farrar JT, Hythornthwaite JA, et al. (2008) Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT Recommendations. The Journal of Pain 9(2):105-21.

5. Cella, D. et. al. (1999) Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. Lung Cancer 12:199-2202.

6. Esper P, Mo F, et. al (1997). Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. Urology 50 (6):920-928.

D. APPENDICES

Appendix A: ECOG PS

ECOG Grade Scale (with Karnofsky conversion)

0	Fully active, able to carry on all pre-disease performance without restriction. (Karnofsky 90-100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work on a light or sedentary nature, eg., light housework, office work. (Karnofsky 70-80)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. (Karnofsky 50-60)
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours. (Karnofsky 30-40)
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. (Karnofsky 10-20)
5	Dead

Appendix B: BPI-SF

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/s/

JESSICA VOQUI
10/03/2012

LAURIE B BURKE
10/04/2012

REGULATORY PROJECT MANAGER
PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW
OF THE PRESCRIBING INFORMATION

To be completed for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Supplements

Application: NDA 202379/S-005/SE1

Application Type: Efficacy Supplement

Name of Drug: Zytiga® (abiraterone acetate) Tablets

Applicant: Janssen Biotech, Inc.

Submission Date: June 13, 2012

Receipt Date: June 14, 2012

1.0 Regulatory History and Applicant's Main Proposals

NDA 202379 was approved on April 28, 2011 for the use of Zytiga (abiraterone acetate) Tablets in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel.

This (S-005) supplemental New Drug Application (sNDA) to NDA 202379 seeks approval of Zytiga® (abiraterone acetate) 250 mg tablets, in combination with prednisone, for the treatment of patients with metastatic castration-resistant prostate cancer (b) (4) (b) (4) and 3 years of marketing exclusivity.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3.0 Conclusions/Recommendations

In Section 12 the first subsection is incorrectly numbered as 12.2 Mechanism of Action and should be numbered as 12.1. The fourth subsection is 12.4 QT Prolongation but should be numbered as 12.6.

5.0 Appendix

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirement of Prescribing Information (SRPI) version 2 is a 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

YES 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

YES 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been is granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select "YES" in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

- **For the Filing Period (for RPMs)**
  - *For efficacy supplements:* If a waiver was previously granted, select "**YES**" in the drop-down menu because this item meets the requirement.
  - *For NDAs/BLAs and PLR conversions:* Select "**NO**" in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.
- **For the End-of Cycle Period (for SEALD reviewers)**
  - The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

YES 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

YES 4. White space must be present before each major heading in HL.

Comment:

YES 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment:

YES 6. Section headings are presented in the following order in HL:

Section	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a Boxed Warning is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES 7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES 8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: **"HIGHLIGHTS OF PRESCRIBING INFORMATION"**.

Comment:

Highlights Limitation Statement

YES 9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

Comment:

Product Title

YES 10. Product title in HL must be **bolded.**

Comment:

Initial U.S. Approval

YES 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded,** and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

Comment:

Selected Requirements of Prescribing Information (SRPI)

Boxed Warning

N/A 12. All text must be **bolded**.

Comment:

N/A 13. Must have a centered heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

N/A 14. Must always have the verbatim statement "***See full prescribing information for complete boxed warning***." centered immediately beneath the heading.

Comment:

N/A 15. Must be limited in length to 20 lines (this does not include the heading and statement "***See full prescribing information for complete boxed warning.***")

Comment:

N/A 16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

YES 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

YES 18. Must be listed in the same order in HL as they appear in FPI.

Comment:

YES 19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section's identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, "Dosage and Administration, Coronary Stenting (2.2) --- 3/2012".

Comment:

YES 20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage

YES 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)]."

Comment:

Selected Requirements of Prescribing Information (SRPI)

Dosage Forms and Strengths

N/A 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

YES 23. All contraindications listed in the FPI must also be listed in HL or must include the statement "None" if no contraindications are known.

Comment:

N/A 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

YES 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: "**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer's U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**".

Comment:

Patient Counseling Information Statement

YES 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION"**

If a product **has** FDA-approved patient labeling:

- **"See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."**
- **"See 17 for PATIENT COUNSELING INFORMATION and Medication Guide."**

Comment:

Revision Date

YES 27. **Bolded** revision date (i.e., "**Revised: MM/YYYY** or **Month Year**") must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

GENERAL FORMAT

YES 28. A horizontal line must separate TOC from the FPI.

Comment:

YES 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: "**FULL PRESCRIBING INFORMATION: CONTENTS"**.

Comment:

YES 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.

Comment:

N/A 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.

Comment:

YES 32. All section headings must be **bolded** and in UPPER CASE.

Comment:

YES 33. All subsection headings must be indented, not bolded, and in title case.

Comment:

YES 34. When a section or subsection is omitted, the numbering does not change.

Comment:

YES 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading "**FULL PRESCRIBING INFORMATION: CONTENTS"** must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

YES 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: "**FULL PRESCRIBING INFORMATION".**

Comment:

YES 37. All section and subsection headings and numbers must be **bolded**.

Comment:

NO 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery

8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment: *In Section 12 the first subsection is incorrectly numbered as 12.2 Mechanism of Action and should be numbered as 12.1. The fourth subsection is 12.4 QT Prolongation but should be numbered as 12.6.*

YES 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

YES 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

N/A 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

N/A 42. All text is **bolded**.

Comment:

N/A 43. Must have a heading in UPPER-CASE, containing the word "**WARNING**" (even if more than one Warning, the term, "**WARNING**" and not "**WARNINGS**" should be used) and other words to identify the subject of the Warning (e.g., "**WARNING: SERIOUS INFECTIONS**").

Comment:

Selected Requirements of Prescribing Information (SRPI)

N/A 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

YES 45. If no Contraindications are known, this section must state "None".

Comment:

Adverse Reactions

YES 46. When clinical trials adverse reactions data is included (typically in the "Clinical Trials Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

N/A 47. When postmarketing adverse reaction data is included (typically in the "Postmarketing Experience" subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

Patient Counseling Information

YES 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- "See FDA-approved patient labeling (Medication Guide)"
- "See FDA-approved patient labeling (Medication Guide and Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information)"
- "See FDA-approved patient labeling (Instructions for Use)"
- "See FDA-approved patient labeling (Patient Information and Instructions for Use)"

Comment:

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

/s/

AMY R TILLEY
08/14/2012

ALICE KACUBA
08/15/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data]

Application Information		
NDA # 202379 BLA#	NDA Supplement #:S- 005 BLA Supplement #	Efficacy Supplement Type SE- 1
Proprietary Name: Zytiga® Established/Proper Name: abiraterone acetate Dosage Form: Tablets Strengths: 250 mg		
Applicant: Janssen Biotech, Inc. Agent for Applicant (if applicable):		
Date of Application: 6-13-12 Date of Receipt: 6-14-12 Date clock started after UN:		
PDUFA Goal Date: 12-14-12	Action Goal Date (if different):	
Filing Date: 8-13-12	Date of Filing Meeting: 7-17-12	
Chemical Classification: (1, 2, 3, etc.) (original NDAs only) N/A		
Proposed indication(s)/Proposed change(s): For the treatment of patients with metastatic castration-resistant prostate cancer (b) (4) (b) (4)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:*** ***http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499*** ***and refer to Appendix A for further information.***		☐ 505(b)(1) ☐ 505(b)(2) ☒ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***		☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐		Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***		☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*): N/A

List referenced IND Number(s): 71023

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.***	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? ***For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	X			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? **If yes,** date notified:				
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.***	Payment for this application: ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.	Payment of other user fees: ☐ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X	
Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**			X	
Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs***			X	
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** *http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm* **If yes**, please list below:			X	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2).Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** *http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm*		X		

If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 3 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***				

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☒ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including:	X			

[1] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☐ legible ☒ English (or translated into English) ☐ pagination ☐ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #				
Forms and Certifications				
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?			X	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	X			

Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications]. ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X X	

Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff*:			X	

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***Note****: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*	X X			PeRC Mtg 10-17-12
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			Full Waiver

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? ***If no, request in 74-day letter***			X	
If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? ***If no, request in 74-day letter***	X			
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***			X	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***		X		
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☒ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☐ Carton labels ☐ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	X			
Is the PI submitted in PLR format?[4]	X			

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?				Will be
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)				Will be
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?				Container labels incorrectly submitted to SE1-005. No prop0sed changes for SE1-005
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***			X	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***			X	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	X			Sent 6-28-2012
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		X		No EOP2 Meeting Prelim Responses sent 2-4-11.

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		X		No Pre sNDA Mtg held. Sponsor sent Format Questions and FDA sent responses 1-30-12.
Any Special Protocol Assessments (SPAs)? **Date(s):** 2-6-09 ***If yes, distribute letter and/or relevant minutes before filing meeting***	X			Post SPA Type A Mtg 12-11-08; 2-6-09

ATTACHMENT

MEMO OF FILING MEETING

DATE: July 17, 2012

BLA/NDA/Supp #: 202379/S-005

PROPRIETARY NAME: Zytiga®

ESTABLISHED/PROPER NAME: abiraterone acetate

DOSAGE FORM/STRENGTH: Tablets, 250 mg

APPLICANT: Janssen Biotech, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): To add an indication "In combination with prednisone, for the treatment of patients with metastatic castration-resistant prostate cancer (b) (4) (b) (4)

BACKGROUND: NDA 2012379 was originally approved on April 28, 2011 for in combination with prednisone is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC) who have received prior chemotherapy containing docetaxel.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Amy Tilley	N
	CPMS/TL:	Alice Kacuba	Y
Cross-Discipline Team Leader (CDTL)	Virginia E. Maher		Y
Clinical	Reviewer:	Paul Kluetz	Y
	TL:	Virginia E. Maher	Y
Social Scientist Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (*for OTC products*)	Reviewer:	N/A	
	TL:	N/A	

Clinical Microbiology (*for antimicrobial products*)	Reviewer:	N/A	
Clinical Pharmacology	Reviewer:	Elimika Pfuma	Y
	TL:	Qi Liu	Y
Biostatistics	Reviewer:	Lijun Zhang	Y
	TL:	Shenghui Tang	N
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Kimberly Ringgold	N
	TL:	Todd Palmby	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Sharon Kelly	Y
	TL:	Haripada Sarker	N
Quality Microbiology *(for sterile products)*	Reviewer:	N/A	
	TL:	N/A	
CMC Labeling Review	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:	N/A	
	TL:	N/A	
OSE/DMEPA (proprietary name)	Reviewer:	N/A	
	TL:	N/A	
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:	N/A	
OC/OSI/DSC/PMSB (REMS)	Reviewer:	N/A	
	TL:	N/A	

Bioresearch Monitoring (OSI)	Reviewer:		
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers			
Other attendees	Techiya Toaff		Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**: ***If no, for an original NME or BLA application, include the reason. For example:*** o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable***	☐ YES Date if known: ☒ NO ☐ To be determined Reason:

○ ***the application did not raise significant safety or efficacy issues*** ○ ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***	
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
Environmental Assessment • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☐ YES ☐ NO
Quality Microbiology (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**:	☒ Not Applicable ☐ YES ☐ NO
Facility Inspection • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? **Comments**:	☒ Not Applicable ☐ YES ☐ NO ☐ YES ☐ NO
Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter

CMC Labeling Review **Comments**:	☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: DOP1/Robert Justice, M.D.

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments: 21st Century Review Planner on the CDER Shared drive/DDOP RPM/Amy Tilley/Zytiga-S-005.

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☐ Standard Review ☒ Priority Review

ACTIONS ITEMS

☒	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
☐	BLA/BLA supplements: If filed, send 60-day filing letter
☐	If priority review: • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices)

	• notify OMPQ (so facility inspections can be scheduled earlier)
☒	Send review issues/no review issues by day 74
☐	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
☐	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

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

/s/

ALICE KACUBA

07/21/2012

Signing for Amy Tilley for the RPM Review section and signing for myself for the Filing Meeting minutes.

DSI CONSULT: Request for Clinical Inspections

Date: June 28, 2012

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: *Paul Kluetz, M.D., Clinical Reviewer/DOP1*
Virginia Maher, M.D., MOTL/Robert Justice, M.D., Diretor/DOP1

From: *Amy Tilley, Regulatory Health Project Manager/DOP1*

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: Supplement NDA 202379/S-005
Applicant/ Applicant contact information (to include phone/email):
Janssen Biotech, Inc./Kelly Johnson Reid/908-927-3137/ kjohnso6@its.jnj.com
Drug Proprietary Name: Zytiga®
NME or Original BLA (Yes/No): No
Review Priority (Standard or Priority): Priority

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): treatment of patients with metastatic castration-resistant prostate cancer [redacted] (b) (4)

PDUFA: 12-14-12
Inspection Summary Goal Date: October 31, 2012

II. Protocol/Site Identification

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
160: Dana Rathkopf Memorial Sloan Kettering 1275 York Avenue New York, NY 10065 (Tel): 646-422-4379 (Fax): 212-988-0701 rathkopd@mskcc.org	COU-AA-302	41	High Accrual, highest number of SAEs and 2 major protocol violations
157: Charles Ryan University of California, San Francisco 1600 Divisadero St., Box 1711 San Francisco, California, 94115 (Tel): 415-353-9279 (Fax): 415-353-7779 ryanc@medicine.ucsf.edu	COU-AA-302	40	High Accrual, 4 major protocol violations
814: Jose Piulats Rodriguez Institut Catalá d'Oncologia L'Hospitalet Servicio Oncologia, Avda. Gran Via de l'Hospitalet, 199-203 Barcelona, 08907 Spain (Tel): 34 932 607 332 (Fax): 34 932 607 741 jmpiulats@iconcologia.net	COU-AA-302	18	High Accrual, 5 major protocol violations
812: Joan Carles Hospital Universitari Vall d´Hebron Servicio Oncologia, Passeig Vall d'Hebron, 119-129 Barcelona, 08035 Spain (Tel): +34 93 274 60 00 (Fax): +34 93 274 60 59 jocarles@vhebron.net	COU-AA-302	17	High Accrual, 2 major protocol violations

III. Site Selection/Rationale

Site selection was based on analyzing the accrual, SAE reporting and major protocol violations for the pivotal trial, COU-AA-302. This trial enrolled 1088 patients. No single site accounted for more than 3.8% of total trial accrual. This efficacy supplement application will be a priority review of a prostate cancer medication to be used in a patient population with limited available, tolerable therapies. The efficacy results reveal a large and statistically significant improvement in radiographic progression free survival. There was a strong trend toward overall survival benefit which did not quite meet the interim analysis statistical boundary for significance.

Domestic Inspections:

Reasons for inspections (please check all that apply):

__X__ Enrollment of large numbers of study subjects
____ High treatment responders (specify):
____ Significant primary efficacy results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
__X__ Other (specify): SAE reporting and # of major protocol violations.

International Inspections:

Reasons for inspections (please check all that apply):

____ There are insufficient domestic data
____ Only foreign data are submitted to support an application
____ Domestic and foreign data show conflicting results pertinent to decision-making
____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
__X__ Other (specify): Enrollment of large numbers of study subjects and report of major protocol violations.

IV. Tables of Specific Data to be Verified (if applicable)

N/A

Should you require any additional information, please contact *Amy Tilley RPM* at *301-796-3994 or the primary clinical reviewer, Paul Kluetz,* at 301-796-9567, or via cellphone at 410-274-4192.

Concurrence: (as needed)

_____ Medical Team Leader
_____ Medical Reviewer
_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

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

/s/

AMY R TILLEY
06/28/2012

VIRGINIA E MAHER
06/28/2012

ROBERT L JUSTICE
06/28/2012

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 202379/ S005

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 202379 SUPPL # SE1-005 HFD # 150

Trade Name Zytiga

Generic Name abiraterone acetate

Applicant Name Janssen Biotech, Inc.

Approval Date, If Known 12/10/12

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☒ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 202379 The parent NDA

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☒

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☒

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

COU-AA-301
COU-AA-302
(Both studies conducted under IND)

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

COU-AA-301
COU-AA-302
(Both studies conducted under IND 71023)

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1		!
		!
IND # 71023	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 71023	YES ☒	! NO ☐
		! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Amy Tilley
Title: Regulatory Project Manager
Date: 12-12-12

Name of Office/Division Director signing form: Amna Ibrahim, M.D.
Title: Deputy Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

ALICE KACUBA
12/12/2012
Signing for Amy Tilley.

AMNA IBRAHIM
12/13/2012

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 202379 BLA #	NDA Supplement # 005 BLA Supplement #	If NDA, Efficacy Supplement Type: SE1
Proprietary Name: Zytiga® Established/Proper Name: abiraterone acetate Dosage Form: Tablets 250 mg		Applicant: Janssen Biotech, Inc. Agent for Applicant (if applicable):
RPM: Amy Tilley		Division: DOP1

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☒ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check: 12-10-12

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 12-14-12	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other Burst

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

Version: 1/27/12

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist[4]	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AP 12-10-12
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	11-30-12
• Original applicant-proposed labeling	7/16/12
• Example of class labeling, if applicable	N/A

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	11-30-12
• Original applicant-proposed labeling	7/16/12
• Example of class labeling, if applicable	N/A
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	6/14/12
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	N/A
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 8/15/12 ☒ DMEPA 9/19/12 ☒ DMPP/PLT (DRISK) 11/20/12 ☒ ODPD (DDMAC) 11/15/12; 11/20/12 ☒ SEALD 10/4/12 ☐ CSS ☐ Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)*	7/21/12
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	☒ Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC 10/17/12 If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	Included
❖ Internal memoranda, telecons, etc.	Included
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ No mtg FDA Response to Format Questions sent 1/30/12
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	N/A
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 12-10-12
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 11/29/12
PMR/PMC Development Templates *(indicate total number)*	☐ None 1 PMC
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	Co-signed Primary Review 11/21/12
• Clinical review(s) *(indicate date for each review)*	11/21/12
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	See MO Review 11/21/12
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☐ None SEALD 10/4/12; DPV 10/12/21
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None

[6] Filing reviews should be filed with the discipline reviews.

❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested 10/9/12
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None Co-signed Primary Review 11/20/12
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None Co-signed Primary Review 11/20/12
Statistical Review(s) *(indicate date for each review)*	☐ None 11/20/12
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None 8/28/12
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 8-28-12
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☒ None
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None Co-signed Primary Review 11/20/12
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 11/20/12
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☒ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None Co-signed Primary Review 8-21-12
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 8-21-12
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☒ None

❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	See CMC Review 8-21-12
☐ Review & FONSI *(indicate date of review)*	N/A
☐ Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☒ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE’s ADRA.

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

/s/

AMY R TILLEY
12/10/2012

ALICE KACUBA
12/10/2012

Organization: DOP1
Appl Type No: NDA 202379
Submission Type #: SUPPL - 5

Product Name: ZYTIGA (ABIRATERONE ACETATE) TABLETS
Applicant: JANSSEN BIOTECH INC
Submission Status: PENDING

FDA Received Date	Dosage Form	Orphan	Subm Status Date	Goal Due Date	Submission Classification/ Supplement Category Level Two	Submission Indication
6/14/2012	TABLET (IMMED./COMP RELEASE), UNCOATED, HYPODERMIC	N	6/14/2012	12/14/2012	INDICATION	FOR THE TREATMENT OF PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (b) (4) (b) (4)

Pediatric Record ID	PREA Study Status	Pediatric Category	Min Value	Max Value	Waiver/ Deferral Reason	Waiver/ Deferral Reason Explanation	Study Due Date
1,777	WAIVED	FULL	0	16	DISEASE/CONDITION DOES NOT EXIST IN CHILDREN	BECAUSE NECESSARY STUDIES ARE IMPOSSIBLE OR HIGHLY IMPRACTICABLE BECAUSE DISEASE DOES NOT EXIST IN CHILDREN. METASTATIC CASTRATION RESISTANT PROSTATE CANCER DOES NOT AFFECT PEDIATRIC PATIENTS.	

Tilley, Amy

From: Suggs, Courtney
Sent: Monday, November 26, 2012 9:05 AM
To: Tilley, Amy; Greeley, George
Subject: RE: PeRC Final Decision re NDA 202379 Zytiga Full Waiver

Hi Amy,

Here is an excerpt of the minutes from October 17th.

Zytiga (abiraterone acetate) Full Waiver

- NDA 202-379, Zytiga (abiraterone acetate) was studied in combination with prednisone, for the treatment of patients with metastatic castration-resistant prostate cancer [redacted] (b) (4)
  - The application was submitted on June 14, 2012, and has a PDUFA date of December 14, 2012.
  - This application triggers PREA as a new indication.
- The PeRC agreed with the Division to full waiver in pediatric patients because studies are impossible or highly impracticable. Metastatic castration resistant prostate cancer does not affect pediatric patients.

Thanks,
Courtney

Courtney M. Suggs, Pharm.D., MPH
CDR, USPHS
Regulatory Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs, Immediate Office
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Ave.
Bldg 22, Room 6471
Silver Spring, MD 20993
Phone: (301) 796-2096
Email: courtney.suggs@fda.hhs.gov

From: Tilley, Amy
Sent: Wednesday, November 21, 2012 3:54 PM
To: Suggs, Courtney; Greeley, George
Subject: RE: PeRC Final Decision re NDA 202379 Zytiga Full Waiver

Courtney & George,

Please send me the minutes as stated in your email below.

Thanks.

Amy

From: Suggs, Courtney
Sent: Wednesday, October 17, 2012 1:08 PM
To: Tilley, Amy; Greeley, George
Subject: RE: PeRC Final Decision re NDA 202379 Zytiga Full Waiver

I will send you an excerpt of the minutes when they have been finalized in a couple of weeks. If I forget please remind me and I will do so.

Courtney M. Suggs, Pharm.D., MPH
LCDR, USPHS
Regulatory Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs, Immediate Office
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Ave.
Bldg 22, Room 6471
Silver Spring, MD 20993
Phone: (301) 796-2096
Email: courtney.suggs@fda.hhs.gov

From: Tilley, Amy
Sent: Wednesday, October 17, 2012 1:06 PM
To: Suggs, Courtney; Greeley, George
Subject: RE: PeRC Final Decision re NDA 202379 Zytiga Full Waiver

Courtney thank you for the prompt response.

Will I be receiving an official email to place in the Action Package for this application?

Amy

From: Suggs, Courtney
Sent: Wednesday, October 17, 2012 1:04 PM
To: Tilley, Amy; Greeley, George
Subject: RE: PeRC Final Decision re NDA 202379 Zytiga Full Waiver

Hi Amy,

The PeRC agreed with the Division's decision to grant a full waiver.

Courtney

Courtney M. Suggs, Pharm.D., MPH
LCDR, USPHS
Regulatory Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs, Immediate Office
Center for Drug Evaluation and Research
US Food and Drug Administration
10903 New Hampshire Ave.
Bldg 22, Room 6471
Silver Spring, MD 20993
Phone: (301) 796-2096
Email: courtney.suggs@fda.hhs.gov

From: Tilley, Amy
Sent: Wednesday, October 17, 2012 1:03 PM
To: Greeley, George; Suggs, Courtney
Subject: PeRC Final Decision re NDA 202379 Zytiga Full Waiver
Importance: High

George and Courtney,

Please update me on the final PeRC decision regarding the Full Waiver for NDA 202379 Zytiga from this morning's PeRC Subcommittee Meeting.

Thank you.

Amy

202379/
S-01-005

CD 6-14-12

janssen

PHARMACEUTICAL COMPANIES OF Johnson & Johnson

DEBARMENT CERTIFICATION

ABIRATERONE ACETATE

Janssen Research & Development, LLC hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Barbara Kolb
Senior Director, Global Regulatory Affairs
Janssen Research & Development, LLC

From:	Venugopal, Rajesh
To:	kjohnso6@its.jnj.com
Subject:	Abiraterone revised manuscript
Date:	Tuesday, September 17, 2013 12:42:46 PM
Attachments:	Abiraterone Article 9-17-2013 REVISED-clean.doc Abiraterone Article 9-17-2013 REVISED-tracked.doc

Dear Kelly and Abiraterone Team,

Attached please find the revised manuscript with clean and tracked changes. Please confirm this is good to go and we will resubmit back to CCR. Please review and offer only high-level comments. Dr. Kluetz would like to get this back to the journal **by 4 PM Wednesday (tomorrow)**.

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

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/s/

RAJESH VENUGOPAL
09/17/2013

From: Venugopal, Rajesh
To: kjohnso6@its.jnj.com
Subject: FW: Clinical Information Request_NDA 202379/S-005
Date: Monday, September 16, 2013 9:18:35 AM

Kelly,

Also, we note that the intra- and inter-patient reliability in scans were higher in the bone scan reads (93-94%) than the RECIST reads (71% to 84%). When you submit the responses to our remaining questions, please confirm these numbers are not reversed as this is not what we expected.

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

From: Venugopal, Rajesh
Sent: Monday, September 16, 2013 9:07 AM
To: 'Johnson Reid, Kelly [JRDUS]'
Subject: RE: Clinical Information Request_NDA 202379/S-005

Hello Kelly,

We understand the need to confirm your data with [redacted] (b) (4) Please do the best you can to get the additional questions answered as we are trying to integrate some of this data into the abiraterone CCR paper which is currently in the review process.

Thank you.

rajesh
Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov

Phone: (301) 796-4730
Fax: (301) 796-9845

From: Johnson Reid, Kelly [JRDUS] [mailto:KJohnso6@ITS.JNJ.COM]
Sent: Sunday, September 15, 2013 8:57 PM
To: Venugopal, Rajesh
Subject: RE: Clinical Information Request_NDA 202379/S-005

Hi Rajesh,

We reference NDA 202379 and efficacy supplement 005. In reviewing the independent review charter by (b) (4) contained in the -302 submission, we noted that in section 8.3 there were secondary reviews performed to analyze intra-observer and inter-observer disagreement and variability in radiographic event determination. We are interested in the intra-observer and inter-observer disagreement in bone scan reads compared with RECIST reads using CT/MRI.

Company Response:
Please find below the Inter & Intra variability results for both Recist and Nuclear reviewers.

RECIST
Inter Variability: 71% agreement rate
Intra Variability: 84% agreement rate.
NUCLEAR
Inter Variability: 94% agreement rate
Intra Variability: 93% agreement rate
The results for both Recist and Nuclear variability reads are within the acceptable range and it is (b) (4) recommendation that no additional reviewer training is needed.

Additional FDA Questions:

1. Were there any instances where there were more than 1 independent reviewer for a single patient?
2. How many independent readers were involved? (radiology charter states 2 nuclear medicine readers for total study)
3. How inconsistent were the readings for those patients with more than one reader?
4. How were inconsistencies above (if any) adjudicated?

Company Response:
The Company would like to confirm and discuss these questions/answers with our vendor (b) (4) Although we aim to provide a response by the deadline of 5pm September 16, it is possible that we may have to kindly as for an extension to ensure that we have consulted with all necessary representatives to provide the most accurate response. Thank you.

Best Regards
Kelly

From: Venugopal, Rajesh [mailto:Rajesh.Venugopal@fda.hhs.gov]
Sent: Friday, September 13, 2013 11:19 AM
To: Johnson Reid, Kelly [JRDUS]
Subject: FW: Clinical Information Request_NDA 202379/S-005

Additionally Kelly please provide responses to the following questions with respect to the bone scan interpretations specifically:

1. Were there any instances where there were more than 1 independent reviewer for a single patient?
2. How many independent readers were involved? (radiology charter states 2 nuclear medicine readers for total study)
3. How inconsistent were the readings for those patients with more than one reader?
4. How were inconsistencies above (if any) adjudicated?

From: Venugopal, Rajesh
Sent: Friday, September 13, 2013 10:55 AM
To: kjohnso6@its.jnj.com
Subject: Clinical Information Request_NDA 202379/S-005

Hello Kelly,

The following clinical information request requires your response:

We reference NDA 202379 and efficacy supplement 005. In reviewing the independent review charter by [redacted] (b) (4) contained in the -302 submission, we noted that in section 8.3 there were secondary reviews performed to analyze intra-observer and inter-observer disagreement and variability in radiographic event determination. We are interested in the intra-observer and inter-observer disagreement in bone scan reads compared with RECIST reads using CT/MRI.

Dr. Kluetz is interested in this data as he finalizes the manuscript for the FDA approval summary following reviewer comments from the journal CCR. Can you ask Dr. Molina if he could provide us with the results of these analyses? Please note we are on a short time schedule to get this paper completed and would like to hear back from you in the next few days.

If possible, please respond by **5 PM Monday, September 16, 2013** if not sooner.

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products

OND/CDER/FDA
Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

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/s/

RAJESH VENUGOPAL
09/16/2013

From: Venugopal, Rajesh
To: kjohnso6@its.jnj.com
Subject: FW: Clinical Information Request_NDA 202379/S-005
Date: Friday, September 13, 2013 11:19:19 AM

Additionally Kelly please provide responses to the following questions with respect to the bone scan interpretations specifically:

1. Were there any instances where there were more than 1 independent reviewer for a single patient?
2. How many independent readers were involved? (radiology charter states 2 nuclear medicine readers for total study)
3. How inconsistent were the readings for those patients with more than one reader?
4. How were inconsistencies above (if any) adjudicated?

From: Venugopal, Rajesh
Sent: Friday, September 13, 2013 10:55 AM
To: kjohnso6@its.jnj.com
Subject: Clinical Information Request_NDA 202379/S-005

Hello Kelly,

The following clinical information request requires your response:

We reference NDA 202379 and efficacy supplement 005. In reviewing the independent review charter by (b) (4) contained in the -302 submission, we noted that in section 8.3 there were secondary reviews performed to analyze intra-observer and inter-observer disagreement and variability in radiographic event determination. We are interested in the intra-observer and inter-observer disagreement in bone scan reads compared with RECIST reads using CT/MRI.

Dr. Kluetz is interested in this data as he finalizes the manuscript for the FDA approval summary following reviewer comments from the journal CCR. Can you ask Dr. Molina if he could provide us with the results of these analyses? Please note we are on a short time schedule to get this paper completed and would like to hear back from you in the next few days.

If possible, please respond by **5 PM Monday, September 16, 2013** if not sooner.

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1

Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

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/s/

RAJESH VENUGOPAL
09/13/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Joan Carles, MD, PhD
Hospital Universitari Vall d'Hebron
Passeig Vall d'Hebron, 119-129
Barcelona, 08035 Spain

Dear Dr. Carles:

The purpose of this letter is to inform you of the findings of a Food and Drug Administration (FDA) inspection conducted at your site. This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of human subjects of those studies have been protected.

Between September 17, 2012 and September 21, 2012, Ms. Teena H. Aiken, representing the U.S. Food and Drug Administration (FDA), met with you and your staff to review your conduct of the clinical study, entitled "Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate Plus Prednisone in Asymptomatic or Mildly Symptomatic Subjects With Metastatic Castration-Resistant Prostate Cancer" (Protocol COU-AA-302), of the investigational drug Zytiga® (abiraterone acetate), performed for Janssen Research and Development, LLC as the study sponsor.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown to Investigator Aiken during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,
{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations,
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave, Bldg 51 Rm 5366
Silver Spring, MD 20993-0002

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/s/

JONG HOON LEE
04/26/2013

JANICE K POHLMAN
04/29/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Maria Ochoa de Olza Amat, M.D.
Institut Catala d'Oncologia
Avinguda Gran Via de l'Hospitalet, 199-203
08907 l'Hospitalet de Llobregat
Barcelona, Spain

Dear Dr. Ochoa:

Between September 25, 2012 and September 28, 2012, Ms. Teena H. Aiken, representing the U.S. Food and Drug Administration (FDA), met with you and your staff to review your conduct of the clinical study, entitled "Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate Plus Prednisone in Asymptomatic or Mildly Symptomatic Subjects With Metastatic Castration-Resistant Prostate Cancer" (Protocol COU-AA-302), of the investigational drug Zytiga® (abiraterone acetate), performed for Janssen Research and Development, LLC as the study sponsor.

This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

At the conclusion of the inspection, Ms. Aiken presented and discussed with you Form FDA 483, Inspectional Observations. We have reviewed the Form FDA 483, the establishment inspection report, and the documents submitted with the report. We acknowledge your October 18, 2012 written response to the inspection findings and note that you have implemented corrective actions to prevent the recurrence of the inspectional findings.

We appreciate the cooperation shown to Investigator Aiken during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations,
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave, Bldg 51 Rm 5328
Silver Spring, MD 20993-0002

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/s/

JONG HOON LEE
04/26/2013

JANICE K POHLMAN
04/29/2013

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

PMR/PMC Description: Submit datasets and the final analysis of overall survival for COU-AA-302

PMR/PMC Schedule Milestones:		
	Final Protocol Submission:	07/12/2012
	Study/Trial Completion:	06/30/2014
	Final Report Submission:	09/30/2014
	Other:	MM/DD/YYYY

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

   ☐ Unmet need
   X Life-threatening condition
   X Long-term data needed
   ☐ Only feasible to conduct post-approval
   ☐ Prior clinical experience indicates safety
   ☐ Small subpopulation affected
   ☐ Theoretical concern
   ☐ Other

Abiraterone received regular approval based on a statistically significant improvement in radiographic progression-free survival and an improvement in overall survival at the 3rd interim analysis. This PMC asks for the datasets and the results of the final analysis of overall survival.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

Not a PMR

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

- **Which regulation?**

☐ Accelerated Approval (subpart H/E)
☐ Animal Efficacy Rule
☐ Pediatric Research Equity Act
☐ FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

☐ Assess a known serious risk related to the use of the drug?
☐ Assess signals of serious risk related to the use of the drug?
☐ Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

☐ Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

☐ Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

☐ Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

☐ Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

An ongoing trial in patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

_____

☐ Meta-analysis or pooled analysis of previous studies/clinical trials
☐ Immunogenicity as a marker of safety
☐ Other (provide explanation)

_____

Agreed upon:

☐ Quality study without a safety endpoint (e.g., manufacturing, stability)
☐ Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
☒ Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
☐ Dose-response study or clinical trial performed for effectiveness
☐ Nonclinical study, not safety-related (specify)

_____

☐ Other

_____

5. Is the PMR/PMC clear, feasible, and appropriate?

X Does the study/clinical trial meet criteria for PMRs or PMCs?
X Are the objectives clear from the description of the PMR/PMC?
X Has the applicant adequately justified the choice of schedule milestone dates?
X Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

☐ *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

_____

(signature line for NDAs)

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/s/

AMY R TILLEY
12/10/2012

GENEVIEVE A SCHECHTER
12/10/2012

From: Lee, John
Sent: Tuesday, November 27, 2012 7:52 PM
To: Tilley, Amy
Subject: RE: Question re Zytiga Clin Inspection Summary

Follow Up Flag: Follow up
Due By: Wednesday, November 28, 2012 12:00 AM
Flag Status: Red

eirs still not received but no new info and no addendum, pls consider current cis final for 12-10 early action, thanks

---

From: Tilley, Amy
Sent: Tuesday, November 27, 2012 2:37 PM
To: Lee, John
Subject: RE: Question re Zytiga Clin Inspection Summary

Just had our last label meeting and would like to take an early action by 12-10-12.

Please confirm if you will be able to complete the EIR's by the 10th.

Thank you in advance.

Amy

From: Lee, John
Sent: Monday, November 26, 2012 8:10 PM
To: Tilley, Amy
Subject: RE: Question re Zytiga Clin Inspection Summary

2 of 4 EIRs (foreign ones) are still pending. will let you know within ... one week ok?

From: Tilley, Amy
Sent: Monday, November 26, 2012 2:01 PM
To: Lee, John
Cc: Kacuba, Alice; Pohlman, Janice; Thompson, Susan (CDER)
Subject: Question re Zytiga Clin Inspection Summary

John,

As stated in your Clinical Inspection Summary dated 10/9/12 for Zytiga NDA 202379 S-005, "An addendum to this CIS will be forwarded to DOP-1 if the classification of the inspection outcome changes or if additional observations of clinical or regulatory significance are discovered after completing the review of the EIRs.".

Please inform me as to whether or not this was resolved. I am assuming no changes were made correct?

Your prompt response to this email is greatly appreciated as the PDUFA date is drawing near (12-14-12), and the Action Package needs to be finalized prior to sending to the signature authority.

Thanks.
Amy

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/s/

AMY R TILLEY
11/29/2012

From: Tilley, Amy
Sent: Tuesday, November 27, 2012 3:47 PM
To: 'Johnson Reid, Kelly kjohnso6@its.jnj.com
Subject: NDA 202379 Zytiga S-005 - FDA Revised PI & PPI

Follow Up Flag: Follow up
Due By: Thursday, November 29, 2012 12:00 PM
Flag Status: Flagged

Attachments: FDA rev PI Zytiga label 11-27-12.doc; FDA rev PPI 11-27-12 tracked-physician-insert.doc

Kelly,

Below is the FDA revised Zytiga PI/PPI for your review. We respectfully request your response regarding our revisions **no later than 12 noon on 11/29/12.**


FDA rev PI
ga label 11-2


FDA rev PPI
27-12 tracked

Kindly confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
11/27/2012

From: Tilley, Amy
Sent: Tuesday, November 20, 2012 4:21 PM
To: 'Johnson Reid, Kelly [JRDUS]'
Subject: NDA 202379 Zytiga S-005 - Status of Indication, 11/20 Clin IR & Revised PPI due date

Importance: High

Follow Up Flag: Follow up
Due By: Tuesday, November 27, 2012 12:00 PM
Flag Status: Flagged

Attachments: FDA Revised PPI NDA 202379 11-20-12.doc

Kelly,

Regarding the indication revision, what you have reviewed in the previous draft conveys our intentions, but needs to be reworded. At this point, we will send the revised indication when we return the label.

With respect to the Clinical IR sent earlier today regarding the FDA laboratory algorithm describing generation of the Study 2 laboratory abnormality table, we respectfully request your response **by Noon on 11/27/12.**

Also, below please find the revised PPI for Janssen's review which can be submitted both via email and official submission along with your response to the Clinical IR on 11/27/12.

FDA Revised
NDA 202379 1

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
11/20/2012

From: Tilley, Amy
Sent: Tuesday, November 20, 2012 1:30 PM
To: 'Johnson Reid, Kelly [JRDUS]'
Subject: NDA 202379 Zytiga S-005 - Clin IR

Importance: High

Kelly,

In reference to Janssen's comment regarding table 4 in section 6 of the current PI for ZYTIGA, please see below the FDA laboratory algorithm describing generation of the Study 2 laboratory abnormality table.

1. Amendment 71-safety update
2. LB.xpt
3. Remove LBSTRESN = blank; LBBLFL = Y; VISIT = BASELINE, CYCLE 1 DAY 1, OL CYCLE 1 DAY 1; LBDY = negative number or 1
4. Kept end of study regardless of date relative to last dose
5. Had missing lab ranges; 23,683 rows missing for LO and 23,636 rows missing for HI. They are both missing for 23,628. Took out the ones where both are missing.
6. In some instances, labs were graded based on an incomplete lab range. For example, LLN was missing, but ULN was there so a lab above normal was graded. FDA analysis includes these.
    a. Looked at the remaining 54 rows with no LLN. Glucose was the only 1 in which a LLN would be significant. Removed this 1 row for pt 129-2017.
    b. Looked at the remaining 6 rows with no ULN. Labs included HDL cholesterol. ULN would matter for this, and I removed these.
7. Added treatment arms from SE.xpt
8. Lab analysis performed on all laboratory locations (not just (b) (4)
9. Grading for hyperglycemia (c/w CTCAE v3.0):

(b) (4)

(b) (4)

Denominator used was # of patients in the safety population.

(b) (4)

Final Table:

- ADR considered lab abnormality occurring >5% more frequently in the AA vs placebo.
- Table includes ADRs occuring in >15% of patients.

Table 4 : Laboratory Abnormalities in > 15% of Patients in the ZYTIGA Arm of Study 2

Laboratory Abnormality	Abiraterone (N = 542)		Placebo (N = 540)	
	Grade 1-4 %	Grade 3-4 %	Grade 1-4 %	Grade 3-4 %
Hematology				
Lymphopenia	38.2	8.7	31.7	7.4
Chemistry				
Hyperglycemia	56.6	6.5	50.9	5.2
High ALT	41.9	6.1	29.1	0.7
High AST	37.3	3.1	28.7	1.1
Hypernatremia	32.8	0.4	25.0	0.2
Hypokalemia	17.2	2.8	10.2	1.7

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
11/20/2012

From: Tilley, Amy
Sent: Tuesday, November 13, 2012 4:38 PM
To: Johnson Reid, Kelly kjohnso6@its.jnj.com
Subject: NDA 202379 Zytiga S-005 - FDA revised PI & PMR

Follow Up Flag: Follow up
Due By: Tuesday, November 20, 2012 10:00 AM
Flag Status: Flagged

Attachments: FDA Revised 11-9-12 marked-physician-insert.doc

Kelly,

Below is a copy of the FDA revised PI only for NDA 202379 Zytiga S-005. Please note that the PPI is still under review and will be sent to you at a later date.

FDA Revised
-12 marked-p

Also, below is the Clinical PMR and Milestone dates.

PMR/PMC Description:	Submit datasets and the final analysis of overall survival for COU-AA-302	
PMR/PMC Schedule Milestones:	Trial Completion:	06/30/2014
	Final Report Submission:	09/30/2014

We respectfully request your response both via email and as an official submission no later than **10 am on November 20, 2012.**

Please confirm receipt of this email.

Thank you.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
11/13/2012

From: Tilley, Amy
Sent: Thursday, November 01, 2012 10:59 AM
To: 'Johnson Reid, Kelly KJohnso6@ITS.JNJ.COM
Subject: RE:Addtl Info needed re NDA 202379 S-005 - Clinical Information Request

Follow Up Flag: Follow up
Due By: Friday, November 02, 2012 12:00 AM
Flag Status: Red

Kelly,

The Clinical Team Leader has stated that your response below needs further clarification.

We still need to know the cutoff for the final analysis of overall survival and when this will be submitted.

Please respond via email and follow up with an official submission to NDA 202379 S-005 once the NJ/PA offices are fully operational to formally submit this information.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

---

From: Johnson Reid, Kelly [JRDUS] [mailto:KJohnso6@ITS.JNJ.COM]
Sent: Thursday, November 01, 2012 8:05 AM
To: Tilley, Amy
Subject: RE: NDA 202379 S-005 - Clinical Information Request

Dear Amy,

The final protocol for Study COU-AA-301(Amendment #3) was submitted to IND 071023 on 30 August 2010. The clinical cutoff was 22 January 2010 and the final clinical study report was provided in the original NDA 202379 Seq 0000 submitted on 20 December 2010 .

Many of the personnel in the NJ/PA offices are not fully operational thus a formal submission to the NDA may be delayed.

Best regards
Kelly

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
S nt: Wednesday, October 31, 2012 12:51 PM
To: Johnson Reid, Kelly [JRDUS]
Subject: NDA 202379 S-005 - Clinical Information Request

Kelly,

Please provide the Final Protocol Submission date, Trial Completion date and the Final Report Submission date for Study COU-AA-301.

Respond to the above Clinical IR as soon as possible both via email and as an official submission to NDA 202379 S-005.

Please confirm receipt of this email.

Thank you.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
11/01/2012

From: Tilley, Amy
Sent: Thursday, November 01, 2012 3:27 PM
To: 'Johnson Reid, Kelly [JRDUS]'
Subject: Clarification to Addtl Info needed re NDA 202379 S-005 – Clinical Information Request

Kelly,

As per our telephone conversation, this IR is referring to your current Study COU-AA-302 which pertains to your Efficacy Supplement S-005.

Thank you.
Amy

From: Johnson Reid, Kelly [JRDUS] [mailto:KJohnso6@ITS.JNJ.COM]
Sent: Thursday, November 01, 2012 12:55 PM
To: Tilley, Amy
Subject: RE: Addtl Info needed re NDA 202379 S-005 - Clinical Information Request

Hi Amy,

I have a very quick clarification request. Please confirm if the request is for Study COU-AA-301 or for the pivotal study currently under review COU-AA-302.

Thanks

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
Sent: Thursday, November 01, 2012 10:59 AM
To: Johnson Reid, Kelly [JRDUS]
Subject: RE:Addtl Info needed re NDA 202379 S-005 - Clinical Information Request

Kelly,

The Clinical Team Leader has stated that your response below needs further clarification.

We still need to know the cutoff for the final analysis of overall survival and when this will be submitted.

Please respond via email and follow up with an official submission to NDA 202379 S-005 once the NJ/PA offices are fully operational to formally submit this information.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

---

From: Johnson Reid, Kelly [JRDUS] [mailto:KJohnso6@ITS.JNJ.COM]
Sent: Thursday, November 01, 2012 8:05 AM
To: Tilley, Amy
Subject: RE: NDA 202379 S-005 - Clinical Information Request

Dear Amy,

The final protocol for Study COU-AA-301(Amendment #3) was submitted to IND 071023 on 30 August 2010. The clinical cutoff was 22 January 2010 and the final clinical study report was provided in the original NDA 202379 Seq 0000 submitted on 20 December 2010 .

Many of the personnel in the NJ/PA offices are not fully operational thus a formal submission to the NDA may be delayed.

Best regards
Kelly

From: Tilley, Amy [mailto:Amy.Tilley@fda.hhs.gov]
S nt: Wednesday, October 31, 2012 12:51 PM
To: Johnson Reid, Kelly [JRDUS]
Subject: NDA 202379 S-005 - Clinical Information Request

Kelly,

Please provide the Final Protocol Submission date, Trial Completion date and the Final Report Submission date for Study COU-AA-301.

Respond to the above Clinical IR as soon as possible both via email and as an official submission to NDA 202379 S-005.

Please confirm receipt of this email.

Thank you.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
11/01/2012

From: Tilley, Amy
Sent: Wednesday, October 31, 2012 12:51 PM
To: Johnson Reid, Kelly kjohnso6@its.jnj.com
Subject: NDA 202379 S-005 - Clinical Information Request sent 10-31-12

Follow Up Flag: Follow up
Due By: Wednesday, November 07, 2012 12:00 AM
Flag Status: Flagged

Kelly,

Please provide the Final Protocol Submission date, Trial Completion date and the Final Report Submission date for Study COU-AA-301.

Respond to the above Clinical IR as soon as possible both via email and as an official submission to NDA 202379 S-005.

Please confirm receipt of this email.

Thank you.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
10/31/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Charles Ryan, M.D.
UCSF Medical Center
1600 Divisadero Street, Box 1711
San Francisco, California 94115-3010

Dear Dr. Ryan:

The purpose of this letter is to inform you of the findings of a Food and Drug Administration (FDA) inspection conducted at your site. This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of human subjects of those studies have been protected.

Between August 9, 2012 and August 21, 2012, Mr. Kevin P. Foley, representing the FDA, met with you and your staff to review your conduct of the clinical investigation (Protocol COU-AA-302, entitled "Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate Plus Prednisone in Asymptomatic or Mildly Symptomatic Subjects With Metastatic Castration-Resistant Prostate Cancer") of the investigational drug Zytiga® (abiraterone acetate), performed for Janssen Research and Development, LLC.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown to Investigator Foley during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Janice K. Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5328
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

JONG HOON LEE
10/19/2012

JANICE K POHLMAN
10/19/2012

From: Tilley, Amy
Sent: Wednesday, October 03, 2012 11:24 AM
To: 'Johnson Reid, Kelly kjohnso6@its.jnj.com
Subject: RE: sNDA 202379 Zytiga S-005- Addtl Clinical IR to 9-13-12 IR

Kelly,

In our database I see you submitted on 09/27/2012 via the Gateway the Clinical/Response to Information Request which I believe is your response to the Clinical IR's sent below on 9/13 and 9/14. However, when we try to access the information through the EDR Global Submit Review the backbone does not show this Sequence # 0075.

Would you please send to us via email the entire submission of your Clinical/Response to the IR's from 9/13 and 9/14 and also resubmit the information through the Gateway as there seems to have been a problem with this submission.

Your prompt response to this request is appreciated as the Clinical Review Team is awaiting your response as soon as possible.

Thank you.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

---

From: Johnson Reid, Kelly [JRDUS] [mailto:KJohnso6@ITS.JNJ.COM]
Sent: Monday, September 17, 2012 9:42 AM
To: Tilley, Amy
Subject: RE: sNDA 202379 Zytiga S-005- Addtl Clinical IR to 9-13-12 IR

Hi Amy,

I received this on Friday. I inadvertently forgot to drop you a note to confirm receipt. Sorry

Thanks
Kelly

From: Tilley, Amy [mailto:AMY.TILLEY@fda.hhs.gov]
Sent: Friday, September 14, 2012 3:04 PM

To: Johnson Reid, Kelly [JRDUS]
Subject: RE: sNDA 202379 Zytiga S-005- Addtl Clinical IR to 9-13-12 IR

Kelly,

Sorry, we have one addition (point e.) to this prior information request that was sent on 9-13-12.

e. Provide a post-marketing review of possible Stevens Johnson syndrome or DRESS. We note you have one safety report of possible DRESS (**TW-JNJFOC-20120607291)** which was potentially confounded by moduretic and a chinese herb. Are there other severe rash events in the database? Provide a strong rationale for the fact that the episode of DRESS was not at least possibly related to abiraterone acetate.

Kindly confirm receipt of this email.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

---

From: Tilley, Amy
Sent: Thursday, September 13, 2012 3:53 PM
To: 'Johnson Reid, Kelly [JRDUS]'
Subject: sNDA 202379 Zytiga - Clinical IR
Importance: High

Kelly,

We have the following Clinical Information Request. Please respond within **10 business days**.

1. Please provide a more thorough analysis of your post-marketing safety database (section 7 of your Summary of Clinical Safety). Include data supporting your determination that there are no new or more severe adverse reactions identified in the post-marketing period which would be appropriate to include in the label.

a. Have there been any fatal liver failure cases that are possibly attributed to abiraterone acetate? Provide any narratives for post-marketing reports of fatal liver failure.

b. A few recent cases of severe diarrhea (2 cases which were associated with death, mfg# AU-JNJFOC-20120610977 and BR-JNJFOC-20120613332) were received by the FDA. Please provide a safety update on diarrhea including narratives for fatal cases and your rationale for why this should not be included in the label.

c. We note an imbalance in pulmonary related deaths in the COU-AA-302 trial. While we acknowledge the number of cases is small and this may be related to chance, please provide a pulmonary adverse event analysis including death narratives from the Zytiga post-marketing database.

d. Provide a cardiac failure post-marketing database review.

Please confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
10/03/2012

From: Tilley, Amy
Sent: Thursday, September 20, 2012 1:57 PM
To: 'Johnson Reid, Kelly [JRDUS]'
Cc: Kacuba, Alice; Cottrell, Christy L.
Subject: NDA 202379 Zytiga S-005 - Pharm/Tox and CMC IR

Follow Up Flag: Follow up
Due By: Thursday, September 27, 2012 12:00 PM
Flag Status: Flagged

Kelly,

Below are two Information Requests from the Pharm/Tox and CMC Review Team for NDA 202379 Zytiga S-005.

1. Please provide clarification as to the purpose of the impurity qualification studies TOX9749, TOX9744 and TOX9780 that were submitted as final study reports on June 14, 2012, with your efficacy supplement-5. It is unclear if there was a proposed change in manufacturing or specifications that prompted conducting these studies since the current specifications appear to be the same as those proposed in the original NDA, which were acceptable based on data in the original NDA submission.

2. To understand the significance of TOX9780, as the Specification for Drug substance and Drug product do not have a limit set for (b) (4) please provide clarification regarding the structure and origin of impurity (b) (4), and why limits were not included in the specifications. Alternatively, please provide a reference to earlier NDA submissions that may have this information.

We respectfully request your response to the above Information Requests **no later than September 27, 2012.** Please reply to all when responding as I will be out of the office on September 27th and 28th.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

APPEARS THIS WAY
ON ORIGINAL

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/s/

AMY R TILLEY
09/20/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Dana E. Rathkopf, M.D.
Memorial Sloan Kettering Hospital
1275 York Avenue
New York, NY 10065

Dear Dr. Rathkopf:

The purpose of this letter is to inform you of the findings of a Food and Drug Administration (FDA) inspection conducted at your site. This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of research and to help ensure that the rights, safety, and welfare of human subjects of those studies have been protected.

Between August 21, 2012 and August 24, 2012, Mr. Thomas P. Hansen, representing the FDA, met with you and your staff to review your conduct of the clinical investigation (Protocol COU-AA-302, entitled "Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate Plus Prednisone in Asymptomatic or Mildly Symptomatic Subjects With Metastatic Castration-Resistant Prostate Cancer") of the investigational drug Zytiga® (abiraterone acetate), performed for Janssen Research and Development, LLC.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown to Investigator Hansen during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

{See appended electronic signature page}

Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations
Office of Compliance
Center for Drug Evaluation and Research
Food and Drug Administration
Building 51, Room 5328
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

JONG HOON LEE
09/13/2012

JANICE K POHLMAN
09/14/2012

From: Tilley, Amy
Sent: Friday, September 14, 2012 3:04 PM
To: 'Johnson Reid, Kelly [JRDUS]'
Subject: RE: sNDA 202379 Zytiga S-005- Addtl Clinical IR to 9-13-12 IR

Follow Up Flag: Follow up
Due By: Thursday, September 27, 2012 12:00 AM
Flag Status: Flagged

Kelly,

Sorry, we have one addition (point e.) to this prior information request that was sent on 9-13-12.

e. Provide a post-marketing review of possible Stevens Johnson syndrome or DRESS. We note you have one safety report of possible DRESS (**TW-JNJFOC-20120607291)** which was potentially confounded by moduretic and a chinese herb. Are there other severe rash events in the database? Provide a strong rationale for the fact that the episode of DRESS was not at least possibly related to abiraterone acetate.

Kindly confirm receipt of this email.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

---

From: Tilley, Amy
Sent: Thursday, September 13, 2012 3:53 PM
To: 'Johnson Reid, Kelly [JRDUS]'
Subject: sNDA 202379 Zytiga - Clinical IR
Importance: High

Kelly,

We have the following Clinical Information Request. Please respond within **10 business days**.

1. Please provide a more thorough analysis of your post-marketing safety database (section 7 of your Summary of Clinical Safety). Include data supporting your determination that there are no new or more severe adverse reactions identified in the post-marketing period which would be appropriate to include in the label.

a. Have there been any fatal liver failure cases that are possibly attributed to abiraterone acetate? Provide any narratives for post-marketing reports of fatal liver failure.

b. A few recent cases of severe diarrhea (2 cases which were associated with death, mfg# AU-JNJFOC-20120610977 and BR-JNJFOC-20120613332) were received by the FDA. Please provide a safety update on diarrhea including narratives for fatal cases and your rationale for why this should not be included in the label.

c. We note an imbalance in pulmonary related deaths in the COU-AA-302 trial. While we acknowledge the number of cases is small and this may be related to chance, please provide a pulmonary adverse event analysis including death narratives from the Zytiga post-marketing database.

d. Provide a cardiac failure post-marketing database review.

Please confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
09/14/2012

From: Tilley, Amy
Sent: Friday, September 14, 2012 1:22 PM
To: 'Johnson Reid, Kelly [JRDUS]'
Subject: NDA 202379 Zytiga S-005 - Clinical IR sent 9-14-12

Importance: High

Follow Up Flag: Follow up
Due By: Monday, September 24, 2012 12:00 AM
Flag Status: Flagged

Kelly,

Please respond to the following information request by **9/24/2012.**

1. We would like to review data on progression criteria for study eligibility (Inclusion criteria 6 in the clinical study protocol).
Please provide us with a table of how progression was determined for patients in both arms to fulfill inclusion criteria 6 and include a dataset containing the following data fields:

Unique Subject ID
Progression Criteria for Study Eligibility
  Progression by PSA (1 or 0)
  Progression by CT/MRI (1 or 0)
  Progression by Bone Scan (1 or 0)
Treatment Group (AA or Placebo)

2. If available, please provide us with a dataset with baseline PSA doubling time and Unique Subject ID.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
09/14/2012

From: Tilley, Amy
Sent: Thursday, September 13, 2012 3:53 PM
To: 'Johnson Reid, Kelly [JRDUS]'
Subject: sNDA 202379 Zytiga - Clinical IR

Importance: High

Follow Up Flag: Follow up
Due By: Thursday, September 27, 2012 12:00 AM
Flag Status: Flagged

Kelly,

We have the following Clinical Information Request. Please respond within **10 business days**.

1. Please provide a more thorough analysis of your post-marketing safety database (section 7 of your Summary of Clinical Safety). Include data supporting your determination that there are no new or more severe adverse reactions identified in the post-marketing period which would be appropriate to include in the label.

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b. A few recent cases of severe diarrhea (2 cases which were associated with death, mfg# AU-JNJFOC-20120610977 and BR-JNJFOC-20120613332) were received by the FDA. Please provide a safety update on diarrhea including narratives for fatal cases and your rationale for why this should not be included in the label.

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d. Provide a cardiac failure post-marketing database review.

Please confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,

CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov


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/s/

AMY R TILLEY
09/13/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:	FROM: Amy Tilley/OHOP/DOP1/ 301-796-3994
Mail: OSE/DPV	

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
September 13, 2012		202379-S-005	Efficacy Supplement	June 14, 2012

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Zytiga	Priority	NME	October 3, 2012

NAME OF FIRM: Janssen, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☒ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☒ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: The DOP1 Zytiga review team is interested in performing an AERs search for both general Empirica safety signal analysis and also to review the database for the following adverse events of concern:

1. Liver Failure: This is a labeled risk, but there have not been deaths due to Zytiga related liver failure. Confirm there are no liver deaths.
2. Cardiac Failure: Known risk, how many cases have been seen? Any deaths related to cardiac failure?
3. Pulmonary adverse events. There were 5 vs 1 treatment emergent deaths due to pulmonary AEs in this trial. Are their a large number of pulmonary AEs in AERs?
4. Diarrhea: We have recently received two safety reports of diarrhea with subsequent death. What is the diarrhea signal with abiraterone in AERs?

We are querying the company as well but would like our team to look into this as well. We understand this consult has a short turnaround time, however we would like this information prior to our safety discussion during our label meetings in October.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Amy Tilley	☒ E-MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

AMY R TILLEY
09/13/2012

Fahnbulleh, Frances

From: Fahnbulleh, Frances
Sent: Tuesday, September 11, 2012 11:34 PM
To: Tilley, Amy
Cc: Fahnbulleh, Frances
Subject: MIDCYCLE /NDA 202379/S-005/Janssen/Zytiga

Hi Amy,
Regarding this supplement, I made note of a few issues and wanted to share them with you so that we are on the same page:

1. In reference to the issue of Zytiga administration with regards to food, DMEPA agrees: Clin Pharm evaluation concludes that Zytiga label does not need to be changed with regard to the food warning. DMEPA (Jibril's) previous Zytiga review noted 2 med errors of taking Zytiga with food but neither noted confusion from the labeling. Additionally, there are no changes to the insert labeling that require DMEPA comment and no change to the carton and container labeling.

2. At the Mid-cycle meeting on 9/11/12: The Team (Dr. Pazdur) requested that OSE (DPV) provides all postmarketing safety data pertinent to this review; will need to clarify with MO (Dr. Kluetz) the details of this request.

Could you withdraw the consult request for review of the PI and PPI, or do you need a memo from DMEPA? Also please have Dr. Kluetz clarify what postmarketing information is needed from OSE...should this be captured under a consult?

thanks much,
Frances

From: Tilley, Amy
Sent: Monday, September 10, 2012 11:05 AM
To: Maher, Virginia E.; Kluetz, Paul; Tang, Shenghui; Zhang, Lijun; Palmby, Todd; Ringgold, Kimberly; Voqui, Jessica; Burke, Laurie B
Cc: Justice, Robert; Ibrahim, Amna; Liu, Qi (CDER); Booth, Brian P; Pfuma, Elimika; Sarker, Haripada; Brown, Janice; Kelly, Sharon L; Claffey, David; Sridhara, Rajeshwari; Fahnbulleh, Frances; CDER DMPQ; Kozeli, Devi; Salis, Olga; Patel, Hasmukh B; Lee, John; Pohlman, Janice; Abdus-Samad, Jibril; Bridges, Todd; Murgo, Anthony; Toscano, Marybeth; Safarik, Michelle; Fedenko, Katherine; Jenney, Susan; Kacuba, Alice
Subject: Slides for MIDCYCLE /NDA 202379/S-005/Janssen/Zytiga
Importance: High

Review Team,

As mentioned during our team mtg to discuss the Midcycle for this application it was stated that the following disciplines would participate.

1. Clin/Stats = 30 Mins
2. PT = 1 min no slides
3. SEALD = 5 - 10 mins to discuss endpoints Slides??

If you plan on having slides for the Midcycle tomorrow please email them to me **no later than 10:30 am tomorrow.**

OPDP's Marybeth Toscano is unable to attend the Midcycle however, she has asked for copies of any handouts/slides that will be used.

Thanks for your cooperation.

Amy

From: Kacuba, Alice
Sent: Monday, September 10, 2012 9:13 AM
To: Safarik, Michelle; Tilley, Amy
Cc: Toscano, Marybeth
Subject: Re: MIDCYCLE /NDA 202379/S-005/Janssen/Zytiga/Kleutz/Tilley

Amy, please provide a response.
Thanks.

From: Safarik, Michelle
Sent: Monday, September 10, 2012 08:17 AM
To: Kacuba, Alice
Cc: Toscano, Marybeth
Subject: RE: MIDCYCLE /NDA 202379/S-005/Janssen/Zytiga/Kleutz/Tilley

Hi Alice,

I am not able to attend this meeting. Will there be handouts/slides available at a later time?

Thanks,
Michelle

From: Kacuba, Alice
Sent: Thursday, August 30, 2012 1:33 PM
To: Kacuba, Alice; Bridges, Todd; Abdus-Samad, Jibril; Toscano, Marybeth; Safarik, Michelle
Subject: FW: MIDCYCLE /NDA 202379/S-005/Janssen/Zytiga/Kleutz/Tilley
When: Tuesday, September 11, 2012 11:30 AM-12:30 PM (GMT-05:00) Eastern Time (US & Canada).
Where: CDER WO 1201 conf rm Bldg22 - AR

When: Tuesday, September 11, 2012 11:30 AM-12:30 PM (GMT-05:00) Eastern Time (US & Canada).
Where: CDER WO 1201 conf rm Bldg22 - AR

Note: The GMT offset above does not reflect daylight saving time adjustments.

~~*~*~*~*~*~*~*~*~*~*

From: Kacuba, Alice

Sent: Tuesday, July 31, 2012 12:49 PM

To: Kacuba, Alice; Tilley, Amy

Subject: FW: MIDCYCLE /NDA 202379/S-005/Janssen/Zytiga/Kleutz/Tilley

When: Tuesday, September 11, 2012 11:30 AM-12:30 PM (GMT-05:00) Eastern Time (US & Canada).

Where: CDER WO 1201 conf rm Bldg22 - AR

When: Tuesday, September 11, 2012 11:30 AM-12:30 PM (GMT-05:00) Eastern Time (US & Canada).
Where: CDER WO 1201 conf rm Bldg22 - AR

Note: The GMT offset above does not reflect daylight saving time adjustments.

~~*~*~*~*~*~*~*~*~*

From: Kacuba, Alice

Sent: Wednesday, July 25, 2012 8:36 PM

To: Kacuba, Alice; Justice, Robert; Ibrahim, Amna; Maher, Virginia E.; Kluetz, Paul; Liu, Qi (CDER); Booth, Brian P; Pfuma, Elimika; Tang, Shenghui; Zhang, Lijun; Palmby, Todd; Ringgold, Kimberly; Sarker, Haripada; Brown, Janice; Kelly, Sharon L; CDER OHOP Meeting Calendar; CDER 150 Calendar

Subject: MIDCYCLE /NDA 202379/S-005/Janssen/Zytiga/Kleutz/Tilley

When: Tuesday, September 11, 2012 11:30 AM-12:30 PM (GMT-05:00) Eastern Time (US & Canada).

Where: CDER WO 1201 conf rm Bldg22 - AR

Need to add OSI and any other consults yet.

Optional: Booth, Brown

Purpose: Midcycle

Team mtg: Thursday, 8-30-2012 10:30-11:30 Room 2201
Midcycle: Tuesday, 9-11-12 11:30-12:30 Room 1201 (you can get lunch at 12:30 but block it now so no one schedules you for 12:30)

AK (for AT) 7-25-2012

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/s/

FRANCES G FAHNBULLEH
09/14/2012

JAMES H SCHLICK on behalf of TODD D BRIDGES
09/19/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:	FROM: (Name/Title, Office/Division/Phone number of requestor)
CDER-DDMAC-RPM – Olga Salis	Amy Tilley/RPM/OHOP/DOP1/301-796-3994

REQUEST DATE	IND NO.	NDA/BLA NO.	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
August 28, 2012		202379/S-005	

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
Zytiga	Priority	NME	November 13, 2012

NAME OF FIRM:	
Janssen Biotech, Inc.	PDUFA Date: December 14, 2012

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☒ PACKAGE INSERT (PI)
- ☒ PATIENT PACKAGE INSERT (PPI)
- ☒ CARTON/CONTAINER LABELING
- ☐ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA
- ☐ IND
- ☒ EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED LABELING
- ☒ LABELING REVISION

EDR link to submission: <\\CDSESUB1\EVSPROD\NDA202379\202379.enx> eCTD Seq #0056, SDN 145

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: September 11, 2012
Labeling Meetings: October 1, 10, 16, 23, & 30; November 8, 13, & 27, December 6, 2012
Wrap-Up Meeting: November 20, 2012

SIGNATURE OF REQUESTER
{See appended electronic signature page}

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one)
	☒ eMAIL and DARRTS ☐ HAND

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/s/

AMY R TILLEY
08/28/2012

From: Tilley, Amy
Sent: Thursday, August 23, 2012 10:32 AM
To: Johnson Reid, Kelly kjohnso6@its.jnj.com
Subject: NDA 202379 Zytiga S-005 - Clinical & Stat IRs

Importance: High

Follow Up Flag: Follow up
Due By: Tuesday, September 04, 2012 12:00 AM
Flag Status: Flagged

Kelly,

We reference NDA 202379 for Zytiga, Supplement 005. We have the following information request from the clinical and statistical teams.

Please provide a response to #1 and #2 by 9/4/2012 if possible.

1. We have a concern regarding the **collection of concomitant medications** supporting your key secondary endpoints: time to cytotoxic chemotherapy and time to first opiate use. We noted that for the long term quarterly follow-up visits (CRF "FU"), there are specific questions asked for opiate use (yes/no/unknown) and cytotoxic chemotherapy or any other prostate cancer therapies (yes/no/unknown) since last follow-up visit. However, no such questions were found for the on-study treatment visits. Without specifically asking these questions, we rely on the lack of reporting of these medications in an overall concomitant medication list. As such, it is unclear if the lack of opiate or cytotoxic during the prior period was a true negative or missing data.

   Please submit your rationale for the reliability of time to opiate and time to cytotoxic chemotherapy given the above limitation. Please list the number of missing data by visit for each of the two endpoints. For both endpoints, perform an analysis by censoring patients who had at least 2 consecutive missing data on the date of the last visit with no event.

2. Perform an analysis on the "**time to deterioration of ECOG PS**" by adding the following censoring rules:

   Censoring patients on the date of the last visit with no deterioration
   a. if the patient received subsequent anti-cancer therapy before deterioration;
   b. if the patient missed ≥2 consecutive visits for ECOG status evaluation.

   Please do the analysis on both ECOG deterioration of ≥ 1 grade endpoints: (1) with no confirmation required; (2) with confirmation.

3. Given your exclusion of visceral disease, the majority of your target lesions for COU-AA-302 are lymph nodes. Comment on the **limitation of the use of longest diameter**, rather than shortest diameter and allowing growth <5mm as progression criteria if it meets the 20% threshold.

- Provide your rationale for why the use of these non-RECIST 1.1 criteria would not materially adversely affect your rPFS results.

4. Provide an analysis supporting the efficacy of Zytiga in patients with visceral metastatic disease. This may include subgroup analysis of the COU-301 trial with respect to PSA decline >50%, time to PSA progression, Objective Response Rate, Duration of Response, rPFS and Overall Survival. Include any data on PRO or other endpoints measuring clinical benefit with a comment on the limitations of this data as appropriate.

5. Provide data supporting the efficacy of Zytiga in patients with moderate or severe baseline pain as measured by the BPI-SF from the COU-AA-301 trial.

6. Provide your brief rationale for the lack of separation of the survival curves in the first year of therapy.

7. Provide an analysis of bone scan discrepancies (between IRC and investigator) by geographic region.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
08/23/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202379/S-005

FILING COMMUNICATION

Janssen Research and Development, LLC
Attention: Kelly Johnson Reid
920 Route 202
P.O. Box 300
Raritan, NJ 08869

Dear Ms. Reid:

Please refer to your New Drug Application (NDA) dated June 13, 2012, received June 14, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Zytiga® (abiraterone acetate) 250 mg Tablets.

We also refer to your amendments dated July 16, 25, August 8 and 9, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is December 14, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by November 23, 2012.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

In the Full Prescribing Information the **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

1. In Section 12 the first subsection is incorrectly numbered as 12.2 Mechanism of Action and should be numbered as 12.1.
2. The fourth subsection is 12.4 QT Prolongation but should be numbered as 12.6.

We request that you resubmit labeling that addresses these issues by September 3, 2012. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the

product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We reference the waiver granted on April 28, 2011, for the pediatric study requirement for this application.

If you have any questions, call Amy Tilley, Regulatory Project Manager, at (301) 796-3994.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ALICE KACUBA
08/13/2012
Signing for Dr. Justice.

From: Tilley, Amy
Sent: Monday, August 13, 2012 11:52 AM
To: Johnson Reid, Kelly kjohnso6@its.jnj.com
Subject: NDA 202379 Zytiga - S-005 - Clinical IRs

Follow Up Flag: Follow up
Due By: Monday, August 20, 2012 10:00 AM
Flag Status: Flagged

Kelly,

Below are four Clinical Information Requests (IR).

1. Please provide the rationale for the difference between the censoring rules found in the statistical analysis plan (pg 68) and the censoring rules documented in your clinical study report (pg 41). Specifically, the following censoring rule was removed from the CSR:

> "6c. the patient has unequivocal progression of non-bone non-target lesions (eg, appearance of nonmeasurable visceral metastases or pathologically confirmed malignant effusions)."

2. Please direct us to where the definition of major vs minor protocol deviation is specified in the submission or provide us with your definition of what consitutes a "major" from a "minor" protocol deviation which forms the basis for the major protocol deviation tracker.

3. Provide us with your planned date of submission for your 120-day updated safety analysis.

a. For your 120-day updated safety analysis, please include SDTM AE dataset for COU-AA-302 and INCLUDE MedRA high level term (HLT) and High Level Grouped Term (HLGT) in addition to the PT.

4. Please resend COU-AA-302 AE SDTM dataset with the HLT and HLGT fields (as above) as soon as possible.

We respectfully request your response to the above first two Clinical Information Requests no later than 10 am on August 20, 2012.

Kindly confirm receipt of this email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring,

MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
08/13/2012

From: Tilley, Amy
Sent: Monday, August 06, 2012 11:31 AM
To: 'Johnson Reid, Kelly [JRDUS]' kjohnso6@its.jnj.com
Subject: RE: NDA 202379 Zytiga S-005 - Corrected 2 Clinical IRs

Follow Up Flag: Follow up
Due By: Thursday, August 09, 2012 12:00 AM
Flag Status: Flagged

Kelly,

My apologies as the first email I sent was incorrect. Please disregard my original email and use the following corrected IR information.

Clinical would like to confirm the method for determining the date of radiographic progression (DOP) by bone scan. Please provide a date of progression given the following ***hypothetical scenarios***:

1. 2 new lesions seen on first scan (C3D1, Wk8)
    a. Two additional new lesions seen at C5D1 scan (4 total). Is progression called at C3D1 or C5D1 scan? (we interpret this as DOP C3D1)
    b. C5D1 scan stable (2 lesions) and scan stays stable until C10D1 scan which shows 2 new (4 total). Do you require another confirmatory scan? What is the date of progression in this scenario? (we interpret this as requiring a confirmation and if confirmed DOP C10D1)

2. 2 new lesions seen C5D1 (Wk16) with a confirmatory scan C7D1 showing those same 2 lesions. Confirm the date of progression would = C5D1.

Since we are currently conducting the RPS analysis we respectfully request your response to the above Clinical IRs as soon as possible.

Kind Regards.

Amy

From: Tilley, Amy
Sent: Monday, August 06, 2012 11:24 AM
To: 'Johnson Reid, Kelly [JRDUS]'
Subject: NDA 202379 Zytiga S-005 - 2 Clinical IRs

Kelly,

Below are two Clinical Information Requests (IR) for sNDA 202379 Zytiga S-005.

1. 2 new lesions seen on first scan (C3D1, Wk8)
    a. Two additional new lesions seen at C5D1 scan (4 total). Is progression called at C3D1 or C5D1 scan? (we interpret this as DOP C3D1)
    b. C5D1 scan stable (2 lesions) and scan stays stable until C10D1 scan

which shows 2 new (4 total). Do you require another confirmatory scan? What is the date of progression in this scenario? (we interpret this as requiring a confirmation and if confirmed DOP C10D1)

2. 2 new lesions seen C5D1 (Wk16) with a confirmatory scan C7D1 showing those same 2 lesions. Confirm the date of progression would = C5D1.

Since we are currently conducting the RPS analysis we respectfully request your response to the above Clinical IRs as soon as possible.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
08/06/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO:

CDER-DMPP-PatientLabelingTeam

FROM: (Name/Title, Office/Division/Phone number of requestor)

Amy Tilley/PM/OHOP/DOP1/301-796-3994

REQUEST DATE:

August 3, 2012

NDA/BLA NO.:

202379

TYPE OF DOCUMENTS:

(PLEASE CHECK OFF BELOW)

NAME OF DRUG:

Zytiga (abiraterone acetate)

PRIORITY CONSIDERATION:

Priority

CLASSIFICATION OF DRUG:

NME

DESIRED COMPLETION DATE

(Generally 2 Weeks after receiving substantially complete labeling)

SPONSOR: Janssen Biotech, Inc.

PDUFA Date: 12-14-12

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:

(Check all that apply)

☒ PATIENT PACKAGE INSERT (PPI)

☐ MEDICATION GUIDE

☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION

☐ ORIGINAL NDA/BLA

☒ EFFICACY SUPPLEMENT

☐ SAFETY SUPPLEMENT

☐ LABELING SUPPLEMENT

☐ MANUFACTURING (CMC) SUPPLEMENT

☐ PLR CONVERSION

REASON FOR LABELING CONSULT

☐ INITIAL PROPOSED LABELING

☒ LABELING REVISION

EDR link to submission: \\CDSESUB1\EVSPROD\NDA202379\202379.enx

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: 9-11-12

Labeling Meetings: October 10, 16, 23, 30; November 8, 13, 27, and December 6, 2012

Wrap-Up Meeting: 11-20-12

SIGNATURE OF REQUESTER

Amy Tilley *{See appended electronic signature page}*

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

☒ eMAIL (BLAs Only) ☒ DARRTS

Version: 12/9/2011

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/s/

AMY R TILLEY
08/03/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:			FROM:	
Mail: OSE/DEMPA			Amy Tilley/OHOP/DOP1 301-796-3994	
DATE August 3, 2012	IND NO.	NDA NO. 202379	TYPE OF DOCUMENT SE1-005	DATE OF DOCUMENT June 14, 2012
NAME OF DRUG Zytiga (abiraterone acetate)	PRIORITY CONSIDERATION Priority		CLASSIFICATION OF DRUG NME	DESIRED COMPLETION DATE November 14, 2012

NAME OF FIRM: Janssen Biotech, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☒ SAFETY/**EFFICACY**
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: DOP1 requests DMEPA to review the labeling submitted with the Efficacy Supplement 005 for NDA 202379.
Mid-Cycle Meeting: 9-11-12
Labeling Meetings: October 10, 16, 23, 30; November 8, 13, 27, and December 6, 2012
Wrap-Up Meeting: 11-20-12

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)	
Amy Tilley *{See appended electronic signature page}*	☒ EMAIL-DARRTS	☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER	

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/s/

AMY R TILLEY
08/03/2012

From: Tilley, Amy
Sent: Wednesday, August 01, 2012 12:03 PM
To: 'Johnson Reid, Kelly [JRDUS]'; kjohnso6@its.jnj.com 'Mazzola, Elise [JRDUS]'
Subject: RE: Information Requests for 202379/S-005 – 2nd Clarification of IR

Kelly,

For further clarification regarding the IR sent 7-27-12, if you can get us the two dates below we will let you know what, if any, additional analyses we would like for the updated interim analysis.

1. Please confirm the date that crossover / unblinding occurred for trial COU-AA-302 and the data cutoff date for the planned updated interim analysis.

If you have any further questions don't hesitate to contact me.

Regards.

Amy

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

---

From: Tilley, Amy
Sent: Wednesday, August 01, 2012 11:11 AM
To: 'Johnson Reid, Kelly [JRDUS]'; Mazzola, Elise [JRDUS]
Subject: RE: Information Requests for 202379/S-005 - Clarification of IR

Kelly,

The following is clarification from the Clinical Review Team regarding the IR sent 7-27-12.

1. Please confirm the date that crossover / unblinding occurred for trial COU-AA-302 and the data cutoff date for the planned updated interim analysis.
2. Please give us a date for when you plan to submit the safety update.

Regards.

Amy

Amy Tilley | Regulatory Project Manager | Division of Oncology Products 1,
CDER, FDA 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎301.796.3994 (phone) ● 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

consider the environment before printing this e-mail

From: Johnson Reid, Kelly [JRDUS] [mailto:KJohnso6@ITS.JNJ.COM]
Sent: Tuesday, July 31, 2012 3:57 PM
To: Kacuba, Alice; Mazzola, Elise [JRDUS]
Cc: Tilley, Amy
Subject: RE: Information Requests for 202379/S-005

Hi Alice,

We are working on this information request but want to confirm that the FDA is only requesting updated overall survival data. May I ask that you clarify if the review team is seeking any additional updates on other endpoints.

Thanks
Kelly

From: Kacuba, Alice [mailto:Alice.Kacuba@fda.hhs.gov]
Sent: Friday, July 27, 2012 12:26 PM
To: Johnson Reid, Kelly [JRDUS]; Mazzola, Elise [JRDUS]
Cc: Tilley, Amy
Subject: RE: Information Requests for 202379/S-005
Importance: High

Hi,

Adding Elise Mazzola.

Thank you.
Alice
Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Oncology Products 1 (new name for DDOP)
Office of Hematology and Oncology Products
OND/CDER/FDA
301-796-1381
(f) 301-796-9845
alice.kacuba@fda.hhs.gov
*Consider setting your email font setting to at least 12 font.

From: Kacuba, Alice
Sent: Friday, July 27, 2012 12:13 PM
To: 'Johnson Reid, Kelly [JRDUS]'
Cc: Tilley, Amy
Subject: Information Requests for 202379/S-005
Importance: High

Hi,

Our Stats reviewer has the following Information Requests:

The following requests are for the pivotal study COU-AA-302. Please respond by 8/10/2012.

1. **Please submit the independent radiology review charter.**

2. If the 3rd OS interim analysis has been conducted, please submit the datasets and results. Otherwise, please let us know when it is expected.

Thank you.
Alice
Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Oncology Products 1 (new name for DDOP)
Office of Hematology and Oncology Products
OND/CDER/FDA
301-796-1381
(f) 301-796-9845
alice.kacuba@fda.hhs.gov
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/s/

AMY R TILLEY
08/01/2012

Kacuba, Alice

From: Kacuba, Alice
Sent: Friday, July 27, 2012 12:26 PM
To: 'Johnson Reid, Kelly [JRDUS]'; Mazzola, Elise [JRDUS]
Cc: Tilley, Amy
Subject: RE: Information Requests for 202379/S-005

Importance: High

Hi,

Adding Elise Mazzola.

Thank you.
Alice
Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
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From: Kacuba, Alice
Sent: Friday, July 27, 2012 12:13 PM
To: 'Johnson Reid, Kelly [JRDUS]'
Cc: Tilley, Amy
Subject: Information Requests for 202379/S-005
Importance: High

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/s/

ALICE KACUBA
07/27/2012

Kacuba, Alice

From: Kacuba, Alice
Sent: Friday, July 27, 2012 12:13 PM
To: 'Johnson Reid, Kelly [JRDUS]'
Cc: Tilley, Amy
Subject: Information Requests for 202379/S-005

Importance: High

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/s/

ALICE KACUBA
07/27/2012

Kacuba, Alice

From: Kacuba, Alice
Sent: Tuesday, July 17, 2012 1:52 PM
To: 'Johnson Reid, Kelly [JRDUS]'
Subject: Good news! There will NOT be an ODAC for Zytiga S-005

Importance: High

Kelly,

Good news! There will NOT be an ODAC for Zytiga S-005. It has been taken off the agenda.

Thank you.
Alice
Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Oncology Products 1 (new name for DDOP)
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/s/

ALICE KACUBA
07/17/2012

Kacuba, Alice

From: Kacuba, Alice
Sent: Friday, July 13, 2012 6:02 PM
To: Johnson Reid, Kelly [JRDUS]
Subject: Zytiga NDA 202379/S-005---Invitation to FDA for a Post submission meeting

Importance: High

Attachments: Just the foreign visitor forms.doc

Hi,

We invite you to the FDA for a Post-submission meeting/presentation on S-005. The date and time that we have available is Friday, August 17, 2012 during the time frame of 1-2:30. The specific 1 hour time will be forth coming.

Please let me know of your availability for this date as son as possible.

Attendees with be the review team, Division and Office management, and any other interested reviewers from any of our 3 divisions.

Please focus your attention on the data that you are using to support your new claim.

Please provide any slides by email to me and Amy Tilley by Thursday, August 16, 2012 by ~ 1 PM so that they can be loaded on to proxima.

Please provide the attached forms in any attendees will be foreign visitors. (If any of the attendees to our meeting are non-US citizens, you will need to fill out the attached form for each person. Please e-mail the completed form(s) to me no later than 3 weeks before the scheduled meeting. Security may not allow the individual(s) in the building if the forms are not sent in time. The non-US citizens will need to show their Passport or other national identity source document (i.e. a document which allowed the immigration into the US) as identification when entering the building at FDA)

Please provide a list of attendees in a simple WORD listing, single spaced, no charts, etc, by email at least 2 weeks prior to the date so we can arrange visitor badges. Amy can provide a list of FDA team members closer to the date. LobbyGuard information/bar code will be sent to you at a later date.

Just the
gn visitor forr

Please notify me with any questions.

Thank you.
Alice
Alice Kacuba, RN, MSN, RAC
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/s/

ALICE KACUBA
07/13/2012

Kacuba, Alice

From: Kacuba, Alice
Sent: Thursday, July 12, 2012 11:54 AM
To: Johnson Reid, Kelly [JRDUS]
Subject: Zytiga, NDA 202379/S-005

Importance: High

Hi,

I m covering this supplement until Amy returns on July 28.

I just left you a VM message but am following up by email. Your supplement will be presented at ODAC in November, 2012.

Please confirm receipt of this message.

Thank you.
Alice
Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Oncology Products 1 (new name for DDOP)
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/s/

ALICE KACUBA
07/13/2012

Kacuba, Alice

From: Johnson Reid, Kelly [JRDUS] [KJohnso6@ITS.JNJ.COM]
Sent: Thursday, July 12, 2012 6:52 PM
To: Kacuba, Alice
Subject: RE: NDA 202379, Zytiga Supplement 005

Hi Alice,

I acknowledge receipt of this IR.

Thanks
Kelly

From: Kacuba, Alice [mailto:Alice.Kacuba@fda.hhs.gov]
Sent: Thursday, July 12, 2012 5:50 PM
To: Johnson Reid, Kelly [JRDUS]
Subject: NDA 202379, Zytiga Supplement 005
Importance: High

Hi,

Enclosed is an Information Request for 202379/S-005.

Please refer to sNDA 202379 submitted on 14 June 2012 (efficacy supplement 5). The following requests are for the pivotal study COU-AA-302. Please respond by July 26, 2012.

1. Provide a dataset summarizing the censoring reasons and event types (i.e., progression by bone scan only, progression by CT/MRI scan only, progression by both, and death) in the rPFS analysis. The dataset should have 3 rows per patient, i.e., progression based on investigator data (cutoff: Dec 20, 2010), progression based on independent reviewed data (cutoff: Dec 20, 2010), and progression based on investigator data (cutoff: Dec 20, 2011). Please note that we have difficulties to understand your dataset "RPFSEV10".

Submit the program for estimating the association between rPFS and OS as summarized in CSR 5.2.3.

We reference section 3.10 of the study report for COU-AA-302 (Data Quality Assurance). Please provide additional details regarding the 4 sites (103, 113, 122 and 919) that were put on screening hold:

a) For these sites, please discuss how the deficiencies occurred, how they were discovered, and how they were resolved. In your discussion, please highlight how the quality of the study data from these sites may have been impacted and/or protected, and how the safety, rights, and welfare of the subjects may have been compromised and/or protected.

1. Include patient #s and specific violations encountered
2. Include information on what attempts were made to remedy the situation at these sites prior to the decision to permanently close accrual.

b) How was the follow up for the enrolled patients handled for sites that did not screen additional subjects (103, 113, 919)? Were they followed at the same site or were they transferred to an alternative site?

Please comment on the 33 of 151 sites that required additional on-site quality monitoring visits. What were the indications for additional site visits?

Regarding potential subject un-blinding, please provide the patient ID #s for all patients who received the debossed tablets and the date they began receiving them. Include a sensitivity analysis of these patients in any updated efficacy

you provide.

6. Please clarify the difference in the discontinuation reasons listed in datasets "DISP10" and "DISP" for the following patients:

Unique subject ID	Reason Study Treatment Discontinued (from dataset: DISP10)	Reason Study Treatment Discontinued (from dataset: DISP)
COU-AA-302_106-2001	Discontinued per Protocol Section 6.6	Other: PI discretion clinical and radiographic progression
COU-AA-302_109-2012	Adverse Event	Discontinued per Protocol Section 6.6
COU-AA-302_139-2001	Discontinued per Protocol Section 6.6	Other: Clinical Progression not meeting sec 6.6 criteria
COU-AA-302_139-2022	Discontinued per Protocol Section 6.6	Other: Investigator discretion
COU-AA-302_152-2001	Other: MD wants to initiate new therapy after wash out.	Discontinued per Protocol Section 6.6
COU-AA-302_192-2002	Other: patient died	Adverse Event
COU-AA-302_226-2008	Discontinued per Protocol Section 6.6	Withdrew Consent to continue treatment
COU-AA-302_229-2002	Adverse Event	Discontinued per Protocol Section 6.6
COU-AA-302_404-2008	Adverse Event	Discontinued per Protocol Section 6.6
COU-AA-302_414-2011	Adverse Event	Discontinued per Protocol Section 6.6
COU-AA-302_416-2005	Adverse Event	Other: bone progression not meeting criteria 6.6
COU-AA-302_423-2012	Adverse Event	Discontinued per Protocol Section 6.6
COU-AA-302_525-2001	Adverse Event	Discontinued per Protocol Section 6.6
COU-AA-302_607-2005	Adverse Event	Discontinued per Protocol Section 6.6
COU-AA-302_610-2005	Adverse Event	Discontinued per Protocol Section 6.6
COU-AA-302_617-2008	Other: commenced diethylstilboestrol	Other: Disease progression not meeting sect 6.6 criteria
COU-AA-302_617-2017	Adverse Event	Discontinued per Protocol Section 6.6
COU-AA-302_814-2008	Adverse Event	Discontinued per Protocol Section 6.6
COU-AA-302_903-2001	Adverse Event	Discontinued per Protocol Section 6.6
COU-AA-302_903-2005	Adverse Event	Discontinued per Protocol Section 6.6
COU-AA-302_907-2007	Other: Patient taken off study medication at investigator	Other: General malaise due to disease progression
COU-AA-302_907-2020	Other: P.I's decision to seek further treatment.	Other: Clinical disease progression not meeting discontin
COU-AA-302_912-2015	Other: Clinical progression not meeting protocol guideline	Adverse Event

Thank you.
Alice
Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff

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/s/

ALICE KACUBA
07/13/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR Patient Reported Outcomes (PRO) ENDPOINTS CONSULTATION

TO: Study Endpoints and Labeling Development (SEALD)
CDER/OND-IO White Oak Bldg 22, Mail Drop 6411
SEALD.ENDPOINTS@FDA.HHS.GOV

FROM: Review Division: Division of Oncology Products 1
Medical Reviewer: Paul Kleutz, M.D.
Project Manager: Alice Kacuba

DATE OF CONSULT REQUEST	Application# IND/NDA/BLA#	LETTER # OR SUBMISSION #	TYPE OF DOCUMENT (Meeting; Protocol/SPA; PDUFA Product Review)	REQUESTED SEALD COMPLETION DATE*
7-13-2012	NDA 202379 Supplement 005	SD 145 eCTD 0056	PDUFA Efficacy Supplement Review	9-14-2012

DRUG ESTABLISHED NAME	DRUG TRADE NAME	NAME OF SPONSOR	SPONSOR SUBMIT DATE
abiraterone acetate	ZYTIGA®	Janssen/Cougar	6-14-2012

DEVELOPMENT PHASE (E.G., pre-IND/NDA/BLA; IND/BB-IND Phase 1, 2, 3; NDA/BLA): **NDA**
GOAL DATE (if NDA/BLA./SPA): **PDUFA Goal Date 12-14-2012**
ELECTRONIC LINK (if applicable): **DAARTs under NDA 202379, eCTD 0056, SD 145**
BACKGROUND PACKAGE : **see above**
MEETINGS (n/a)
July 17, 2012 Filing meeting for this application will be held in WO22: 2201

*** of note: a brief review by Päivi Miskala dated 1-30-2008 in DAARTs for this product when reviewing their initial application ***

Contact Paul Kleutz, M.D. if any further information is needed.

Instrument(s): Time to First Opiate Use, Brief Pain Index- Short Form (BPI-SF)

Indication(s): Sponsor is seeking the indication: "treatment of patients with metastatic castration-resistant prostate cancer (b) (4) (b) (4)

Specific Questions/Comments for SEALD: The applicant has submitted a randomized phase 3 trial of Zytiga vs Placebo in asymptomatic or minimally symptomatic metastatic prostate cancer patients prior to docetaxel. Coprimary endpoints include radiographic progression free survival (rPFS) and overall survival. The rPFS endpoint was statistically superior at the second interim analysis with a strong OS trend (HR 0.752)which did not meet pre-specified statistical O'brien-Fleming boundary (P=0.0097, required 0.0008). Multiple secondary endpoints are presented including time to opiate use, time to cytotoxic therapy initiation, (b) (4) (b) (4) P.

Because this application intends to seek approval based on a surrogate endpoint for which there is no regulatory precedence in this setting (rPFS in prostate cancer), careful evaluation of the secondary endpoints will be critical and this application will be the topic of an oncology drug advisory committee scheduled for early November, 2012. We seek SEALD input regarding the robustness of:

(b) (4)

2. Time to Opiate Use - endpoint definition, data collection and results

Requester: Paul Kluetz, M.D.

White Oak Bldg 22: 2223
paul kluetz@fda hhs.gov, office: 301-796-9567

Name/Phone number/email address/office location _____

Glossary:
Concept: The specific goal of a measurement (i.e. the *thing* that is to be measured by a PRO instrument).
Instrument: A means to capture data (e.g. questionnaire, diary) plus all the information and documentation that supports its use. Generally, that includes clearly defined methods and instructions for administration or responding, a standard format for data collection, and well-documented methods for scoring, analysis, and interpretation of results.
*For voluminous study endpoint submissions (e.g. PRO "dossier" or content validity documentation greater than 50 pages), SEALD requests 60 days after receiving the background/briefing package document to complete the review.

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/s/

ALICE KACUBA
07/13/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 202379/S-005

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

Janssen Research & Development, LLC
Attention: Kelly Reid
Associate Director, Regulatory Affairs
920 Route 202, P.O. Box 300
Raritan, NJ 08869

Dear Ms. Reid:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 202379

SUPPLEMENT NUMBER: 005

PRODUCT NAME: Zytiga® (abiraterone acetate) Tablets 250, mg

DATE OF SUBMISSION: June 13, 2012

DATE OF RECEIPT: June 14, 2012

This supplemental application proposes the following change: Study Report titled "Phase 3, Randomized, Double-blind, Placebo-controlled Study of Abiraterone Acetate Plus Prednisone in Asymptomatic or Mildly Symptomatic Subjects With Metastatic Castration-Resistant Prostate Cancer" and labeling revisions providing for the study results and modifying the Indications and Usage and other sections of the package insert for a new indication of "in combination with prednisone, for the treatment of patients with metastatic castration-resistant prostate cancer (b) (4) (b) (4)

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 13, 2012, in accordance with 21 CFR 314.101(a).

If the application is filed, the PDUFA goal date will be December 14, 2012.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under

21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 1
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me, at (301) 796-3994.

Sincerely,

{See appended electronic signature page}

Amy R. Tilley
Regulatory Project Manager
Division of Oncology Products 1
Office of Hematology & Oncology Products
Center for Drug Evaluation and Research

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/s/

AMY R TILLEY
06/27/2012