

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202379Orig1s000

OTHER REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Label Review

Date: April 25, 2011

Reviewer(s): Jibril Abdus-Samad
Division of Medication Error Prevention and Analysis

Team Leader: Todd Bridges, RPh, Acting Deputy Director
Division of Medication Error Prevention and Analysis

Division Director: Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

Drug Name(s): Zytiga (Abiraterone Acetate) Tablets, 250 mg

Application Type/Number: NDA 202379

Applicant/sponsor: Centocor Ortho Biotech, Inc.

OSE RCM #: 2010-2722-1

*** This document contains proprietary and confidential information that should not be released to the public.***

1 INTRODUCTION

This review evaluates the revised container label for Zytiga for areas of vulnerability that can lead to medication errors. Centocor Ortho Biotech, Inc. submitted a revised container label on April 22, 2011. DMEPA reviewed the initial proposed container label under OSE Review 2010-2722, dated April 12, 2011.

2 METHODS AND MATERIALS REVIEWED

The Division of Medication Error Prevention and Analysis (DMEPA) uses Failure Mode and Effects Analysis (FMEA)¹, principals of human factors, and lessons learned from post-marketing experience in our evaluation of the container label submitted April 22, 2011

3 CONCLUSIONS AND RECOMMENDATIONS

Review of the revised container label shows that the Applicant implemented DMEPA's recommendations. The Applicant's revisions did not introduce any additional areas of vulnerability that could lead to medication errors.

DMEPA concludes that the revised container label is acceptable. We do not have any additional comments at this time. If you have questions or need clarification, please contact Sarah Simon, OSE Project Manager, at 301-796-5205.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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

/s/

TODD D BRIDGES

04/25/2011

Signing for Jibril Abdus-Samad

CAROL A HOLQUIST

04/26/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

PATIENT LABELING REVIEW

Date: April 19, 2011

To: Robert Justice, MD, Director
Division of Drug Oncology Products (DDOP)

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)
Barbara Fuller, RN, MSN, CWOCN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)

From: Steve L. Morin, RN, BSN, OCN
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Patient Package Insert)

Drug Name (established name): ZYTIGA (abiraterone acetate)

Dosage Form and Route: Tablets

Application Type/Number: NDA 202-379

Applicant: Centocor Ortho Biotech, Inc.

OSE RCM #: 2011-105

1 INTRODUCTION

This review is written in response to a request by the Division of Drug Oncology Products (DDOP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Patient Package Insert (PPI) for ZYTIGA (abiraterone acetate) Tablets.

On December 20, 2010 Centocor Ortho Biotech Inc, submitted New Drug Application (NDA) 202-379 for ZYTIGA (abiraterone acetate) Tablets for use in combination with prednisone for the treatment of metastatic castration-resistant prostate cancer who have received prior chemotherapy containing docetaxel.

2 MATERIAL REVIEWED

- Draft ZYTIGA (abiraterone acetate) Tablets Patient Package Insert (PPI) received on December 20, 2010 and revised by the review division throughout the review cycle, and provided to DRISK on March 31, 2011.
- Draft ZYTIGA (abiraterone acetate) Tablets prescribing information (PI) received on December 20, 2010 revised by the review division throughout the current review cycle, and provided to DRISK on March 31, 2011.

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 APFont 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 our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the PPI are appended to this memo. Consult DRISK 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.

11 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

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

/s/

STEVE L MORIN
04/19/2011

LASHAWN M GRIFFITHS
04/19/2011

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

*****Pre-decisional Agency Information*****

Memorandum

Date: April 19, 2011

To: Amy Tilley, RPM, Division of Drug Oncology Products, (DDOP)

From: Adora Ndu, Regulatory Reviewer Officer
Division of Drug Marketing, Advertising, and Communications,
(DDMAC)

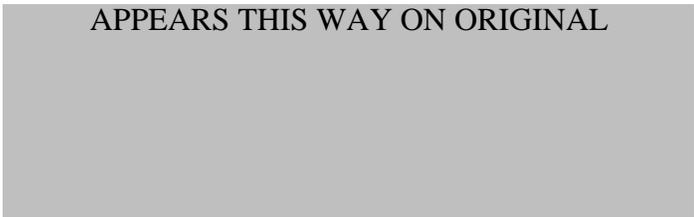
Subject: Comments on draft labeling (Patient Information) for Zytiga
(abiraterone acetate) Tablets

NDA 202379

In response to your consult request dated January 14, 2011, we have reviewed the proposed Patient Information for Zytiga (abiraterone acetate) Tablets.

The following comments are provided using the proposed Patient Information sent via email on April 19, 2011 by CDR Steve Morin.

APPEARS THIS WAY ON ORIGINAL



5 pages of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

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

/s/

ADORA E NDU
04/19/2011

Internal Consult

Pre-decisional Agency Information

To: Amy Tilley, RPM, Division of Drug Oncology Products, (DDOP)

From: Adam George, Regulatory Reviewer Officer
Division of Drug Marketing, Advertising, and Communications,
(DDMAC)

CC: Karen Rulli, Professional Review Group II Leader, DDMAC

Date: April 18, 2011

Re: Comments on draft labeling (Package Insert) for Zytiga (abiraterone
acetate) Tablets

NDA 202379

In response to your consult request dated January 14, 2011, we have reviewed the draft version of the Package Insert for Zytiga (abiraterone acetate) Tablets which was discussed during the April 18, 2011 review division labeling meeting. We offer the following comments.

1 page of draft labeling has been withheld in full as B(4) CCI/TS immediately following this page

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

/s/

ADAM GEORGE
04/18/2011

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: April 15, 2011

TO: Amy Tilley, Regulatory Project Manager
Y. Max Ning, Medical Officer
Paul Kluetz, Medical Officer
Division of Drug Oncology Products

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 202379

APPLICANT: Ortho Biotech Oncology Research & Development
Unit of Cougar Biotechnology, Inc.

DRUG: Zytiga™ (Abiraterone acetate)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: With prednisone for the treatment of metastatic (b) (4) (b) (4) (b) (4)
(castration-resistant prostate cancer) in patients who have received prior
chemotherapy containing a (b) (4)

CONSULTATION REQUEST DATE: 1/13/2011

DIVISION ACTION GOAL DATE: 4/29/11

PDUFA DATE: 6/20/11

I. BACKGROUND:

The applicant seeks approval of abiraterone acetate with prednisone for the treatment of metastatic (b) (4) (b) (4) (b) (4) (castration-resistant prostate cancer) in patients who have received prior chemotherapy containing a (b) (4). In support of this application, the applicant presents data from a phase III study, COU-AA-301, entitled, "A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate (CB7630) Plus Prednisone in Patients with Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy." Study COU-AA-301 was a multinational, multicenter, randomized, double-blind, placebo-controlled study conducted at 147 clinical sites in the U.S., Europe, Australia, and Canada, which compared the efficacy and safety of abiraterone acetate and prednisone with placebo and prednisone in men with metastatic castration-resistant prostate cancer whose disease had progressed on or after 1 or 2 chemotherapy regimens (at least one of which contained the taxane docetaxel). Subjects were randomly assigned in a 2:1 ratio to receive abiraterone acetate and prednisone or placebo and prednisone, respectively. This pivotal study was designed to demonstrate a clinically significant overall survival benefit for abiraterone acetate. The study period started on May 8, 2008 when the first subject was enrolled, and the last subject was enrolled on July 28, 2009; the clinical cut-off (534 death events observed) for interim analysis was reached on January 22, 2010 (552 actual death events observed). Planned enrollment was approximately 1,158 subjects; however, 1,195 subjects were actually randomized (797 subjects: abiraterone acetate and prednisone; 398: placebo and prednisone).

The study was halted in August 2010 by the study Independent Data Monitoring Committee (IDMC) after a protocol-specified interim analysis demonstrated that a pre-specified efficacy boundary had been crossed, and that there was significant benefit in overall survival (OS) for subjects receiving abiraterone acetate and prednisone/prednisolone. Based on recommendations by the IDMC, the blinded portion of the study was terminated. The study protocol was then amended to allow subjects in the placebo group who were either still participating in the treatment phase or were in the long-term survival follow-up phase to receive abiraterone acetate provided that they met the criteria specified in the subsequently amended protocol (page 36 of protocol dated August 26, 2010).

Cougar Biotechnology, Inc. (the Sponsor of IND 71,023 for abiraterone acetate) was acquired by, and became a wholly-owned subsidiary of Johnson & Johnson (J&JPRD) on July 09, 2009. Ortho Biotech Oncology Research & Development, a unit of Cougar Biotechnology, Inc., works with sister units situated within, and partners with other companies in the Johnson & Johnson family of companies to develop oncology treatments and supportive medicines. J&JPRD staff stated that they carried out a due-diligence compliance evaluation before the purchase of 'Cougar' and continued with focused follow-up after the acquisition was completed. According to J&JPRD, GCP compliance related activities included the following:

- The J&JPRD and Cougar Quality Assurance (QA) units were merged together
- Clinical investigator site audits performed post-acquisition were carried out under J&JPRD QA Standard Operating Procedures (SOPs)
- J&JPRD Global R&D QA function conducted a system audit of Cougar, including aspects of Clinical Operations, Regulatory, Safety, and Data Management

- Observations were noted and all corrective and preventative actions were accepted; the audit is closed.
- J&JPRD conducted a system audit of the primary clinical CRO, (b) (4) from 22 July 2009 to 24 July 2009. Observations were noted; all corrective and preventative actions have been addressed and the audit is closed.

The total GCP QA audit plan (Cougar audits pre-acquisition and subsequent J&JPRD audits) for the metastatic (b) (4) prostate cancer NDA submission consisted of 36 clinical investigator (CI) site audits. As a result of audit findings (most notably inadequate site monitoring) and J&JPRD Quality Management findings, an extensive program of CI site re-monitoring was also conducted for sites enrolling subjects in the pivotal study COU-AA-301 to ensure data submitted to NDA 202379 are reliable. Results apparently demonstrated the high quality of the primary efficacy endpoint and SAE reporting.

Approval of this application depends on results from a single study halted prior to completion by the IDMC for efficacy findings of improved survival on study treatment. In addition, the Applicant identified that original site monitoring was inadequate, which then necessitated they undertake an extensive re-monitoring program to ensure data submitted is reliable. Confirmation of data reliability is considered essential to support approval and appropriate labeling.

Five clinical Sites were inspected in accordance with the CDER Clinical Investigator Data Validation Inspection using the Bioresearch Monitoring Compliance Program (CP 7348.811); that of Dr. Johann de Bono (site number 600), Dr. Stephen Harland (site number 601), Dr. Cora Sternberg (site number 701), Dr. Christopher Logothetis (site number 139), and Dr. Mansoor Saleh (site number 159). The study parent sponsor, J&JPRD, was also inspected, in accordance with the CDER Sponsor/Monitor/CRO Inspection using the Bioresearch Monitoring Compliance Program (CP 7348.810).

The foreign CI Sites were chosen for inspections based on high enrollment numbers and because they are significant drivers of positive efficacy result for study drug. The domestic CI sites, Sites 139 and 159 were chosen for inspection to confirm that the sponsor/applicant re-monitoring plan was successfully implemented at a site that had not also received sponsor/applicant audit. Of additional note, reports of protocol violations for Site 601 were significantly below that for study mean raising concern that monitoring/re-monitoring of site may have been suboptimal. The parent sponsor, J&JPRD, has been previously inspected on multiple occasions. However, J&JPRD was also inspected for this application, applying an abbreviated inspection strategy focusing on the sponsor's conduct of the pivotal study, COU-AA-301, and the targeted clinical investigators noted below.

II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol #: and # of Subjects:	Inspection Date	Final Classification
CI#1: Site #139 – Dr. Christopher Logothetis Cancer Center Dept. Of Genitourinary Medical Oncology 1155 Pressler St. Unit 1374 Houston, Texas 77030	Protocol: COU-AA-301 Site Number: 139 Number of Subjects: 48	February 14-17 and 22-24, 2011	Pending Interim classification: NAI
CI#2: Site #159 – Dr. Mansoor Saleh 1835 Savoy Drive Suite 300 Atlanta, Georgia 30341	Protocol: COU-AA-301 Site Number: 159 Number of Subjects: 15		Pending Interim classification: NAI
CI#3: Site #600 – Dr. Johann de Bono Royal Marsden Hospital NHS Foundation Trust, Downs Road, Sutton, Surrey, SM2 5PT United Kingdom	Protocol: COU-AA-301 Site Number: 600 Number of Subjects: 49	March 22-25, 2011	Pending Interim classification: NAI
CI#4: Site # 601 – Dr. Stephen Harland University College Hospital 1 st Floor Central, Oncology 250 Euston Road, London NW1 2PQ United Kingdom	Protocol: COU-AA-301 Site: 601 Number of Subjects: 18	March 28 - April 1, 2011	Pending Interim classification: VAI
CI#5: Site # 701 – Dr. Cora Sternberg Hospital San amillo Forlanini O.U. Medical Oncology New pavilions, 4 th floor Circonvallazione Gianicolense 87 Rome, 00152 Italy	Protocol: COU-AA-301 Site: 701 Number of Subjects: 17	April 4-7, 2011	Pending Interim classification: NAI
Sponsor: J&JPRD, LLC 920 Route 202 Raritan, New Jersey 08869	Study: COU-AA-301 Sites: 139, 159, 600, 601, 701	April 5 – 12, 2011	Pending Interim classification: NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field and EIR has not been received from the field or complete review of EIR is pending and final classification letter has not issued.

- 1. CI#1:** – Dr. Christopher Logothetis
(Site Number 139)
Cancer Center Dept. Of Genitourinary Medical Oncology
1155 Pressler St. Unit 1374
Houston, Texas 77030

- a. What was inspected:** The site screened 50 subjects, 48 of those were randomized and treated. A total of 43 subjects completed the study. The study records of 10 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The study records of all 48 subjects were specifically assessed for concomitant drugs, major protocol violations, SAEs, and all deaths occurring within 30 days of discontinuing study. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, primary and secondary efficacy endpoints, clinical laboratory results, adverse events, and reporting of AEs in accordance with the protocol. The FDA field investigator also assessed informed consent documents, test article accountability, 1572s, clinical site staff qualifications, randomization and blinding procedures, IRB committee membership information, monitoring and safety reports, and financial disclosure forms.

Note: The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data were verifiable against source records at the site. The FDA field investigator reviewed subject records, CRFs and source documents, assessed inclusion/exclusion criteria satisfaction and verified subject treatment regimens. No subjects had waivers of eligibility. There was no evidence of under-reporting of AEs. However, there were minor protocol deviations observed, such as subjects not returning on an exact date for a test. The site staff explained that many of the patients live out of state and could not travel to Houston for a test. The site was able to provide documentation to show that the tests were performed, but at an outside laboratory.

Consistent with the routine clinical investigator compliance program assessments, the inspection verified data found in source documents and compared those measurements with that reported by the sponsor to the agency in NDA 202379. No Form FDA 483 was issued.

- c. Assessment of data integrity:** The data for Dr. Logothetis' site, associated with Study COU-AA-301 submitted to the Agency in support of NDA 202379, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

2. CI#2: Dr. Mansoor Saleh
(Site Number 159)
1835 Savoy Drive Suite 300
Atlanta, Georgia 30341

- a. What was inspected:** The site screened 17 subjects, 15 of those were randomized and treated. A total of 9 subjects completed the study. The study records of 17 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, primary and secondary efficacy endpoints, clinical laboratory results, adverse events, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, and monitoring and safety reports, and financial disclosure forms.

Note: The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data were verifiable against source records at the site. The FDA field investigator reviewed subject records, CRFs and source documents, assessed inclusion/exclusion criteria compliance and verified subject treatment regimens. There was no evidence of under-reporting of AEs.

There were several minor observations that were discussed with the site. Specifically, Subject 0011 had prior Ketoconazole (1 dose) use, a direct violation of Exclusion Criteria 11; however, the subject had a wash out for Ketoconazole before starting study procedures and study drug. A waiver request was granted by the Sponsor before Subject 0011 started the study. There were several other minor observations, as follows, the site did not have the baseline PSA lab source document for Subject 0001, and certain laboratory records/reports for Subject 0017, dated October 13, 2009, were not available for audit (PSA, coagulation, CDC and Chemistry). The inspection also found that for Subject 0017 a protocol deviation (failure to complete the Brief Fatigue Inventory [BFI] instrument for Cycle 4, Day 1, July 21, 2009) was listed in the source documents and the eCRF but not listed in the NDA data listings. There was also a protocol deviation (PD) in the NDA data listing for Subject 0017 that appears to have been listed in error. The NDA data listings indicated that for Subject 0017 the functional status assessment using the FACT-P questionnaire was not performed at Cycle 13. However, Subject 0017 only completed study Cycle 10, and was subsequently discontinued at the Cycle 11 Day 1 visit, January 20, 2009, due to disease progression. There was no mention of this alleged PD in the subject's eCRF or supported by source documents. Finally, Subject 0009 had an unscheduled visit that was supported in the subject's source records and the eCRF, but was listed in the NDA. These inspectional observations are isolated,

and of limited import on study safety and efficacy assessments, and not likely to importantly impact data reliability for the site.

Consistent with the routine clinical investigator compliance program assessments, the inspection verified data found in source documents and compared those measurements with that reported by the sponsor to the agency in NDA 202379. No Form FDA 483 was issued.

- c. Assessment of data integrity:** Notwithstanding the minor observations noted above, the data for Dr. Saleh's site, associated with Study COU-AA-301 submitted to the Agency in support of NDA 202379, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

- 3. CI#3:** Dr. Johann de Bono
(Site Number 600)
Royal Marsden Hospital NHS Foundation Trust
Downs Road, Sutton, Surrey, SM2 5PT
United Kingdom

- a. What was inspected:** The site screened 59 subjects, and 49 were treated. The study records of 15 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 202379, with particular attention paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol, and drug records. The FDA investigator also assessed informed consent documents. The FDA field investigator also conducted a limited audit of all remaining subjects; to include verification of selected data listings including survival/death date, randomization date, off-treatment date, medication numbers dispensed, reporting of adverse events, and in many cases PSA values.

Note: The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data were verifiable against source records at the site. The FDA field investigator reviewed subjects' records, CRFs and source documents, for the primary efficacy values and verified their treatment regimens. There was no evidence of under-reporting AEs. The study was found to be well documented and controlled.

With respect to adequacy of monitoring at the site, the FDA field investigator noted that the records had been extensively monitored; the monitoring sign-in log found at the site is 45 pages long. Records were found to have multiple corrections, additions, explanations, etc., all carefully signed and dated. The site had very little documentation regarding the “re-monitoring” program other than the record of monitoring visits. However, re-monitoring did appear to take place. Overall, the heavily-monitored, revised, and corrected source documents support the data listings submitted to NDA 202379. Any inadequate source records have been fixed or explained. There were no patterns of problems.

DSI Reviewer’s Note: During the conduct of the inspection of Site 601 (Dr. Harland), the FDA field investigator discovered a discrepancy between the Site’s source records and CRFs, and the data listings submitted to NDA 202379. This discrepancy was not noted during the conduct of this inspection of Dr. de Bono’s Site, nor that of Dr. Logothetis or Dr. Saleh. Once found, the FDA field investigator at Dr. Harland’s Site called Dr. de Bono’s Site and requested additional information to determine if Dr. de Bono’s Site also showed a similar discrepancy. Briefly, for both Sites (600 [Dr. de Bono] and 601 [Dr. Harland]; and also subsequently Site 701 [Dr. Sternberg]) the FDA field investigator noted that the data with respect to adverse event reporting and causality attribution as recorded in source documentation and Case Report Forms for all subject records reviewed did not match the respective data listings submitted to the IND and provided to DSI as background material for inspection of Study COU-AA-301.

This observation was brought to the attention of the review division (DDOP) and a meeting was held to discuss the same between DSI and DDOP on March 30, 2011. As a result of the inspectional observation an Information Request (IR) from the clinical review team (DDOP) was sent to the applicant, J&JPRD, requesting an explanation, assessment of the scope of this problem as it affects all study sites, and a corrective action plan to ensure the data listings submitted in support of the NDA are accurate reflections of the source data and CRFs. Finally, the IR requested that the applicant amend the NDA as necessary so that the data and study reports are correct. The IR was sent on March 31, 2011. According to preliminary communications from the applicant, it appears that the data listings for AE causality attribution column headings for abiraterone acetate and prednisone were inadvertently reversed in the IND, but correct in the NDA.

Briefly, the 5 clinical sites inspected by FDA field investigators, upon further review of the data listings provided in the IND and those provided in the NDA, were found to have what appeared to be a systematic error regarding the causality attribution of adverse events to either abiraterone or prednisone. For the 3 sites inspected in Europe, Sites 600, 601 and 701, the source records found at the site and the data listings provided for verification, taken from the IND did not match, but conversely did match those same data listings provided in the NDA. It was determined by the sponsor that the AE data listings submitted to the IND for the 5 sites were different than the AE data listings submitted to the NDA. The column headings ‘Causality (Abiraterone)’ and ‘Causality (Prednisone/Prednisolone)’ were reversed in the IND submission. This error

was confirmed by the DDOP safety reviewer, Dr. Paul Kluetz, and it was verified by random spot-check that the resubmitted corrected IND AE data listing matched the NDA data listing. DSI agrees that the discrepancy between AE data listing and the source documents at the sites could be explained by this programming error for the IND data listing.

The discrepancy discovered during inspection of the 3 European sites (Sites 600, 601 and 701) between data listings found in the IND and site source records is not a site issue but rather a sponsor issue. The source documents found at the 3 sites in Europe did support the information on the CRFs and were consistent with those data found in the data listings submitted to the NDA. Consequently, this finding is unlikely to impact data reliability as the accurate dataset was submitted to the NDA.

Consistent with the routine clinical investigator compliance program assessments, the inspection verified data found in source documents and compared those measurements with that reported by the sponsor to the agency in NDA 202379. No Form FDA 483 was issued.

- c. **Assessment of data integrity:** The data for Dr. de Bono's Site, associated with Study COU-AA-301 submitted to the Agency in support of NDA 202379, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon final review of the EIR.

- 4. **CI#4:** Dr. Stephen Harland
(Site Number 601)
University College Hospital
1st Floor Central, Oncology
250 Euston Road, London NW1 2PQ
United Kingdom

- a. **What was inspected:** The site screened 23 subjects, and 18 were treated. The study records of 15 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 202379, with particular attention paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol, and drug records. The FDA investigator also assessed informed consent documents. The FDA field investigator also conducted a limited audit of all remaining subjects; to include consent documentation, verification of the screening and randomization dates, baseline ECOG status, prior chemotherapy, type of progression for eligibility, all adverse event reporting (serious and non-serious) including causality (noting that causality information was switched between the blinded medication and the prednisone in the AE listing [**See DSI Reviewers Note below**]), all

death/survival information including cause of death, drug dispensing records and protocol deviations.

Note: The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data were verifiable against source records at the site. The FDA field investigator reviewed subjects' records, CRFs and source documents, for the primary efficacy values and verified their treatment regimens. There was no evidence of under-reporting of AEs. The study was found to be well documented and controlled.

With respect to adequacy of monitoring at the site, the FDA field investigator noted that the records had been extensively monitored. The remonitoring took place in June 2010. The records show some late additions/corrections, however, limited compared to that of Dr. de Bono's site. There were no transcription errors found, thus, the site appeared to have been monitored adequately both initially and recently. There were no patterns of problems.

DSI Reviewer's Note: During the conduct of this inspection the FDA field investigator discovered a discrepancy between the site's source records and CRFs, and the data listings submitted to NDA 202379. The FDA field investigator noted that the data with respect to adverse event reporting and causality attribution as recorded in source documentation and Case Report Forms for all subject records reviewed did not match the respective data listings submitted to the NDA for Study COU-AA-301.

This was brought to the attention of the review division (DDOP) and a meeting was held to discuss the same between DSI and DDOP on March 30, 2011. As a result of the inspectional observation an Information Request (IR) from the clinical review team (DDOP) was sent to the applicant, J&JPRD, requesting an explanation, assessment of the scope of this problem as it affects all study sites, and a corrective action plan to ensure the data listings submitted in support of the NDA are accurate reflections of the source data and CRFs. Finally, the IR requested that the applicant amend the NDA as necessary so that the data and study reports are correct. The IR was sent on March 31, 2011. [**DSI Reviewers Note:** Please see DSI Reviewers Note, above under review of Site 600, for complete assessment and resolution of this observation.]

Consistent with the routine clinical investigator compliance program assessments, the inspection verified data found in source documents and compared those measurements with that reported by the sponsor to the agency in NDA 202379. The FDA field investigator noted that the Pharmacy did not directly dispense study drug to subjects, but instead provided the study drug to a study nurse who then transported the study drug to

the clinic and dispensed to study subjects as appropriate. A Form FDA 483 was issued to the clinical investigator citing 1 inspectional observation.

Observation 1: Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation.

Specifically, documentation of the actual dispensing of Abiraterone Acetate/Placebo, to the COU-AA-301 study subjects, after the bottles are released from the Pharmacy to the study nurse, is insufficient to show that subjects received the correct medication numbers.

DSI Reviewer's Note: The FDA field investigator noted that the Pharmacy kept drug accountability source records which seemed complete and accurate. However, upon interview, it was found out that the Pharmacy didn't actually dispense the drug bottles to the study subjects. Instead, the Pharmacy issued study medication to the study nurse, who would transport the bottles (2 or 3 at a time) to the site clinic. The study medication bottles were apparently labeled by the Pharmacy with the study Subject's name prior to release to the study nurse. The study nurse documented the details of the study visit and study drug issuance in the subject's visit notes, but did not document the actual study drug bottle number issued to the subject. The study nurse informed that she did read the "name" on the study drug bottle out loud to the subject at the time of issuance. When the subject returned unused study drug material, the site nurse counted returned pills and documented this in the site study notes, and then returned the unused study medication to the Pharmacy for disposition. The Pharmacy also did a pill count and documented the returned study drug bottle for each study subject. According to the FDA investigator, there were reportedly no mix-ups or errors in pill counts between the pharmacy and clinic records. So, when the pharmacy received a bottle back from the site and counted the pills, it reportedly always matched the pill counts in the clinic notes for that subject. Therefore, the findings are unlikely to impact data reliability.

Subsequent to this drug dispensing practice, in their later recordkeeping (after the data cut-off), the Site started using a form to collect the subject visit data. This form includes dispensing information. There were no known bottle mix-ups at this site.

- c. **Assessment of data integrity:** Notwithstanding the regulatory violation noted above, the data associated with Study COU-AA-301 submitted to the Agency in support of NDA 202379, appear reliable in support of the application.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

5. CI#5: Dr. Cora Sternberg
(Site Number 701)
Hospital San amillo Forlanini
O.U. Medical Oncology
New pavilions, 4th floor
Circonvallazione Gianicolense 87
Rome, 00152
Italy

- a. What was inspected:** The site screened 21 subjects, and 17 were treated. The study records of 10 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 202379, with particular attention paid to inclusion/exclusion criteria compliance and reporting of AEs in accordance with the protocol, and drug records. The FDA field investigator also assessed informed consent documents. The FDA field investigator also conducted a limited audit of all remaining subjects; to include consent documentation, verification of the screening and randomization dates, baseline ECOG status, prior chemotherapy, type of progression for eligibility, all adverse event reporting (serious and non-serious) including causality (noting that causality information was apparently switched between the blinded medication and the prednisone in the AE listing [**See DSI Reviewers Note below**]), all death/survival information including cause of death, all central lab PSA values, drug dispensing records and major protocol deviations.

Note: The EIR was not available at the time this CIS was written. The EIR is currently being finalized and will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

- b. General observations/commentary:** The investigator's execution of the protocol was found to be well controlled and well documented. The primary efficacy endpoint data were verifiable against source records at the site. The FDA field investigator reviewed subjects' records, CRFs and source documents, for the primary efficacy values and verified their treatment regimens. There was no evidence of under-reporting AEs.

With respect to adequacy of monitoring at the site, the FDA field investigator noted that the protocol deviations occurred as reported in the data listings. The site blames these deviations on two factors, their staffing problems at the beginning of the study and inadequate monitoring. The site's two main data managers were out unexpectedly during the busiest months of enrollment/treatment in late 2008. Also, the site staff (including Dr. Sternberg) complained about a series of inexperienced monitors with no knowledge of oncology trials. They stated that they had "at least five different monitors for this study." The data listings show that there were less deviations later in the study. All three of the deviations listed as "major" were approved by the sponsor and a waiver given before the subjects were enrolled. The FDA field investigator did not find any

“new” protocol deviations of any kind that were not reported in the NDA data listings. The remonitoring took place in April 2010. There were no patterns of problems.

DSI Reviewer’s Note: During the conduct of the inspection of Site 601 (Dr. Harland) the FDA field investigator discovered a discrepancy between the site’s source records and CRFs, and the data listings submitted to NDA 202379. The FDA field investigator noted that the data with respect to adverse event reporting and causality attribution as recorded in source documentation and Case Report Forms for all subject records reviewed did not match the respective data listings submitted to the NDA for Study COU-AA-301. This discrepancy was also observed at this Site during the inspection.

This was brought to the attention of the review division (DDOP) and a meeting was held to discuss the same between DSI and DDOP on March 30, 2011. As a result of the inspectional observation an Information Request (IR) from the clinical review team (DDOP) was sent to the applicant, J&JPRD, requesting an explanation, assessment of the scope of this problem as it affects all study sites, and a corrective action plan to ensure the data listings submitted in support of the NDA are accurate reflections of the source data and CRFs. Finally, the IR requested that the applicant amend the NDA as necessary so that the data and study reports are correct. The IR was sent on March 31, 2011. [**DSI Reviewers Note:** Please see DSI Reviewers Note, above under review of Site 600, for complete assessment and resolution of this observation.]

Consistent with the routine clinical investigator compliance program assessments, the inspection verified data found in source documents and compared those measurements with that reported by the sponsor to the agency in NDA 202379. A Form FDA 483 was not issued.

- c. **Assessment of data integrity:** The data for Dr. Sternberg’s site, associated with Study COU-AA-301 submitted to the Agency in support of NDA 202379, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

6. Sponsor:

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
920 Route 202
Raritan, NJ 08869

- a. **What was inspected:** The sponsor, J&JPRD, was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The study, COU-AA-301, was conducted at 147 Centers in the U.S., Europe, Australia, and Canada. Planned enrollment was approximately 1,158 subjects; however, 1,195 subjects were actually randomized (797 subjects: abiraterone acetate and prednisone; 398: placebo and prednisone). The study was terminated early because an interim analysis

had demonstrated that a pre-specified efficacy boundary (significant overall survival for subjects on the active study drug) had been crossed. The inspection covered adherence to Protocol, and review of the firm's SOPs, including monitoring SOPs, monitoring reports, actions related to monitoring deficiencies and re-monitoring of study sites, Ethics Committee/IRB approvals, completed Form FDA 1572s, communications with the sites, subjects' randomization, drug accountability and review of data management from the clinical study sites to the submission of the NDA to the Agency.

The FDA field investigator specifically audited subjects' records from 5 clinical study Sites; Site 139 (Dr. Christopher Logothetis, 48 subjects), Site 159 (Dr. Mansoor Saleh; 15 subjects), Site 600 (Dr. Johann de Bono; 49 subjects), Site 601 (Dr. Stephen Harland; 18 Subjects), and Site 701 (Dr. Cora Sternberg; 17 subjects) against the data listings submitted to NDA 202379.

Note: The EIR was not available at the time this CIS was written. The EIR will be submitted to DSI upon completion. The general observations described below are based on preliminary communication from the field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

- b. General observations/commentary:** Once J&JPRD acquired Cougar, appropriate and aggressive steps for oversight are evident to have been taken. For example monitor deficiencies noted during review of monitoring reports were also noted by J&JPRD and a plan was initiated with corrective actions for the 5 Sites to be audited. The records and procedures were clear, and generally well organized. There was nothing to indicate under-reporting of AEs/SAEs. The inspection completed audit of all 5 study Sites. The primary efficacy endpoint data are verifiable.

During the re-monitoring of sites, under-reporting of AEs was noted and corrective actions were taken and appear adequate. For example AE and SUSARs were not being processed or reported in a timely manner. J&JPRD took immediate actions and according to trending reports, the number of late reporting had decreased significantly and root cause analyses were then being conducted. Overall re-monitoring of sites appear adequate, and follow-up of corrective actions required at sites appears adequate. Issues that required escalation were noted to be escalated, actions implemented, and closed in a timely manner. The FDA field investigator did not identify any deficiencies in the implementation or follow-up of the corrective actions required by sites noted to have issues as a result of the re-monitoring. The 5 Sites reviewed appear adequate.

Consistent with the sponsor compliance program assessments, the inspection verified data found in source documents and compared those measurements with that reported by the sponsor to the agency in NDA 202379. A Form FDA 483 was not issued.

- c. Assessment of data integrity:** The data generated at this site, as it pertains to Study COU-AA-301 were audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. The findings are that the data from this Sponsor submitted to the agency in support of NDA 202379 appear reliable.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon completion of the current inspection and, receipt and review of the final EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for clinical investigators Dr. Logothetis, Dr. Saleh, Dr. de Bono, Dr. Harland, Dr. Sternberg, and study parent sponsor, Johnson & Johnson Pharmaceutical Research & Development (J&JPRD), L.L.C., the study data collected appear reliable. Of the 5 clinical Sites inspected, only Dr. Harland (Site 601) was issued a Form FDA 483 citing one inspectional observation.

The inspection of the sponsor, J&JPRD, targeted the effectiveness of monitoring and re-monitoring of study sites, specifically Sites 139, 159, 600, 601 and 701. In general, inspectional findings report that the overall re-monitoring of these sites appear adequate. The FDA field investigator did not identify any deficiencies in the implementation or follow-up of the corrective actions required by sites noted to have issues as a result of the re-monitoring. The 5 clinical Sites reviewed revealed nothing to indicate under-reporting of AEs/SAEs. The primary efficacy endpoint data are verifiable for those sites audited.

Although a regulatory violation was noted as described above, for Site 601, it is unlikely to significantly impact primary safety and efficacy analyses. The overall data in support of this application may be considered reliable based on available information.

Note: Observations noted above are based on the preliminary communications provided by the FDA field investigators and preliminary review of available Form FDA 483, inspectional observations. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

Follow-Up Actions: DSI will generate an inspection summary addendum if the conclusions change significantly upon final review of the EIRs and supporting inspection evidence and exhibits.

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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

/s/

LAUREN C IACONO-CONNORS
04/15/2011

TEJASHRI S PUROHIT-SHETH
04/15/2011

PMR 1

PMR Description:

Perform an *in vitro* screen to determine if abiraterone is an inhibitor of human CYP2C8. Based on results from the *in vitro* screen, a clinical drug-drug interaction trial may be needed.

PMR Schedule Milestones:

Final protocol Submission Date:	<u>N/A</u>
Study/Clinical trial Completion Date:	<u>01/30/2012</u>
Final Report Submission Date:	<u>06/30/2012</u>
Other: _____	<u>MM/DD/YYYY</u>

1. During application review, explain why this issue is appropriate for a PMR instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

In vitro studies with human hepatic microsomes showed that abiraterone is a strong inhibitor of CYP1A2 and CYP2D6 and a moderate inhibitor of CYP2C9, CYP2C19 and CYP3A4/5. In an *in vivo* drug-drug interaction study, the C_{max} and AUC of dextromethorphan (sensitive CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively when dextromethorphan 30 mg was given with abiraterone acetate 1000 mg daily (plus prednisone 5 mg twice daily). However, the potential to inhibit CYP2C8 *in vitro* was not reported in the NDA submission. An *in vitro* screen of the potential of abiraterone to inhibit CYP2C8 will help determine the likelihood of an *in vivo* interaction. This would help determine the likelihood that abiraterone could increase concentrations of sensitive CYP2C8 substrates *in vivo*.

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.”

The potential of abiraterone to inhibit CYP2C8 *in vitro* was not reported in the NDA submission. An *in vitro* screen of the potential of abiraterone to inhibit CYP2C8 will help determine the likelihood of an *in vivo* interaction. This would help determine the likelihood that abiraterone could increase concentrations of sensitive CYP2C8 substrates *in vivo*.

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.

The required study will be an *in vitro* screen of the effect of abiraterone on CYP2C8, which may be done using human liver microsomes.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- 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)
- 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?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR 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 BLAs)

PMR 2

PMR Description:

Conduct a trial to determine the pharmacokinetics of abiraterone after an oral dose of abiraterone acetate in individuals with severe hepatic impairment. The proposed protocol should contain the rationale for dose selection, and must be submitted for review prior to trial initiation. In the design of the trial, consider development of lower dosage strengths to allow for administration of a safe dose in patients with severe hepatic impairment.

PMR Schedule Milestones:

Final protocol Submission Date:	<u>10/31/2011</u>
Study/Clinical trial Completion Date:	<u>10/31/2013</u>
Final Report Submission Date:	<u>04/30/2014</u>
Other: _____	<u>MM/DD/YYYY</u>

4. During application review, explain why this issue is appropriate for a PMR instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

In a dedicated hepatic impairment trial, systemic exposure (AUC) of abiraterone after a single oral 1000 mg dose increased by approximately 1.1-fold and 3.6 fold in subjects with mild and moderate pre-existing hepatic impairment, respectively. The increase in exposure is expected to be higher in individuals with severe hepatic impairment. However, the formal hepatic impairment trial did not include individuals with severe hepatic impairment and a specific dose adjustment cannot be recommended in this population. Therefore, a clinical trial in severe hepatic impairment is required to identify a safe dose for patients with severe hepatic impairment.

5. 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.”

In a dedicated hepatic impairment trial, systemic exposure (AUC) of abiraterone after a single oral 1000 mg dose increased by approximately 1.1-fold and 3.6 fold in subjects with mild and moderate pre-existing hepatic impairment, respectively. The increase in exposure is expected to be higher in individuals with severe hepatic impairment. Therefore, a clinical trial in severe hepatic impairment is required to identify a safe dose for patients with severe hepatic impairment.

6. 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.

The required clinical trial will be a trial designed to assess the pharmacokinetics of abiraterone after oral abiraterone acetate in individuals with severe hepatic impairment compared to those with normal hepatic function.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- 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)
 - 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
-

6. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- 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 BLAs)

PMR 3

PMR Description:

Conduct a drug-drug interaction trial to evaluate the effect of a strong CYP3A inducer (e.g., rifampin) on the pharmacokinetics of abiraterone after an oral dose of abiraterone acetate. The proposed trial must be submitted for review prior to trial initiation.

PMR Schedule Milestones:

Final protocol Submission Date:	<u>10/31/2011</u>
Study/Clinical trial Completion Date:	<u>04/30/2013</u>
Final Report Submission Date:	<u>11/31/2013</u>
Other: _____	<u>MM/DD/YYYY</u>

7. During application review, explain why this issue is appropriate for a PMR instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The NDA review indicated the need for an *in vivo* study. CYP3A4 and SULT2A1 are the enzymes involved in the formation of N-oxide abiraterone sulphate (an inactive metabolite that accounts for about 43% of human plasma exposure after an oral dose of abiraterone acetate) from abiraterone. Thus, co-administration of abiraterone acetate with potent CYP3A inducers can decrease abiraterone concentrations and lead to efficacy and safety concerns. However, no clinical drug-drug interaction trial has been conducted to address this issue. Therefore, a clinical trial of with a strong CYP3A inducer, such as rifampin, is required to identify a safe dose when abiraterone acetate is co-administered with CYP3A inducer.

8. 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.”

CYP3A4 and SULT2A1 are the enzymes involved in the formation of N-oxide abiraterone sulphate (an inactive metabolite that accounts for about 43% of human plasma exposure after an oral dose of abiraterone acetate) from abiraterone. A clinical trial with a potent CYP3A inducer, such as rifampin, is needed to accurately determine the magnitude of abiraterone exposure changes when a strong CYP3A4 inducer is co-administered with abiraterone acetate. Depending on the results, a safe and efficacious dose of abiraterone acetate will be identified when it is co-administered with potent CYP3A inducers.

9. 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.

This required drug-drug interaction clinical trial will likely be a crossover trial to evaluate the effects of a strong CYP3A inducer (e.g., rifampin) on the pharmacokinetics of abiraterone after a dose of abiraterone acetate.

Required

- Observational pharmacoepidemiologic study
- Registry studies

Continuation of Question 4

- 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)
 - 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
-

7. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- 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 BLAs)

PMR 4

PMR Description:

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

PMR Schedule Milestones:

Final protocol Submission Date:	<u>10/31/2011</u>
Study/Clinical trial Completion Date:	<u>04/30/2013</u>
Final Report Submission Date:	<u>11/31/2013</u>
Other: _____	<u>MM/DD/YYYY</u>

10. During application review, explain why this issue is appropriate for a PMR instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The NDA review indicated the need for an *in vivo* study. CYP3A4 and SULT2A1 are the enzymes involved in the formation of N-oxide abiraterone sulphate (an inactive metabolite that accounts for about 43% of human plasma exposure after an oral dose of abiraterone acetate) from abiraterone. Thus, co-administration of abiraterone acetate with strong CYP3A inhibitors can lead to an increase in abiraterone concentrations and risk of toxicity. However, no clinical drug-drug interaction trial has been conducted to address this issue. Therefore, a drug interaction trial with a strong CYP3A inhibitor, such as ketoconazole, is required.

11. 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.”

CYP3A4 and SULT2A1 are the enzymes involved in the formation of N-oxide abiraterone sulphate (an inactive metabolite that accounts for about 43% of human plasma exposure after an oral dose of abiraterone acetate) from abiraterone. A clinical trial with a strong CYP3A inhibitor, such as ketoconazole, is needed to accurately determine the magnitude of abiraterone exposure changes when a strong CYP3A4 inhibitor is co-administered with abiraterone acetate. Depending on the results, a safe dose of abiraterone acetate will be identified when co-administered with strong CYP3A inhibitors.

12. 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.

The required drug-drug interaction trial will likely be a crossover trial to evaluate the effect of a CYP3A4 inhibitor, ketoconazole, on the pharmacokinetics of abiraterone after a dose of abiraterone acetate.

Required

- Observational pharmacoepidemiologic study
 - Registry studies
- Continuation of Question 4*
- 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)

- 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
-

8. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- 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 BLAs)

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

/s/

ELIMIKA PFUMA
04/14/2011

NITIN MEHROTRA
04/14/2011

JEANNE FOURIE
04/14/2011
Concurrence with primary reviewer noted.

CHRISTINE E GARNETT
04/14/2011

NAM ATIQR RAHMAN
04/20/2011

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: April 12, 2011

Application Type/Number: NDA 202379

Through: Todd Bridges, RPh, Team Leader
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Jibril Abdus-Samad, PharmD, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Zytiga (Abiraterone Acetate) Tablet, 250 mg

Applicant: Centocor Ortho Biotech, Inc

OSE RCM #: 2010-2722

1 INTRODUCTION

This review evaluates the proposed container label and insert labeling for Zytiga (NDA 202379) for areas of vulnerability that can lead to medication errors. Centocor Ortho Biotech, Inc. submitted the proposed label and labeling on December 20, 2010.

2 METHODS AND MATERIALS

The Division of Medication Error Prevention and Analysis (DMEPA) used Failure Mode and Effects Analysis¹ (FMEA) and lessons learned from postmarketing experience to evaluate the proposed container labels and insert labeling for their vulnerability to contribute to medication errors (see Appendix A, no image of insert labeling).

3 RECOMMENDATIONS

Our evaluation identified areas of needed improvement in order to minimize the potential for medication errors for this product. We provide recommendations to the insert labeling in label in Section 3.1, *Comments to the Division* and Section 3.2, *Comments to the Applicant*, provides recommendations to the container label.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have any questions or need clarification, contact Sarah Simon, OSE Project Manager, at 301-796-5205.

3.1 COMMENTS TO THE DIVISION

We provide the following recommendations to the insert labeling to emphasize Zytiga dose instructions with regard to food, improve readability, and remove error-prone symbols within the dose modification section.

A. Full Prescribing Information, Section 2.1 - Recommended Dosage

Highlights of Prescribing Information

Revise the dosing instructions, (b) (4) to read as follows:

The recommended dosage of Zytiga is 1 g (four 250 mg tablets) as a single daily dose that must be taken on an empty stomach.

Please note the change from, (b) (4), *be taken on an empty stomach*. We request this change to a positive statement to prevent misinterpretation.

B. Full Prescribing Information, Section 2.2 - Dose Modification Guidelines

1. Add the statement, *Zytiga must be taken on an empty stomach*, directly following the each dose recommendation.

¹ Institute for Healthcare Improvement (IHI). Failure Mode and Effects Analysis. Boston. IHI:2004.

2. Revise the symbols, > and <, to read, *greater than* or *less than*. These symbols are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations² and have been misinterpreted as opposite of their intended meaning.
3. Separate the sequential steps in hepatotoxicity dose modification by creating separate paragraphs to improve readability.

C. Full Prescribing Information, Section 17 – Patient Counseling Information

Revise the statement, [REDACTED] (b) (4)

[REDACTED] (b) (4)

Patients should be informed that Zytiga must be taken on an empty stomach.

Please note the change from, [REDACTED] (b) (4) to, *be taken on an empty stomach*. We request change to a positive statement to prevent misinterpretation.

3.2 COMMENTS TO THE APPLICANT

A. Container Label, 250 mg

1. Decrease the prominence of the graphic located on the left-side of the proprietary name.
2. Delete the box surrounding the proprietary name.
3. Ensure the established name is at least ½ size of proprietary name and has a commensurate prominence with proprietary name, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. See 21 CFR 201.10(g)(2).
4. Relocate the dosage form, tablets, to follow directly after the established name, abiraterone acetate. The presentation of the proprietary and established name and the strength should read:

Zytiga

(Abiraterone Acetate) Tablets

250 mg

5. Revise the dosage form, tablets, to match the font and weight of the established name.
6. Increase the prominence of the product strength, *250 mg*.
7. Revise the statement, Dosage: See accompanying product literature, to read:
Usual Dosage: See package insert for dosing information.
8. Add a warning statement consistent with the handling instructions located in Section 16 - How Supplied /Storage and Handling of the insert label that provides warning and instruction for women that may handle Zytiga. Adding this warning to the container label may reduce the exposure of Zytiga to pregnant women.

² <http://www.ismp.org/Tools/errorproneabbreviations.pdf>, Last accessed 4/04/2011

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

/s/

JIBRIL ABDUS-SAMAD
04/13/2011

CAROL A HOLQUIST
04/13/2011

**Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review**

IND or NDA	NDA 202379
Brand Name	Zytiga
Generic Name	Abiraterone Acetate
Sponsor	Centocor Ortho Biotech, Inc.
Indication	Treatment of Prostate Cancer
Dosage Form	Tablet
Drug Class	Androgen biosynthesis inhibitor
Therapeutic Dosing Regimen	1 g (4 x 250 mg) abiraterone acetate p.o. q.d.
Duration of Therapeutic Use	Till disease progression or DLT
Maximum Tolerated Dose	Maximum tolerated dose was not reached. Maximum studied dose was 2 g p.o. q.d.
Submission Number and Date	SDN 001
Review Division	DDOP / HFD 150

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No large changes in QTc interval (i.e., >20 ms) was detected in the trial following the treatment of abiraterone acetate (1 g p.o. q.d.) in combination with prednisone (5 mg p.o. b.i.d) up to Day 2 Cycle 2. The largest upper bound of the 2-sided 90% confidence interval (CI) for the mean change from baseline was 4.2 ms, observed at 0.5 hours post-dose on Day 1 Cycle 1. In addition, no significant concentration-QT relationship was detected using the pooled data from multiple treatment cycles.

In this multi-center, open-label, single-arm study, 33 evaluable patients with metastatic castration resistant prostate cancer (CRPC) received abiraterone acetate 1 g once daily in combination with 5 mg prednisone 5 mg twice daily for multiple cycles. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bound for Abiraterone Acetate (1g p.o. q.d.) In Combination with Prednisone (5 mg p.o. b.i.d) (FDA Analysis)

Treatment	Cycle	Day	Time (h)	Δ QTcI (ms)	90% CI (ms)
Abiraterone Acetate 1 g p.o. q.d.	1	1	0.5	1.3	(-1.5, 4.2)
Abiraterone Acetate 1 g p.o. q.d.	2	1	1	-2.9	(-6.8, 1.1)

The dose tested in the trial represents the anticipated therapeutic exposure. Abiraterone exposure is remarkably increased under the following two scenarios: 1.) low- or high-fat meal increases abiraterone exposure by 7- or 17-fold respectively, and 2.) about 2.6-fold increase in abiraterone exposure is observed in patients with moderate hepatic impairment. Per the current package insert, abiraterone must not be taken with food. In addition, the drug is contraindicated in patients with moderate to severe hepatic impairment. Therefore, the tested exposure appears to be adequate.

2 PROPOSED LABEL

2.1

(b) (4)

(b) (4)

2.2 QT-IRT RECOMMENDED LABEL

We have the following label recommendations which are suggestions only. We defer the final labeling decisions to the review division.

Section 12.2 Pharmacodynamics:

The effect of abiraterone acetate (1 g p.o. q.d.) in combination with prednisone (5 mg p.o. b.i.d) on QTc interval was evaluated in a multi-center, open-label, single-arm study in 33 evaluable patients with metastatic castration resistant prostate cancer (CRPC) up to Day 2 Cycle 2. No large changes in QTc interval (i.e., >20 ms) from baseline were detected in the trial. However, small increases in QTc interval (i.e., <10 ms) with the use of abiraterone acetate cannot be excluded due to study design limitations.

3 BACKGROUND

3.1 PRODUCT INFORMATION

Abiraterone acetate is converted in vivo to abiraterone, an inhibitor of the enzyme 17 α -hydroxylase/C17, 20-lyase (CYP17). This enzyme is required for androgen biosynthesis and is expressed in testicular, adrenal and prostatic tumor tissues. CYP 17 catalyzes the conversion of pregnenolone and progesterone into the testosterone precursors, DHEA and androstenedione, respectively.

The sponsor has submitted this NDA to support the use of abiraterone acetate with prednisone or prednisolone for the treatment of metastatic (b) (4) (b) (4) (b) (4) (castration resistant prostate cancer- CRPC) in adult patients who have received prior chemotherapy containing a (b) (4)

The recommended dose for the indication is 1 g (four 250-mg tablets) orally as a single daily dose that **must not be taken with food.**

3.2 MARKET APPROVAL STATUS

Abiraterone acetate is not approved for marketing in any country

Best Available Copy

3.3 PRECLINICAL INFORMATION

Source: Pharmacology tabulated Summary, eCTD module 2.6.3

Organ Systems Evaluated	Species/Strain Sex/No. Per Group	Route* (Vehicle/Formulation)	Doses* [mg/kg]	Noteworthy Findings	Testing Facility	GLP Compliance	Study No./ Location in CTD	
Cardiovascular	HEK293 cells n = 3 for compound	In Vitro (1% BSA)	ABT: 10 and 27 µM AA: 1.1, 3, 10 and 27 µM	ABT inhibited the hERG potassium current at 10 and 27 µM by 2% and 6%, respectively. IC50 ABT could not be determined due to the modest level of inhibition observed at highest concentration (close to limits of solubility). AA inhibited the hERG potassium current at 1.3, 3, 10 and 27 µM by 2, 10, 38 and 84%, respectively. Inhibition with vehicle alone = 0.3% ± 0.1%, inhibition cisapride (90 nM) = 92% ± 0.2%. IC50 for the inhibitory effect of AA on hERG potassium current was 12.2 µM (Hill coefficient = 2.0).	(b) (4)	(b) (4)	Yes	(b) (4)

* Single dose unless specified otherwise
AA = abiraterone acetate; ABT = abiraterone; BSA = bovine serum albumin; hERG = human ether-a-go-go related gene; HEK = human embryonic kidney; M = male

Organ Systems Evaluated	Species/Strain Sex/No. Per Group	Route* (Vehicle/Formulation)	Doses* [mg/kg]	Noteworthy Findings	Testing Facility	GLP Compliance	Study No./ Location in CTD
Cardiovascular	Cynomolgus Monkey (M) n = 4 (Latin square Crossover design) per group	Oral, gavage (Solution, Methocel A4M (0.5% w/v), Tween 80 (0.1% w/v) and NaCl (0.9% w/v) in deionized water)	0 (vehicle), 250, 750, 2,000	The administration of AA at dose levels up to 2,000 mg/kg had no effect on the hemodynamic and the electrocardiographic intervals (RR, PR, QRS, QT and QTc) in male cynomolgus monkeys following a 24-hour monitoring period. In addition, no overt arrhythmias/abnormalities were found on inspection of the ECG tracings over the 24 h recording period.	(b) (4)	Yes	(b) (4) # 692409/4.2.1.3.

* Single dose unless specified otherwise
AA = abiraterone acetate; ABT = abiraterone; M = male

3.4 PREVIOUS CLINICAL EXPERIENCE

Source: Summary of Clinical Safety, eCTD 2.7.4

The integrated safety population consists of 1,070 subjects with CRPC who were treated with abiraterone acetate 1 g administered as a continuous daily dose with or without prednisone 5 mg twice daily and 394 subjects treated with placebo and prednisone, totaling 1,464 subjects.

Consistent with the pharmacologic mechanism of action of abiraterone, mineralocorticoid-related toxicities such as hypokalemia (35%), edema peripheral (28%), and hypertension (22%) were reported in the early stage Phase 1/2 studies. Uniform administration of prednisone in Study COU-AA-301 decreased the incidence and severity of these AEs compared with some of the early stage studies, which did not include the uniform administration of low-dose glucocorticosteroids. However, the incidence of these AEs was higher in the Study COU-AA-301 abiraterone acetate group compared with the placebo group: hypokalemia (17% versus 8%), edema peripheral (25% versus 17%), and hypertension (9% versus 7%). The deaths due to cardiac disorders are as follows.

Table 13: Treatment-Emergent Adverse Events Leading to Death (Integrated Safety Population)

	Placebo COU-AA-301 (N=394)	AA COU-AA-301 (N=791)	AA Pooled Phase 1/2 (N=279)	Overall AA (N=1070)
MedDRA SOC Term				
MedDRA Preferred Term				

Best Available Copy

Cardiac disorders	5 (1.3%)	9 (1.1%)	3 (1.1%)	12 (1.1%)
Cardio-respiratory arrest	0	5 (0.6%)	0	5 (0.5%)
Myocardial infarction	1 (0.3%)	1 (0.1%)	2 (0.7%)	3 (0.3%)
Cardiac arrest	2 (0.5%)	1 (0.1%)	1 (0.4%)	2 (0.2%)
Arrhythmia	0	1 (0.1%)	0	1 (0.1%)
Cardiac failure congestive	0	1 (0.1%)	0	1 (0.1%)
Cardiac failure	1 (0.3%)	0	0	0
Myocardial ischaemia	1 (0.3%)	0	0	0
Nervous system disorders	1 (0.3%)	1 (0.1%)	0	1 (0.1%)
Haemorrhage intracranial	0	1 (0.1%)	0	1 (0.1%)
Cerebrovascular accident	1 (0.3%)	0	0	0

AA=abiraterone acetate; MedDRA=Medical Dictionary for Regulatory Activities; SOC=System Organ Class

Note: Deaths summarized in this table could have occurred at any time during the study or during survival follow-up, through the clinical cutoff date.

PROD\RE504 [AE16.SAS], 22SEP2010 7:19

Source: Table 13, Summary of Clinical Safety

Cardiac-related SAEs were reported in 3% of subjects in the Study COU-AA-301 abiraterone acetate group, 1% of subjects in the placebo group, and 3% of subjects in the Phase 1/2 studies abiraterone acetate group. Treatment emergent cardiac disorders overall were as follows. The most frequently reported cardiac disorder events were the preferred terms of tachycardia (3% and 2% of subjects in the abiraterone acetate and placebo groups, respectively) and atrial fibrillation (2% and 1%, respectively).

Table 15: Treatment-Emergent Adverse Events of Special Interest (continued)
(Integrated Safety Population)

Adverse Event of Special Interest MedDRA Preferred Term	Placebo	AA	AA Pooled	Overall AA (N=1070)
	COU-AA-301 (N=394)	COU-AA-301 (N=791)	Phase 1/2 (N=279)	
Cardiac Disorders	42 (10.7%)	106 (13.4%)	28 (10.0%)	134 (12.5%)
Atrial fibrillation	5 (1.3%)	17 (2.1%)	5 (1.8%)	22 (2.1%)
Tachycardia	6 (1.5%)	21 (2.7%)	1 (0.4%)	22 (2.1%)
Syncope	6 (1.5%)	8 (1.0%)	5 (1.8%)	13 (1.2%)
Angina pectoris	2 (0.5%)	10 (1.3%)	2 (0.7%)	12 (1.1%)
Arrhythmia	0	9 (1.1%)	1 (0.4%)	10 (0.9%)
Myocardial infarction	3 (0.8%)	6 (0.8%)	4 (1.4%)	10 (0.9%)
Palpitations	3 (0.8%)	7 (0.9%)	3 (1.1%)	10 (0.9%)
Cardiac failure congestive	1 (0.3%)	8 (1.0%)	0	8 (0.7%)
Ejection fraction decreased	0	7 (0.9%)	0	7 (0.7%)
Cardio-respiratory arrest	0	6 (0.8%)	0	6 (0.6%)
Loss of consciousness	1 (0.3%)	5 (0.6%)	0	5 (0.5%)
Pulmonary oedema	0	5 (0.6%)	0	5 (0.5%)
Bradycardia	1 (0.3%)	4 (0.5%)	0	4 (0.4%)
Cardiac failure	2 (0.5%)	3 (0.4%)	0	3 (0.3%)
Heart rate increased	0	3 (0.4%)	0	3 (0.3%)
Supraventricular tachycardia	0	2 (0.3%)	1 (0.4%)	3 (0.3%)
Syncope vasovagal	1 (0.3%)	1 (0.1%)	2 (0.7%)	3 (0.3%)
Acute myocardial infarction	1 (0.3%)	2 (0.3%)	0	2 (0.2%)
Arrhythmia supraventricular	1 (0.3%)	1 (0.1%)	1 (0.4%)	2 (0.2%)
Blood creatine phosphokinase increased	1 (0.3%)	0	2 (0.7%)	2 (0.2%)
Cardiac arrest	2 (0.5%)	1 (0.1%)	1 (0.4%)	2 (0.2%)
Left ventricular dysfunction	1 (0.3%)	1 (0.1%)	1 (0.4%)	2 (0.2%)
Sinus tachycardia	3 (0.8%)	2 (0.3%)	0	2 (0.2%)
Ventricular extrasystoles	0	1 (0.1%)	1 (0.4%)	2 (0.2%)
Ventricular tachycardia	0	1 (0.1%)	1 (0.4%)	2 (0.2%)
Acute pulmonary oedema	0	1 (0.1%)	0	1 (0.1%)
Atrial tachycardia	1 (0.3%)	1 (0.1%)	0	1 (0.1%)
Brain natriuretic peptide increased	0	1 (0.1%)	0	1 (0.1%)
Cardiogenic shock	0	1 (0.1%)	0	1 (0.1%)
Cardiomegaly	0	1 (0.1%)	0	1 (0.1%)
Cor pulmonale	0	1 (0.1%)	0	1 (0.1%)
Coronary artery disease	0	0	1 (0.4%)	1 (0.1%)
Dyspnoea paroxysmal nocturnal	0	1 (0.1%)	0	1 (0.1%)
Extrasystoles	1 (0.3%)	1 (0.1%)	0	1 (0.1%)
Heart rate irregular	0	1 (0.1%)	0	1 (0.1%)
Myocardial ischaemia	1 (0.3%)	1 (0.1%)	0	1 (0.1%)
Orthopnoea	0	0	1 (0.4%)	1 (0.1%)
Sudden death	0	1 (0.1%)	0	1 (0.1%)
Troponin increased	1 (0.3%)	0	1 (0.4%)	1 (0.1%)
Angina unstable	1 (0.3%)	0	0	0
Atrial flutter	1 (0.3%)	0	0	0
Supraventricular extrasystoles	1 (0.3%)	0	0	0
Venous pressure jugular increased	1 (0.3%)	0	0	0

AA=abiraterone acetate; MedDRA=Medical Dictionary for Regulatory Activities; SOC=System Organ Class;
LFT=liver function test
PROD/RE504 [AE13.SAS]. 29OCT2010 7:36

Reviewer's Comment: While cardiac deaths were similar on drug and placebo, cardiac SAEs were more frequent with abiraterone. Consistent with pharmacology, heart failure (congestive heart failure, EF decreased, cardiac failure) was not frequent with abiraterone. Atrial fibrillation was also more frequent (2% vs 1%). AEs linked to QT prolongation (sudden death, cardiac arrest, cardio-respiratory arrest, ventricular tachycardia) were seen in the program. However given the patient population, relationship to study drug will be difficult to assess. Also, arrhythmia secondary to hypokalemia is also possible.

ECG

ECG data were available for some subjects in Studies COU-AA-006, COU-AA-301, COU-AA-004, and COU-AA-002.

COU-AA-002 (Phase 1 study in 33 patients):

One set of three ECGs (triplicate) was acquired at Screening. Additional sets of ECGs were to be taken during Cycle 1 on Day 1 immediately prior to dosing, and at Hours 1, 2, 4, and 6 post-dose. Triplicate ECG collections were also to be performed on day 1 of

Cycles 2, 4, 7, and 10, prior to study regimen dosing (Pre-dose), and at EOS. ECGs were transferred to the central ECG laboratory (b) (4) for analysis. The sponsor reports that no subject developed QTcF prolongation of ≥ 60 ms, and no subject developed a QTcF prolongation of >500 ms during treatment. The changes in mean heart rate, PR interval, and QRS duration were clinically insignificant.

COU-AA-004 (phase 2 study in 58 patients):

12-lead ECGs were performed in triplicate at the same time points as COU-AA-002 and centrally read. The sponsor reports that no patients entered the study with a QTcF interval greater than 500 ms, and no patients experienced a QTcF Interval greater than 500 ms at any time during the study. Additionally, no patients had any instances of QTcF Interval increases equal to or greater than 60 ms.

COU-AA-301 (phase 3 study):

ECGs were collected in Study COU AA-301 for screening purposes and to monitor individual subject safety during the study. A single ECG was recorded per visit. The outlier analysis was as follows. There was a trend for higher number of outliers in the abiraterone group compared to placebo although absolute QTcFs over 500 ms are comparable.

Date: 15OCT2010
 Table TSAF10: QTc Change from Baseline > 30 and > 60 ms
 (Study COU-AA-301: Safety Population)

	AA (N=791)	Placebo (N=394)
Total number subjects with baseline and any postbaseline measurement	654	306
QTcF (ms)		
>30	104 (15.9%)	31 (10.1%)
>60	34 (5.2%)	7 (2.3%)
QTcB (ms)		
>30	122 (18.7%)	38 (12.4%)
>60	39 (6.0%)	9 (2.9%)

Note: Percentages calculated with the number of subjects with baseline and any postbaseline measurement in each group as denominator.
 PRODR456 [TSAF10.SAS], 15OCT2010 16:56

Best Available Copy

Date: 15OCT2010
 TSAF11: Postdose QTc Greater Than 450, 480 and 500 ms
 (Study COU-AA-301: Safety Population)

Best Available
 Copy

QTc Group	AA (N=791)	Placebo (N=394)
Number of subjects with any postdose QTc measure	675	311
QTcF(ms)		
>450	141 (20.9%)	48 (15.4%)
>480	38 (5.6%)	12 (3.9%)
>500	15 (2.2%)	6 (1.9%)
QTcB(ms)		
>450	257 (38.1%)	112 (36%)
>480	86 (12.7%)	32 (10.3%)
>500	32 (4.7%)	10 (3.2%)

Note: Percentages calculated with the number of subjects with any postdose measurement in each group as denominator.
 PROCURE456 [TSAF11.SAS], 15OCT2010 16:24

Source: Attachment 6.21 and 6.2.2, CSR for COU-AA-301

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of abiraterone acetate's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 71023. The sponsor submitted the interim analysis (up to Cycle 2 day 2) of Study COU-AA-006, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A QT/QTc and Multi-Dose PK Study of Abiraterone Acetate (CB7630) Plus Prednisone in Patients with Metastatic Castration-Resistant Prostate Cancer (CRPC)

4.2.2 Protocol Number

Protocol COU-AA-006; Phase 1B

4.2.3 Objectives

Primary Objectives

The primary objective of this study was to evaluate effects of abiraterone acetate plus prednisone on cardiac QT/QTc interval by using pharmacokinetic and time-matched ECGs in subjects with metastatic CRPC.

Secondary Objectives

- To evaluate the pharmacokinetics of abiraterone acetate and abiraterone after multiple doses of abiraterone acetate
- To evaluate the anti-tumor effects of abiraterone acetate plus prednisone
- To evaluate the effects of abiraterone acetate plus prednisone on adrenal function as measured by Cortrosyn stimulation test at baseline and after abiraterone acetate/prednisone administration

4.2.4 Study Description

4.2.4.1 Design

This was a multi-center, open-label, single arm study of abiraterone acetate plus prednisone conducted at 4 investigative sites in approximately 34 subjects with metastatic CRPC who failed gonadotrophin releasing hormone (GnRH) therapy and have a PSA \geq 2 ng/mL, who were medically or surgically castrated, and received no more than 1 course of chemotherapy. The study period consists of the following phases: Screening, Treatment, and Follow-up periods. Subjects were to have Cycle 1 Day -1 procedures and subsequently begin receiving study treatment (daily abiraterone acetate plus twice-daily prednisone) beginning on Cycle 1 Day 1. There was no study Day 0, Day 1 followed immediately after Day -1 and each cycle of treatment was 28 days.

4.2.4.2 Controls

The sponsor did not use either placebo or positive (moxifloxacin) controls in this study.

4.2.4.3 Blinding

The active treatment arm was open-label and unblinded.

4.2.5 Treatment Regimen

4.2.5.1 Treatment Arms

The study included only a single, active treatment arm. Patients (n=34) were instructed to take four 250-mg tablets orally (P.O.) at least 1 hour before a meal or 2 hours after a meal. Patients were also instructed to take 5 mg prednisone, twice daily. If either an abiraterone acetate or prednisone dose was missed, it was omitted and not made up. Subjects were to receive study treatment (abiraterone acetate plus prednisone) until disease progression. Two dose reductions were allowed for use in adverse event management. Subjects who experienced sustained abiraterone or prednisone toxicities such as hypokalemia, hypertension, hyperglycemia, and edema, which did not return to Grade 1 or less (NCICTCAE, Version 3) after being treated, were to have been discontinued from the study.

4.2.5.2 Sponsor's Justification for Doses

“The dose of abiraterone acetate in this study is 1000 mg daily based on results of two Phase I dose-finding studies. In the first Phase I study with capsule formulation (COU-AA-001), abiraterone acetate was evaluated for safety, pharmacokinetics, and its effects on adrenal steroid synthesis at dose levels ranging from 250 mg to 2000

mg. Preliminary analysis showed that abiraterone acetate was well tolerated at all dose levels. Patients have received abiraterone acetate in this study and an extension protocol for up to 30 months.

In the second Phase 1 study (COU-AA-002) that evaluated the safety and tolerability of abiraterone acetate tablet formulation at doses ranging from 250 to 1000 mg, a daily dose of 1000 mg has also been found to have an acceptable safety profile for further development. Data from dose-finding studies indicated that when PK, adrenal CYP17 inhibition, and efficacy signals are taken into consideration, the 1000-mg dose offered consistent pharmacological effects without additional side effects. Therefore, the 1000-mg dose has been chosen for further efficacy and safety evaluation in this Phase IB study and in the ongoing Phase III study COU-AA-301, which is intended to support registration of abiraterone acetate in CRPC.”

Sponsor’s cou-aa-006-report.pdf, page 174-175

Reviewer’s Comment: The dose tested in the trial represents the anticipated therapeutic exposure. Abiraterone exposure is remarkably increased under the following two scenarios: 1.) low- or high-fat meal increases abiraterone exposure by 7- or 17-fold, and 2.) about 2.6-fold increase in abiraterone exposure is observed in patients with moderate hepatic impairment. Per the current package insert, abiraterone must not be taken with food. In addition, the drug is contraindicated in patients with moderate to severe hepatic impairment. Therefore, the tested exposure appears to be adequate.

4.2.5.3 Instructions with Regard to Meals

Subjects were instructed to take four 250 mg tablets of abiraterone acetate p.o. at least 1 h before a meal or 2 h after a meal.

Reviewer’s Comment: Acceptable. Per the current label, abiraterone acetate must not be taken with food.

4.2.5.4 ECG and PK Assessments

ECG Assessments

Serial sets of three time-matched ECGs were obtained on the following schedule (Table 2):

- Cycle 1 Day -1: Pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post-dose. ECG collection using Central Laboratory 12-Lead Holter machine on Cycle 1 Day -1 will be time-matched on the clock (within 30 minutes) to the time the ECGs will be obtained on Cycle 1 Day 1.
- Cycle 1 Day 1: Pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours post-dose. ECGs will be collected using Central Laboratory 12-Lead Holter machine.
- Cycle 2 Day 1: Pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours post-dose. ECGs will be collected using Central Laboratory 12-Lead Holter machine.
- Cycle 4 Day 1: Pre-dose ECGs will be obtained using Central Laboratory surface ECG machine.
- Every 3 cycles on Day 1 after Cycle 4 until Cycle 10 Day 1: Pre-dose ECGs will be obtained using Central Laboratory surface ECG machine
- End of study visit ECGs will be obtained using local site ECG machine

Table 2: ECG Collection Scheme

Visit		ECG Visit 1										
Time		Cycle 1, D -1										
ECG ^c		1 st	2 nd	3 rd	4 th	5 th	6 th	7 th	8 th	9 th	10 th	11 th
Window (Hour) ^{b,e}		0 ^{c,g}	0.5	1	1.5	2	3	4	6	8	12	24 ^h
Visit		ECG Visit 2 ^{a,d}										
Time		Cycle 1, D 1										
ECG		1 st	2 nd	3 rd	4 th	5 th	6 th	7 th	8 th	9 th	10 th	
Window (Hour) ^{b,e}		0 ^{c,g}	0.5	1	1.5	2	3	4	6	8	12	
Visit		ECG Visit 3										
Time		Cycle 1, D 2										
ECG		1 st										
Window (Hour) ^{b,e}		0 ^{g,i}										
Visit		ECG Visit 4 ^a										
Time		Cycle 2, D 1										
ECG		1 st	2 nd	3 rd	4 th	5 th	6 th	7 th	8 th	9 th	10 th	
Window (Hour) ^{b,e}		0 ^{j,g}	0.5	1	1.5	2	3	4	6	8	12	
Visit		ECG Visit 5										
Time		Cycle 2, D 2										
ECG		1 st										
Window (Hour) ^{b,e}		0 ^{g,k}										
Visit		ECG Visit 6										
Time		Cycle 4, D 1										
ECG		1 st										
Window (hr) ^{b,f}		0 ^g										
Visit		ECG visit every 3 cycles after Visit 6 until Cycle 10										
Time		Cycle 7 and 10 D 1										
ECG		1 st										
Window (Hour) ^{b,f}		0 ^g										

Sponsor's cou-aa-006-report.pdf, page 194

Reviewer's Comment: Acceptable. ECGs collected on Day 1 Cycle 2 represents the steady state following multiple doses of abiraterone acetate. However the baseline ECGs were collected prior to the start of Cycle 1 (i.e., about 28 days prior to the ECG assessment day).

PK Assessments

PK blood sampling was drawn over 7 study visits according to the following schedule (Table 3):

- Cycle 1 Day 1: Pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 hours post-dose
- Cycle 1 Day 2: 24 hours after the 1st dose and before the administration of the 2nd dose
- Cycle 1 Day 6: Pre-dose
- Cycle 1 Day 7: Pre-dose

- Cycle 1 Day 8: Pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 hours post-dose
- Cycle 1 Day 9: 24 hours after the 8th dose and before the administration of the 9th dose
- Cycle 2 Day 1: Pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 hours post-dose
- Cycle 2 Day 2: 24 hours after Cycle 2 Day 1 dose and before Cycle 2 Day 2 dose.

Sampling time windows are relative to clinically administered doses and were taken after ECG timepoints, within 5 minutes after corresponding ECG for timepoints within the first hour post-dose, or within 15 minutes for timepoints after the first hour post-dose.

Table 3: PK Sampling Scheme

Visit	PK Visit 1 ^a										
Time	Cycle 1 Day 1										
Sample	1 st	2 nd	3 rd	4 th	5 th	6 th	7 th	8 th	9 th	10 th	11 th
Hour	0 ^{c,g}	0.25	0.5	1	1.5	2	3	4	6	8	12
Visit	PK Visit 2										
Time	Cycle 1 Day 2										
Sample	1 st										
Hour	0 ^{d,f,g}										
Visit	PK Visit 3										
Time	Cycle 1 Day 6										
Sample	1 st										
Hour	0 ^{c,f,g}										
Visit	PK Visit 4										
Time	Cycle 1 Day 7										
Sample	1 st										
Hour	0 ^{c,f,g}										
Visit	PK Visit 5										
Time	Cycle 1 Day 8										
Sample	1 st	2 nd	3 rd	4 th	5 th	6 th	7 th	8 th	9 th	10 th	11 th
Hour	0 ^{c,f,g}	0.25	0.5	1	1.5	2	3	4	6	8	12
Visit	PK Visit 6										
Time	Cycle 1 Day 9										
Sample	1 st										
Hour	0 ^{e,f,g}										
Visit	PK Visit 7										
Time	Cycle 2 Day 1										
Sample	1 st	2 nd	3 rd	4 th	5 th	6 th	7 th	8 th	9 th	10 th	
Hour	0 ^{l,g}	0.5	1	1.5	2	3	4	6	8	12	
Visit	PK Visit 8										
Time	Cycle 2 Day 2										
Sample	1 st										
Hour	0 ^{h,f,g}										

Sponsor's cou-aa-006-report.pdf, page 193

Reviewer's Comment: Acceptable. PK samples collected on Day 1 Cycle 2 represents the steady state concentration. Additional PK samples collected prior to steady state allow us to further explore exposure-response relationship.

4.2.5.5 Baseline

Time-matched baseline from Day -1 was used.

4.2.6 ECG Collection

Patients wore a Mortara H12+ Holter recorder (Mortara Instruments, Milwaukee, WI) during each treatment period. The H12+ continuously recorded the 12-lead ECG on a flashcard. Timing, reviewing, and recording techniques for ECGs were standardized for all subjects.

Flashcards were sent to [REDACTED] ^{(b) (4)} for analysis. Ten-second, 12-lead ECGs were extracted from the continuous recordings at pre-determined time points. The 12-lead ECG extractions were performed in triplicate, within a 5-minute window of the time points specified above.

The ECGs were analyzed by a central core laboratory with a standardized ECG methodology, including a single reader for a given subject, with all ECGs being measured in random order. The over-reading cardiologist was blinded to time and date of recording.

Twelve-lead ECGs were interpreted and annotated by a cardiologist, using the Mortara E-Scribe (Mortara Instruments, Milwaukee, WI) in Global Superimposed Median Beat Mode.

4.2.7 Sponsor's Results

4.2.7.1 Study Subjects

The subject population consisted of 33 males with metastatic CRPC ranging from 42 to 85 years old. These subjects continued to be treated beyond Cycle 2 Day 2 until disease progression.

4.2.7.2 Statistical Analyses

4.2.7.2.1 Primary Analysis

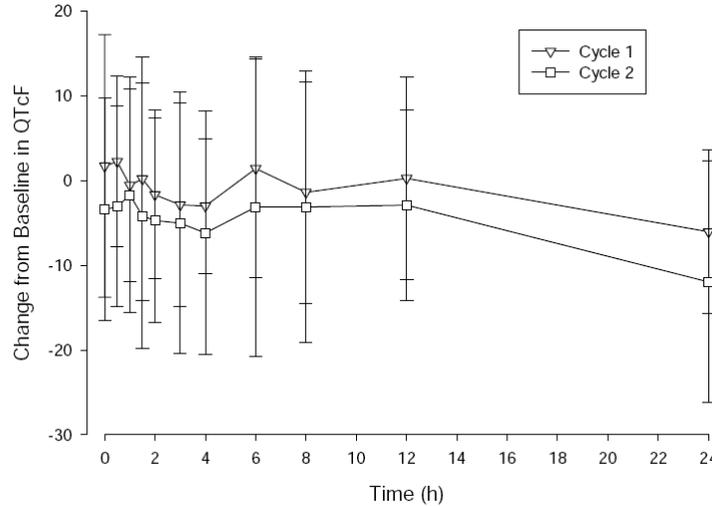
E14 analysis was not conducted as no placebo arm was included in this study. Instead, time-matched change from baseline was evaluated to assess QT prolongation resulting from abiraterone treatment.

The primary endpoint was the Fridericia's corrected QT interval (QTcF). Fridericia's formula performs better with higher heart rates than other formulae. Upon visual inspection, there was a minor difference in the mean QTcF profile when comparing Cycle 1 and Cycle 2. There was no significant difference or notable trend between cycles, considering the wide variability around each mean QTcF value at each time point (Figure 1 and Table 4).

At both Cycles 1 Day 1 and Cycle 2 Day 1, the mean QTcF changes remained stable after initial dosing and after multiple dosing of abiraterone acetate (Figure 1). The mean QTcF change ranged from -3.4 to 2.3 ms on Cycle 1 Day 1 from -10.1 to -1.7 ms on Cycle 2 Day 1 (Table 4). The upper limit of the 90% CI of the mean baseline corrected QTcF

change at each post-dose timepoint was below 10 ms for both Cycle 1 Day 1 (maximum of upper limits = 5.4 ms) and Cycle 2 Day 1 (maximum of upper limits = 2.4 ms).

Figure 1: Mean (\pm SD) Change from Baseline in QTcF-Time Profiles after Once Daily Administration of Abiraterone Acetate to Male Subjects With Metastatic CRPC



Sponsor's cou-aa-006-report.pdf, pg 51

Table 4: Summary Statistics for Changes From Baseline of QTcF Interval

Cycle	Day	Time Point	N	MEAN(SD) msec	MEDIAN msec	MIN:MAX msec	Q1:Q3 msec	90% CI msec
1	1	Pre-dose	31	1.7(15.5)	-0.3	-30.3:45.7	-8.3:8.0	-3.0:6.4
		0.5	32	2.3(10.1)	2.7	-25.3:23.0	-5.2:9.5	-0.8:5.3
		1	32	-0.5(11.4)	-2.0	-18.0:27.7	-9.7:4.8	-4.0:2.9
		1.5	32	0.2(14.3)	-0.3	-23.7:27.7	-10.7:11.3	-4.1:4.5
		2	32	-1.7(10.0)	-2.0	-20.0:19.0	-8.5:5.3	-4.6:1.3
		3	31	-2.9(12.0)	-5.3	-24.3:20.7	-12.7:5.7	-6.5:0.8
		4	31	-3.0(8.0)	-1.0	-20.3:11.7	-7.3:2.3	-5.4:-0.6
		6	31	1.4(13.0)	1.0	-35.0:21.7	-7.7:14.7	-2.5:5.4
		8	32	-1.4(13.1)	-1.3	-44.0:22.7	-9.3:6.2	-5.3:2.5
		12	31	0.3(11.9)	4.0	-37.7:22.0	-7.0:6.7	-3.4:3.9
		24	28	-6.0(9.7)	-5.2	-37.0:6.7	-8.5:-1.2	-9.1:-2.9
2	1	Pre-dose	29	-3.4(13.2)	-3.3	-38.7:18.3	-13.3:6.7	-7.6:0.8
		0.5	32	-3.1(11.8)	-3.2	-32.0:18.3	-9.7:5.7	-6.6:0.5
		1	33	-1.7(13.9)	0.0	-31.7:20.3	-11.3:9.0	-5.8:2.4
		1.5	33	-4.2(15.6)	-1.0	-37.7:34.0	-13.7:4.0	-8.8:0.4
		2	33	-4.7(12.1)	-3.3	-27.0:19.7	-14.0:4.0	-8.3:-1.1
		3	33	-5.0(15.4)	-2.0	-42.0:19.0	-15.7:7.3	-9.6:-0.5
		4	32	-6.2(14.4)	-5.3	-30.3:28.7	-17.7:3.3	-10.5:-1.9
		6	30	-3.1(17.6)	-6.2	-42.0:27.0	-12.0:9.3	-8.6:2.4
		8	32	-3.1(16.0)	-6.2	-37.0:35.7	-12.5:7.7	-7.9:1.7
		12	33	-2.9(11.2)	-4.7	-21.7:23.3	-9.0:4.3	-6.2:0.4
		24	29	-11.9(14.2)	-12.7	-38.0:21.7	-20.7:-3.7	-16.4:-7.4

Sponsor's cou-aa-006-report.pdf, pg 52

Reviewer's Comments: Fridericia's correction method resulted in an under-correction of the heart rate effect on QT interval was inappropriate for this analysis. Instead, the reviewer presents the results based on an individual heart rate correction method (QTcI) in the subsequent analysis. No changes in heart rate on Day 1 Cycle 1 or Day 1 Cycle 2 were observed following treatment with 1 g abiraterone acetate p.o. q.d.

The mean and 90% confidence intervals reported by the sponsor were obtained using Fridericia's correction method. The reviewer will not reproduce these tables as Fridericia's correction method was not the ideal correction method for eliminating bias between QT interval and heart rate.

Based on both QTcF and QTcI, no large changes in QTc interval were observed in the trial.

4.2.7.2.2 Categorical Analysis

The QTcF was considered prolonged if one of the three criteria below occurred:

- an increase in QTcF of greater than 30 ms but less than 60 ms from baseline
- an increase of 60 ms or greater from baseline
- an increase to over 500 ms in QTcF intervals

QTcF were categorized by timepoint as:

- 450 ms or less
- greater than 450 ms, but less than or equal to 480 ms
- greater than 480 ms, but less than or equal to 500 ms
- greater than 500 ms

There were 33 subjects evaluable for ECG analysis on Cycle 1 Day -1 and Cycle 2 Day 1. On Cycle 1 Day 1, only 32 subjects were included in the analysis as Subject 163-100 had all ECG timepoints missing for that period due to an unconnected Holter monitor. Only 2 subjects (Subjects 299-300 and 299-304) in this study had a postdose QTcF value > 450 ms while they did not have any such a value at predose. The QTcF changes for these 2 subjects were less than 30 ms. All other subjects who had a postdose QTcF value > 450 ms also had a predose QTcF value >450 ms, which implies that they had a high value coming into the study and the study drug did not contribute to their high QTcF value. Some of the subjects who had a QTcF >450 ms value did not have any postdose QTcF value >450 ms. The number and percentage of subjects with at least 1 QTcF value >450 ms were 9 (28.2%) and 7 (21.2%) on Cycle 1 Day 1 and Cycle 2 Day 1 respectively compared to 11 (33.3%) on baseline. No subjects had at any instances a QTcF of greater than 480 or 500 ms. The overall number and percentage of subjects by QTcF measurement category are shown in Table 5.

Table 5: Overall Number and Percentage of Subjects by QTcF Measurement Category

CATEGORY	Cycle					
	1				2	
	Day				Day	
	-1		1		1	
	N	(%)	N	(%)	N	(%)
<= 450 msec	22	66.7	23	71.9	26	78.8
> 450 TO <= 480 msec	11	33.3	9	28.1	7	21.2
> 480 TO <= 500 msec	0	0.0	0	0.0	0	0.0
> 500 msec	0	0.0	0	0.0	0	0.0

Sponsor's cou-aa-006-report.pdf, pg 53

Two subjects (Subjects 112-009 and 163-106; 6.5%) had QTcF changes equal to or greater than 30 ms but less than 60 ms at Cycle 1 Day 1 Pre-dose (prior to any abiraterone acetate dosing) and did not have any cardiovascular related adverse events. Two subjects (Subjects 299-307 and 299-308; 6.1%) had QTcF changes greater than or equal to 30 ms, but less than 60 msec on Cycle 2 Day 1. No subject had a change in QTcF of greater than 60 ms at any time point during this report period (Table 6).

Table 6: Overall Number and Percentage of Subjects Experiencing a Change in QTcF Categories From Baseline

CATEGORY	GROUP					
	C1D1PRE		C1D1POS		C2D1	
	N	(%)	N	(%)	N	(%)
< 0 msec	17	54.8	1	3.1	4	12.1
>= 0 TO < 30 msec	12	38.7	31	96.9	27	81.8
>= 30 TO < 60 msec	2	6.5	0	0	2	6.1
>= 60 msec	0	0	0	0	0	0

Sponsor's cou-aa-006-report.pdf, pg 53

4.2.7.2.3 Additional Analyses

QRS Duration

The QRS duration was stable after abiraterone acetate administration. The largest postdose mean increase was 1.0 ms (SD of 4.8) occurred at Cycle 2 Day 1 hour 0.5, and the largest post-dose decrease was -1.8 ms (SD of 4.2) at Cycle 1 Day 1 hour 1.5.

The QRS duration for this study was considered normal (NML) if it was measured at 100 ms or less. However, for a QRS reading to be considered APCS, the reading had to increase from baseline by 10% or more and have an absolute value greater than 120 ms, as defined in the SAP. This combination did not occur in any of the subjects.

There were 14 subjects who had QRS readings that exceeded 100 ms at various time points during the study. Thirteen of the 14 subjects with a QRS duration greater than 100 ms displayed these QRS readings during both baseline and post-baseline extractions.

4.2.7.3 Safety Analysis

At the time of interim analysis data cutoff (Cycle 2 Day 2), no Grade 4 adverse events, serious TEAEs, TEAE leading to discontinuation, or deaths were reported. Five (15%) subjects had a TEAE of interest. They included: LFT abnormalities (4 subjects; 12%), hypokalemia (2 subjects; 6%), and fluid retention/edema (1 subject; 3%).

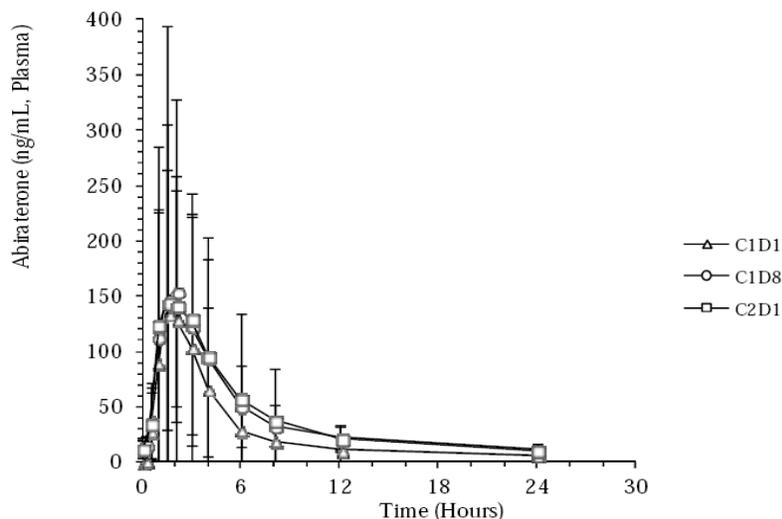
4.2.7.4 Clinical Pharmacology

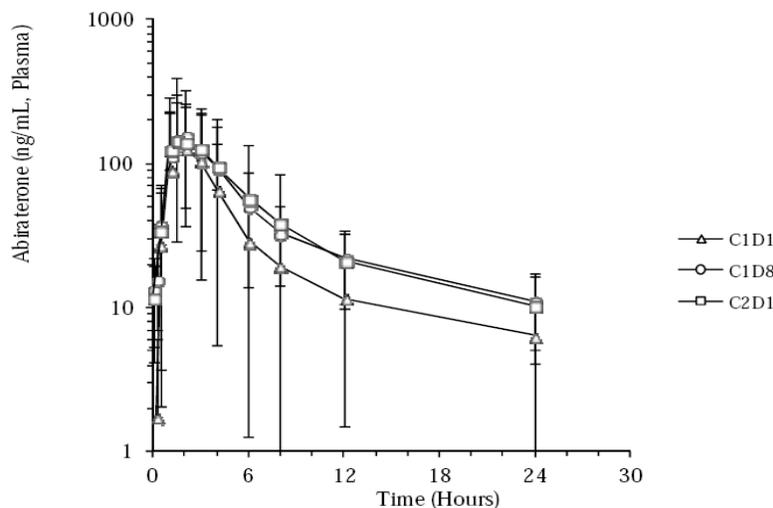
4.2.7.4.1 Pharmacokinetic Analysis

The mean (\pm SD) plasma concentration-time profiles for abiraterone after a single administration and after daily administration of 1000 mg abiraterone acetate to fasting subjects with metastatic CRPC are shown in Figure 2. Peak abiraterone concentrations were reached at approximately the same time after a single (Cycle 1 Day 1) and multiple doses (Cycle 1 Day 8 and Cycle 2 Day 1) of abiraterone acetate with median t_{max} occurring at approximately 2 h after administration. Plasma abiraterone concentrations declined in a biphasic manner. After a single dose of abiraterone acetate systemic exposure, as assessed by C_{max} and AUC_{24h} , was 182 ng/mL and at 675 ng*h/mL, respectively (Table 7).

Systemic exposure values were comparable after multiple dosing on Cycle 1 Day 8 and Cycle 2 Day 1. Mean C_{max} values of 207 ng/mL and 226 ng/mL were observed on Cycle 1 Day 8 and Cycle 2 Day 1, respectively. Mean AUC_{24h} values were estimated at 965 ng*h/mL and 993 ng*h/mL on Cycle 1 Day 8 and Cycle 2 Day 1, respectively. Mean accumulation ratios (AR) after multiple dosing were on the order of 1.8 and 2.0 for C_{max} and AUC_{24h} were 1.8 and 2.0, respectively, on Cycle 1 Day 8. The ARs remained consistent since AR was similar on Cycle 1 Day 8 and Cycle 2 Day 1, 2.0 and 2.2, respectively.

Figure 2: Mean (\pm SD) Plasma Concentration-Time Profiles of Abiraterone After a Single Administration and After Once Daily Administration of Abiraterone Acetate to Male Subjects With Metastatic CRPC





Sponsor's cou-aa-006-report.pdf, pg 48

Table 7: Mean (\pm SD) Pharmacokinetic Parameters for Abiraterone After Once Daily Administration of Abiraterone Acetate to Male Subjects With Metastatic CRPC

Parameter	unit	Cycle 1 Day 1 (N=33)	Cycle 1 Day 8 (N=33)	Cycle 2 Day 1 (N=33)
C_{max}	ng/mL	182 (254)	207 (142)	226 (178)
t_{max}	h	2 (1-4)	2 (1-4)	2 (1-6)
AUC_{24h}	ng*h/mL	675 (725)	965 (520)	993 (639)
AR C_{max}		---	1.8 (1.8)	2.0 (2.4)
AR AUC		---	2.0 (1.5)	2.2 (2.3)

AR = C1D8/C1D1 and C2D1/C1D1. Mean of the individual subject ARs.

Median (Min-Max) reported for t_{max}

Sponsor's cou-aa-006-report.pdf, pg 49

As most of the plasma concentrations for abiraterone acetate were below the level of quantification (BLQ), pharmacokinetic analysis was not performed for abiraterone acetate.

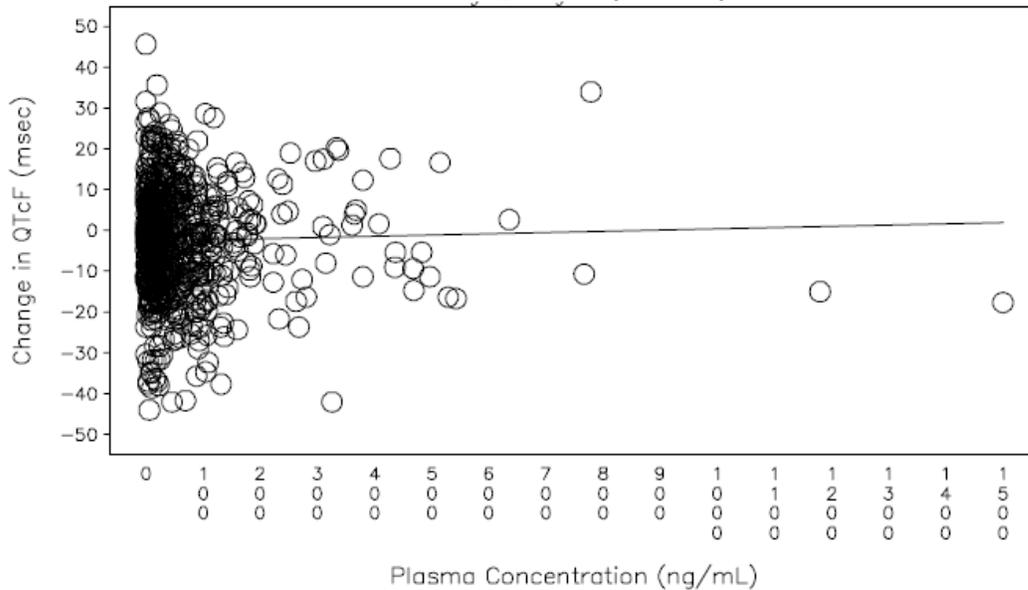
Reviewer's comment: It was appropriate not to include an analysis of abiraterone acetate due to most exposures being below the level of quantification. However, Table 7 demonstrates that higher abiraterone exposures were obtained as Cycle 1 progressed. Assessment of QT prolongation based on Cycle 1 Day 1 exposure may under predict QT prolongation at steady state, and the reviewer, instead focuses on QTcI change from baseline from Day 1 Cycle 2 in the Δ QTcI versus time analysis.

4.2.7.4.2 Exposure-Response Analysis

All available abiraterone concentrations on Cycle 1 Day1 and Cycle 2 Day 1 were included in the pharmacokinetic-pharmacodynamic analyses. The relationship between QTcF and the corresponding abiraterone concentrations were evaluated by applying a linear mixed effects model. The expected changes from baseline in the QTcF intervals (and corresponding 95% confidence intervals) were also presented.

The individual change from baseline in QTcF interval and corresponding abiraterone plasma concentrations exhibited no apparent relationship as shown in Figure 3. The statistical analysis results (Table 8) indicate no significant correlations between the change in QTcF from baseline and plasma concentration (estimated slope was 0.0031 with the associated 90% CI [-0.0040, 0.0102], that includes 0). Similar observation was made upon further examination of individual peak concentrations (C_{max}) and the corresponding change from baseline in QTcF at individual T_{max} by applying a similar model (not shown).

Figure 3: Scatter Plot of Plasma Concentration of Abiraterone versus Change From Baseline in QTcF Day 1 of Cycles 1 and 2



The reference line was based on a linear mixed effects model with Intercept=-2.7015 (p-value=0.0214) and Slope=0.0031 (p-value=0.4737).

Sponsor's cou-aa-006-report.pdf, pg 58

Table 8: Relation between QTc and Plasma Concentration of Abiraterone (Linear Mixed Effects Model) Cycle 1 Day 1 and Cycle 2 Day 1

Dataset	Correction	Estimated Slope	SE of the Estimated Slope	90% CI
All concentration data	Change in QTcF (msecs)	0.0031	0.0043	(-0.0040, 0.0102)
C_{max}	Change in QTcF (msecs)	0.0036	0.0071	(-0.0084, 0.0156)

Sponsor's cou-aa-006-report.pdf, pg 59

The predicted values of mean change from baseline in QTcF at mean C_{max} and the associated 90% CI (Table 9) further confirms the above finding.

Table 9: Predicted Value of the Change in Baseline in QTcF Intervals (Linear Mixed Effects Model) (Cycles 1 & 2)

Correction Methods	C _{max} (ng/mL)	Estimated Change from Baseline (msecs)	Standard Error	90% CI
QTcF	204.1	-1.99	1.915	(-5.2387, 1.2542)

Sponsor's cou-aa-006-report.pdf, pg 59

Reviewer's Analysis: The sponsor plot of Δ QTcF versus abiraterone concentration shows a trend on increasing QT prolongation with increasing concentration; however, the estimated slope was not significant. This result indicates that at typical abiraterone concentrations at 1 g p.o. q.d. substantial QT prolongation is not observed, which is confirmed by the reviewer's analysis below. The sponsor only provided predictions for the high exposure scenario at the observed C_{max} and should have included a discussion on potential QT prolongation for patients with moderate hepatic impairment or patients that take abiraterone concomitantly with food. These scenarios will also be explored in the reviewer's analysis below.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and reviewer derived QTcI). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

We used the mixed model of the pooled post-dose data of QTcF and QTcI distinguished by an indicator of correction method to evaluate the linear relationships between different correction methods and RR. The model included RR, correction type (QTcF or QTcI), and the interaction term of RR and correction type. The slopes of QTcF, and QTcI versus RR are compared in magnitude as well as statistical significance in difference. As shown in Table 10, it appears that QTcI had smaller absolute slopes than QTcF. Therefore, QTcI is a better correction method for the study data.

Table 10: Comparison of QTcF and QTcI Using the Mixed Model

Treatment Groups	Slope of QTcF (p-value)	Slope of QTcI (p-value)
Abiraterone 1 g p.o. q.d.	0.0339 (p<0.0001)	-0.0007 (p=0.206)

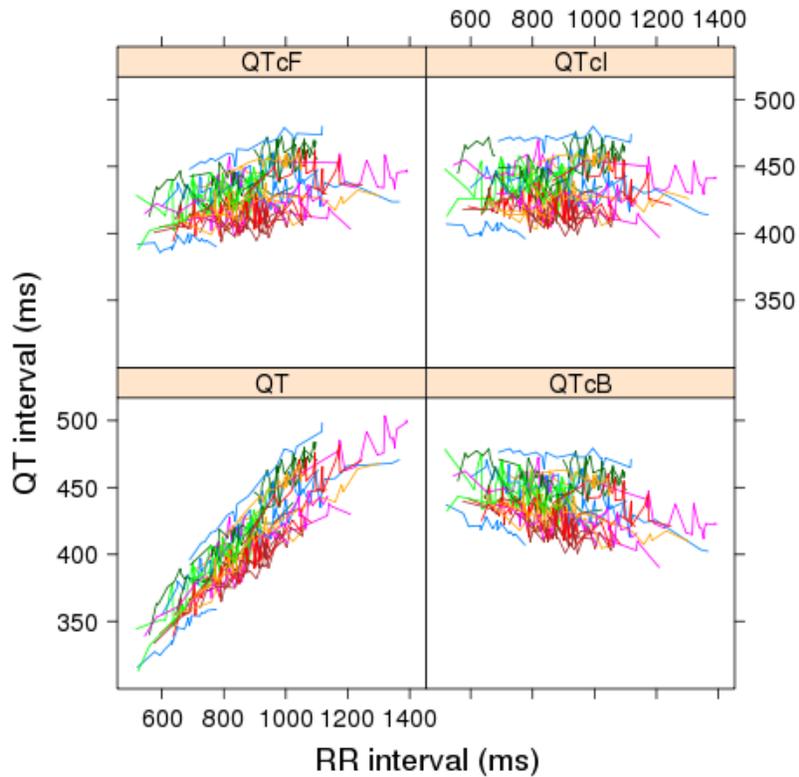
We also confirmed this conclusion by using the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR. The smaller this value is, the better the correction. Based on the results listed in Table 11, it also appears that QTcI is the best correction method. Therefore, this statistical reviewer used QTcI for the primary statistical analysis. This is not consistent with the sponsor's choice of QTcF for their primary analysis; however, QTcI was not explored during the sponsor's analysis.

Table 11: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

Treatment Group	QTcF		QTcI	
	N	MSSS	N	MSSS
Abiraterone 1 g p.o. q.d.	33	0.0017	33	0.0002

The relationship between different correction methods and RR is presented in Figure 4.

Figure 4: QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line)



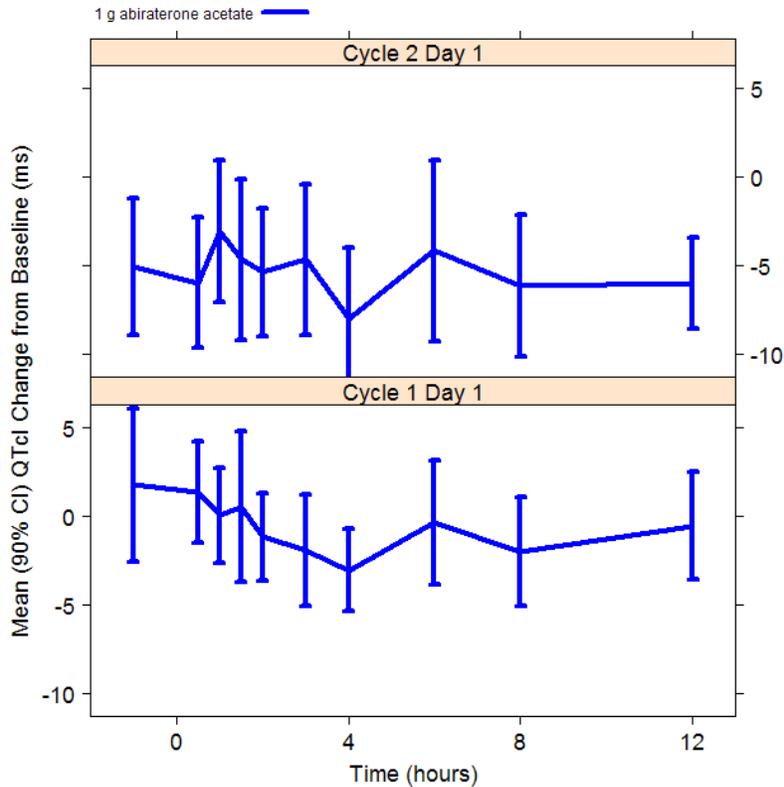
5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 Graph of Δ QTcI Over Time

Figure 5 displays the time profile of Δ QTcI for abiraterone 1 g p.o. q.d. on Day 1 of Cycle 1 (bottom) and Cycle 2 (top).

Figure 5: Mean and 90% CI Δ QTcI Timecourse for Abiraterone 1 g p.o. q.d. on Cycle 1 Day 1 (Bottom) and Cycle 2 Day 2 (Top)



The mean Δ QTcI for Day 1 of Cycle 1 and Cycle 2 are summarized in Table 12. The largest upper bound of the 2-sided 90% confidence interval (CI) for the mean change from baseline at steady state (Day 1 Cycle 2) was 1.1 ms at 6 h. Maximum mean change on Cycle 1 Day 1 ranged between -4.3 and 2.2 ms compared to -10.9 and -2.9 ms on Cycle 2 Day 1. The values are similar to those obtained by the sponsor (Table 4).

Table 12: Mean and 90% CI of Δ QTcI

Time (h)	Cycle	Day	N	Δ QTcI	Lower 90% CI	Upper 90% CI
-1	1	1	31	2.16	-2.18	6.50
0.5	1	1	32	1.34	-1.51	4.20
1	1	1	32	0.16	-2.45	2.76
1.5	1	1	32	0.59	-3.52	4.71
2	1	1	32	-1.03	-3.56	1.50
3	1	1	31	-1.94	-5.08	1.21
4	1	1	31	-3.00	-5.32	-0.68
6	1	1	31	-0.16	-3.50	3.18
8	1	1	32	-1.63	-4.79	1.54
12	1	1	31	-0.52	-3.63	2.60

24	1	1	28	-4.25	-7.00	-1.50
-1	2	1	29	-4.79	-8.82	-0.77
0.5	2	1	32	-6.00	-9.67	-2.33
1	2	1	33	-2.85	-6.84	1.14
1.5	2	1	33	-4.39	-8.79	0.00
2	2	1	33	-5.21	-8.87	-1.55
3	2	1	33	-4.64	-8.92	-0.35
4	2	1	32	-7.84	-11.73	-3.96
6	2	1	30	-3.93	-9.00	1.14
8	2	1	32	-5.69	-9.80	-1.57
12	2	1	33	-5.76	-8.47	-3.04
24	2	1	29	-10.93	-14.97	-6.89

5.2.1.2 Categorical Analysis

Table 13 lists the number of subjects as well as the number of observations whose QTcI values are ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcI was above 480 ms.

Table 13: Categorical Analysis for QTcI

Treatment Group	Total N		Value \leq 450 ms		450 ms<Value \leq 480 ms	
	# Subj.	# Obs.	# Subj. (%)	# Obs. (%)	# Subj. (%)	# Obs. (%)
Abiraterone 1 g p.o. q.d.	33	966	15 (45.5%)	749 (77.5%)	18 (54.5%)	217 (22.5%)

Table 14 lists the categorical analysis results for Δ QTcI. No subject's change from baseline was above 60 ms.

Table 14: Categorical Analysis of Δ QTcI

Treatment Group	Total N		Value \leq 30 ms		30 ms<Value \leq 60 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Abiraterone 1 g p.o. q.d.	33	964	31 (93.9%)	962 (99.8%)	2 (6.15)	2 (0.2%)

5.2.2 PR Analysis

The outlier analysis results for PR showing absolute values (average of replicates) of the subject with baseline or post-treatment values over 200 ms are presented in Table 15.

Table 15: Categorical Analysis for PR

USUBJID	CY-CLE	DAY	H				H				H6	H8	H12	H24	
			H-1	0.5	H1	1.5	H2	H3	H4	H3					
COU-AA-006029900310	1	-1	218	201	212	214	215	213			188	162	156	200	192
COU-AA-006029900310	1	1	192	188	206	196	202	182		202	189	184	191	206	

COU-AA- 218
 006029900310 2 1 216 232 230 221 228 194 178 208 214 190

5.2.3 QRS Analysis

The outlier analysis results for QRS showing absolute values (average of replicates) of the subjects with baseline or post-treatment values over 100 ms are presented in Table 16.

Table 16: Categorical Analysis for QRS

USUBJID	CYCLE	DAY	H-1	H0.5	H1	H1.5	H2	H3	H4	H6	H8	H12	H24
COU-AA-006011200005	1	-1	100	99	100	97	98	101	98	105	104	99	102
COU-AA-006011200005	1	1	102	99	102	93	97	98	99	102	106	99	105
COU-AA-006011200005	2	1	96	96	95	90	88	92	93	95	90	95	93
COU-AA-006011200011	1	-1	104	105	106	105	111	107	107	106	101	104	105
COU-AA-006011200011	1	1	105	104	107	104	105	107	104	104	102	106	109
COU-AA-006011200011	2	1	104	105	103	104	103	105	104	102	104	104	103
COU-AA-006016300102	1	-1		96	95	97	96	115	107	96	104	96	95
COU-AA-006016300102	1	1	95	93	98	98	97	97	94	98	97	94	
COU-AA-006016300102	2	1	98	97	97	97	98	97	98	98	92	96	
COU-AA-006027700204	1	-1	115	112	111	113	109	117	111	115	111	107	105
COU-AA-006027700204	1	1	105	105	102	105	104	107	111	107	105		
COU-AA-006027700204	2	1	113	113	114	112	110	108	104		110	105	
COU-AA-006029900307	1	-1	130	131	128	130	131	133	132	130	129	130	127
COU-AA-006029900307	1	1	127	131	129	132	136	133	131	129	136	126	130
COU-AA-006029900307	2	1	126	127	128	131	133	129	134	132	135	131	128
COU-AA-006029900310	1	-1	110	106	108	109	111	109	104	107	96	104	103
COU-AA-006029900310	1	1	103	106	105	104	103	100	104	108	101	106	108

COU-AA-006029900310	2	1	102	104	106	106	105	106	107	105	103	105	105
---------------------	---	---	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean drug concentration-time profile is illustrated in Figure 2.

The relationship between Δ QTcI and abiraterone concentrations was investigated by linear mixed-effects modeling. Abiraterone exposure data and QT measurements from Day 1 Cycle 1 and Day 1 Cycle 2 were combined in this analysis.

The following three linear models were considered:

Model 1 is a linear model with an intercept

Model 2 is a linear model with mean intercept fixed to 0 (with variability)

Model 3 is a linear model with no intercept

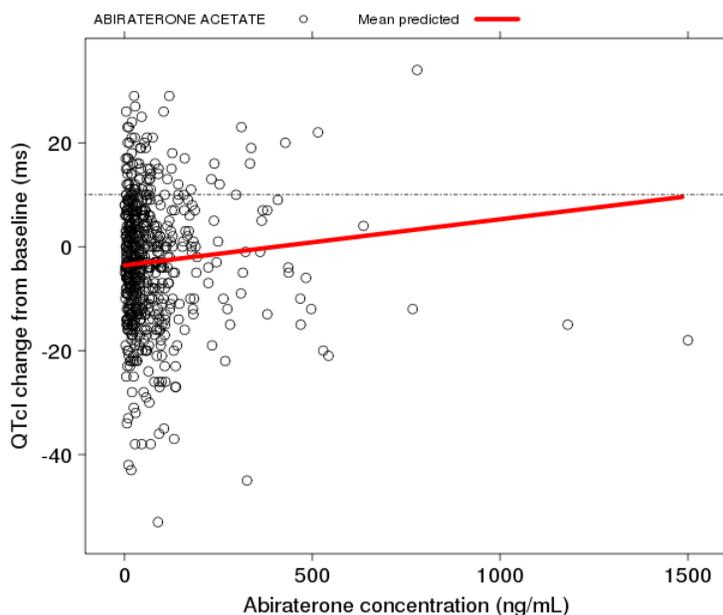
Table 17 summarizes the results of the abiraterone- Δ QTcI analyses. Model 1 was used for further analysis since the model with intercept was found to fit the data best.

Table 17: Exposure-Response Analysis of Abiraterone Associated Δ QTcI Prolongation.

	Parameter	Estimate (90% CI)	p-value	Inter-individual variability
Model 1: Δ QTcI = Intercept + slope * abiraterone Concentration				
	Intercept (ms)	-3.35 (-5.47; -1.23)	0.01	6.3
	Slope (ms per ng/mL)	0.012 (0.001; 0.023)	0.09	0.01
	Residual Variability (ms)	10.46		
Model 2: Δ QTcI = Intercept + slope * abiraterone Concentration (Fixed Intercept)				
	Intercept (ms)	0		7.06
	Slope (ms per ng/mL)	0.0077 (-0.003; 0.019)	0.24	0.01
	Residual Variability (ms)	10.46		
Model 3: Δ OTcI = slope * abiraterone Concentration				
	Slope (ms per ng/mL)	-0.024 (-0.048; -0.001)	0.09	0.07
	Residual Variability (ms)	11.4		

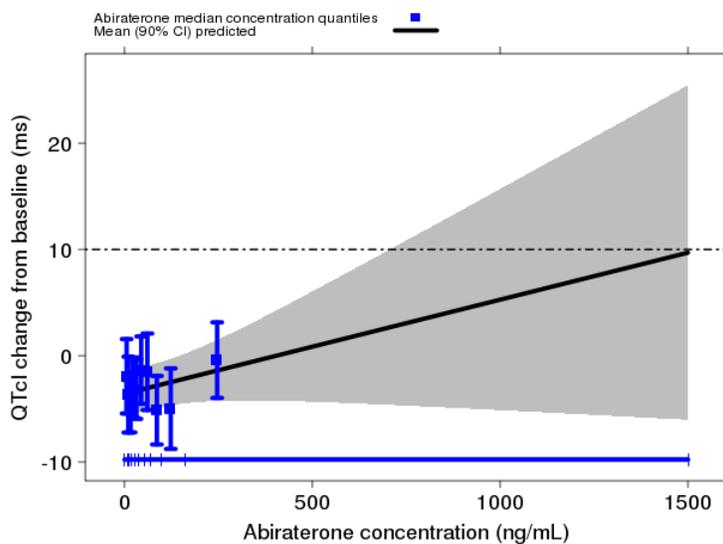
The relationship between Abiraterone concentrations and Δ QTcI is visualized in the Figure 6.

Figure 6: Δ QTcI Versus Abiraterone Concentration



The goodness-of-fit plot in Figure 7 shows the observed median-quantile abiraterone concentrations and associated mean (90% CI) Δ QTcI (90% CI) together with the mean (90% CI) predicted Δ QTcI.

Figure 7: Observed Median-Quantile Abiraterone Concentrations and Associated Mean (90% CI) Δ QTcI (Colored Dots) Together with the Mean (90% CI) Predicted Δ QTcI (Black Line with Shaded Grey Area).



The predicted Δ QTcI at the geometric mean peak abiraterone concentrations can be found in Table 18 and visualized in Figure 8. The abiraterone dose explored in this study

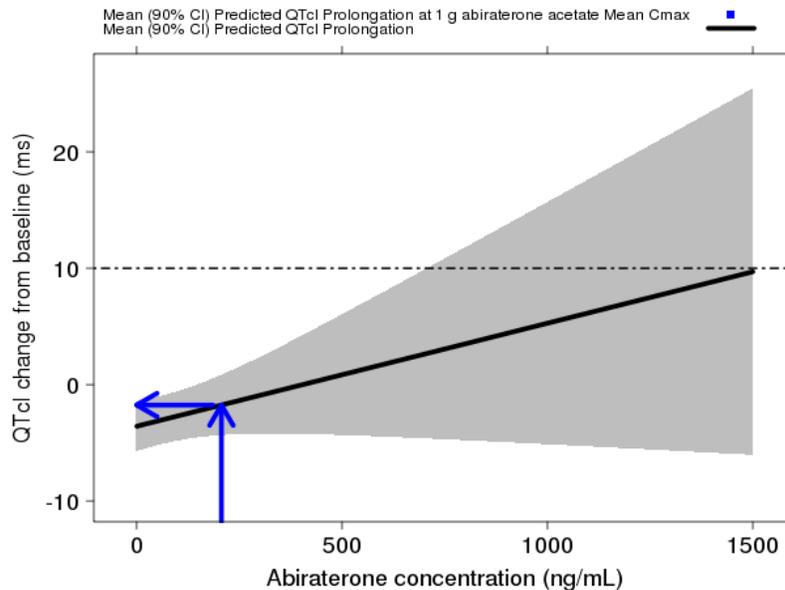
was not sufficient to address QT prolongation for the high exposure scenario of patients taking abiraterone with a low- or high-fat meal (7- and 17-fold increase in C_{max} , respectively), or patients with moderate renal impairment (2.6-fold increase in C_{max}). The sponsor is recommending abiraterone not be taken concomitantly with food; so only the high exposure scenario for patient with moderate hepatic impairment was evaluated. Predicted mean $\Delta QTcI$ for this scenario was 1.1 ms (upper 90% CI: 6.6 ms) and is <10 ms. The prediction should be interpreted with caution as only 1% of observed abiraterone concentrations exceeded 536 ng/mL.

Table 18: Predicted $\Delta QTcI$ Interval at Geometric Mean Peak Abiraterone Concentration Using Model 1

Treatment	C_{max}	$\Delta QTcI$	90% CI
1 g p.o. q.d. abiraterone	206 ng/mL	-1.7	(-4.3; 0.8)
<i>Moderate Hepatic Impairment*</i>	536 ng/mL	1.1	(-4.4; 6.6)

*Predicted $\Delta QTcI$ based on Model 1 and high exposure scenario

Figure 8: Mean (90% CI) Predicted $\Delta QTcI$ at Geometric Mean C_{max}



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms submitted to the ECG warehouse were reviewed. The global superimposed median beat with 12-lead overlay was annotated. According to the Mortara automated algorithm, less than 0.7% of the ECGs had significant QT bias, which is within range of other QT assessments in patients that we have reviewed. Overall, ECG acquisition and interpretation in this study seems acceptable.

5.4.3 PR and QRS Interval

There were no clinically relevant effects on the PR and QRS intervals. Subjects with post-treatment PR over 200 ms or QRS interval over 110 ms had elevated baseline values with changes from baseline much less than 25%.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Highlights of Clinical Pharmacology

Therapeutic Dose	<p>Include maximum proposed clinical dosing regimen. 1 g (4 x 250 mg) abiraterone acetate taken orally, once daily</p>
Maximum Tolerated Dose	<p>Include if studied or NOAEL dose MTD was not reached and no NOAEL was found. 1 g is neither the MTD nor NOAEL dose. MTD has not been established for this compound.</p>
Principal Adverse Events	<p>Include most common adverse events; dose limiting adverse events The principal (most frequent) adverse events observed in subjects with metastatic prostate cancer are related to underlying disease. In pivotal Study COU-AA-301, the most frequently reported AEs were fatigue (44% and 43% in the abiraterone acetate and placebo groups, respectively), back pain (30% and 33%, respectively), nausea (30% and 32%, respectively), and constipation (26% and 31%, respectively) (Table 32 of COU-AA-301 Clinical Study Report). Most of these events were Grade 1 or 2.</p> <p>The most common adverse reactions to AA administration are related to the pharmacologic inhibition of CYP17 activity. The resulting ACTH feedback increases adrenal steroids with mineralocorticoid biological activity upstream of CYP17. Concomitant treatment with prednisone normalizes the level of ACTH and minimizes these effects. Mineralocorticoid adverse events were peripheral edema (25% and 17% in the abiraterone acetate and placebo groups, respectively), hypokalemia (17% and 8%, respectively), and hypertension (9% and 7%, respectively).</p> <p>Urinary tract infection (12% and 7%, respectively), alanine aminotransferase increased (3% and 1%), tachycardia (3% and 2%), atrial fibrillation (2% and 1%), and cardiac failure which also includes congestive heart failure, left ventricular dysfunction and ejection fraction decreased (2% and 1%) were also observed.</p>

	<p>The longer patients are observed, the more adverse events may be observed. In Study COU-AA-301 the median duration of treatment in the abiraterone acetate group was 8 cycles versus 4 cycles in the placebo group. An analysis standardizing for the difference in treatment duration (event rate per 100 patient-years of exposure) reduces the differences between the treatment groups for the events considered adverse reactions.</p> <p>No dose limiting toxicity was defined during development of abiraterone acetate. However, in Study COU-AA-301, the company required one patient to stop abiraterone acetate due to observation of a Grade 4 increase in alanine aminotransferase.</p>	
Maximum Dose Tested	Single Dose	<p>Specify dose</p> <p>1 g abiraterone acetate in healthy subjects</p> <p>2 g in subjects with metastatic castration-resistant prostate cancer (mCRPC) in Study COU-AA-001</p>
	Multiple Dose	<p>Specify dosing interval and duration</p> <p>1 g abiraterone acetate in healthy subjects taken daily</p> <p>2 g in subjects with mCRPC (Study COU-AA-001)</p>
Exposures Achieved at Maximum Tested Dose	Single Dose	<p>Mean (%CV) C_{max} and AUC</p> <p>PK study data is derived after administration of 1-g dose.</p> <p>From Non-Compartmental Analysis (NCA):</p> <p>Healthy Subjects:</p> <p>Pooled (see Module 2.7.2/Table 17): C_{max}= 93.5 (62.7) ng/ml, AUC_{last}= 493 (60.4) ng*h/ml</p> <p>Patients (006):</p> <p>C1D1: C_{max}= 182 (140) ng/ml, AUC_{24h}= 675 (107) ng*h/ml</p> <p>From POP-PK:</p> <p>CL was 33% lower in patients compared to healthy volunteers.</p>
	Multiple Dose	<p>Mean (%CV) C_{max} and AUC</p> <p>Multiple dose was tested only in patients in Study COU-AA-006.</p> <p>From NCA:</p> <p>Patients:</p> <p>C1D8: C_{max}= 207 (68.6) ng/ml, AUC_{24h}= 965 (53.9) ng*h/mL</p> <p>C2D1: C_{max}= 226 (78.8) ng/ml, AUC_{24h}= 993 (64.4) ng*h/mL</p>

Range of Linear PK	<p>Specify dosing regimen</p> <p>Dosing range = 250 mg to 1000 mg (250, 500, 750 & 1000 mg). (Study COU-AA-016)</p>
Accumulation at Steady State	<p>Mean (%CV); specify dosing regimen</p> <p>Multiple dose data is available only in patients (Study COU-AA-006).</p> <p>Mean accumulation ratios for the exposure parameters on Cycle 1 Day 8 (1.8 for C_{max} and 2.0 for AUC_{24h}) and Cycle 2 Day 1 (2.0 for C_{max} and 2.2 for AUC_{24h}) were similar.</p>
Metabolites	<p>Include listing of all metabolites and activity</p> <p>In Vitro</p> <p>In vitro studies have shown that CYP3A4 is involved in the formation of many oxidated and hydroxylated Phase I metabolites of abiraterone. Sulfotransferase (SULT2A1) is involved in the formation of abiraterone sulphate, a major human in vitro and in vivo metabolite. Additionally, Phase II glucuronidated metabolites are formed mainly by UDP-glucuronosyl transferase (UGT) 1A4 and to a lesser extent UGT1A3.</p> <p>In Vivo</p> <p>In man, abiraterone sulphate (M45) and the N-oxide of abiraterone sulphate (M31) are the main metabolites in plasma, each representing approximately 43% of radioactivity (total drug-related material) in human plasma.</p> <p>Abiraterone, abiraterone sulphate and N-oxide abiraterone sulphate were inactive when tested for glucocorticoid receptor binding, estrogen receptor-alpha binding, estrogen receptor-beta binding and androgen receptor binding. N-oxide abiraterone sulphate was inactive in the progesterone receptor binding assay. Abiraterone and abiraterone sulphate showed weak binding activity (IC_{50} = 0.23 and 0.4 μM) to the progesterone receptor (PR). This was 100 times less potent than the control ligand and studies in a cellular PR reporter assay revealed no agonist or antagonist activity (Module 2.6.2/Section 2)</p> <p>Abiraterone sulphate and N-oxide abiraterone sulphate, the two major human metabolites, exhibited weak pharmacological activity (CYP17 inhibition) in human adrenocortical carcinoma cell lines with IC_{50} values ranging from 0.73 to 6.2 μM depending upon the steroid measured. In the same studies, maximal inhibition of androgen biosynthesis was observed at the lowest tested concentration of 3.1 nM of abiraterone. An IC_{50} could not be calculated for androgen biosynthesis, but an IC_{50} of 3.0 nM was observed for inhibition of cortisol biosynthesis (Module 2.6.2/Section 2).</p> <p>The systemic exposure to 9 other quantified metabolites (M23, M38, M61/73, M62, M65, M68, M70, M72 and M74) was similar or up to 4-fold higher than that of abiraterone. (Please see Appendix 1 for structures and pathways.)</p>

Absorption	Absolute/Relative Bioavailability	<p>Mean (%CV)</p> <p>Since no IV formulation is available for abiraterone acetate, the absolute bioavailability could not be determined.</p> <p>In a relative bioavailability study (Study COU-AA-010), systemic exposure to abiraterone was approximately 4.5-fold higher (geometric mean treatment ratios: 4.6 for C_{max} and 4.4 for AUC) following 1 g oral dose administration of abiraterone acetate as an oral liquid olive oil formulation compared with 1 g oral dose administration of abiraterone acetate tablets.</p> <p>From PopPK:</p> <p>The relative bioavailability (F1) of abiraterone was coded into the model relative to the fasted state, for which F1 was assumed to be 1 (100%). When abiraterone acetate is taken together with a low or high fat meal, the predicted relative bioavailability was 3.8 times and 7.6 times higher compared to abiraterone acetate taken under a fasted state, respectively. These model-predicted population relative bioavailability values are lower compared to the observed non-compartmental mean increase in exposure, when abiraterone is taken with a low-fat or high-fat meal compared with a fasted state (factor 4.6 and 9.7, respectively). The reason for this difference could be attributed to the complex absorption process and to that of translating increase in relative bioavailability to increase in total exposure (AUC). However, the patients taking the drug under a modified fasting state showed a rather small increase in bioavailability, 1.14 times higher, compared to the fasted state, suggestive of good adherence to the protocol instructions.</p>
	T _{max}	<ul style="list-style-type: none"> • Median (range) for parent Abiraterone median T_{max} = 2 (1-8) hours for parent. • Median (range) for metabolites For main metabolites M45 and M31, median T_{max} = 4 (3-8) hours.
Distribution	Vd/F or Vd	<p>Mean (%CV)</p> <p>From PopPK:</p> <p>The distribution parameters, namely the central</p>

		<p>volume of distribution (V₂/F) and peripheral distribution volume (V₃/F) were estimated to be 5,630 L and 17,400 L, respectively. The large volumes of distribution could be explained by multiple factors such as the low bioavailability observed, the high fraction bound to plasma proteins (>99%) and presence of other drug targets in the body resulting in extensive tissue distribution.</p> <p>The inter-individual variability (IIV) was not estimable, hence the %CVs are not reported for the volumes of distribution.</p>
	% Bound	<p>Mean (%CV)</p> <p>The protein binding of ¹⁴C-abiraterone in human plasma is 99.8%.</p>
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated <p>Following administration of ¹⁴C-abiraterone acetate as capsules, on average approximately 55% of an orally administered radioactive dose of abiraterone acetate was recovered as the parent drug in feces. Approximately 5% of the dose was recovered in urine, all as secondary metabolites of abiraterone.</p> <ul style="list-style-type: none"> • Other routes
	Terminal t _{1/2}	<ul style="list-style-type: none"> • Mean (%CV) for parent <p>The mean terminal half-life of abiraterone in healthy subjects under fasting conditions was 15.7 hours following administration of 1 g abiraterone acetate administered as four 250 mg tablets. When administered immediately after a meal, the calculated terminal half-life was slightly increased to 17.9 hours (Module 2.7.1\Section 2.3).</p> <ul style="list-style-type: none"> • Mean (%CV) for metabolites
	CL/F or CL	<p>Mean (%CV)</p> <p>From PopPK:</p> <p>2240 L/hr is the typical CL/F for a healthy volunteer. A 33% drop in apparent clearance is estimated for patients with mCRPC resulting in a typical apparent clearance in patient of 1,505 L/hr. Inter-individual variability on CL/F was estimated to be 30% (CV%). Limited shrinkage (9%) in CL/F was observed in the random effects during model development.</p>
Intrinsic Factors	Age	Specify mean changes in C_{max} and AUC

		No formal clinical Phase 1 study evaluated effect of age on abiraterone acetate. In population PK analysis, no statistically significant effect of age on clearance was evident. Abiraterone acetate has not been tested in pediatric indications.
	Sex	Specify mean changes in C_{max} and AUC Abiraterone acetate is intended for use in males with prostate cancer (mCRPC), and clinical studies evaluated PK differences only in males. All clinical study information described in this NDA is derived from male subjects, either healthy volunteers or patients.
	Race	Specify mean changes in C_{max} and AUC The potential effects of race/ethnicity on the PK of abiraterone were not formally investigated. The vast majority of subjects enrolled in the clinical studies were caucasian males for those studies in which race/ethnicity was documented. Given the relative lack of data in other ethnicities, no conclusions could be drawn regarding potential effects of race/ethnicity on the PK of abiraterone. In population PK analysis, no statistically significant effect of race on clearance was evident.
	Hepatic & Renal Impairment	Specify mean changes in C_{max} and AUC Hepatic Impairment: The systemic exposure to abiraterone following a single 1 g dose of abiraterone acetate in the fasting state increased by approximately 260% in subjects without cancer, but with pre-existing moderate hepatic impairment (Child-Pugh Class B) compared with matched healthy control subjects with normal hepatic function. In subjects with mild hepatic impairment (Child-Pugh Class A), no relevant change in systemic exposure to abiraterone was observed. Renal Impairment: The systemic exposure to abiraterone following a single 1 g dose of abiraterone acetate in the fasting state between hemodialysis sessions was not increased in subjects with ESRD on stable hemodialysis compared to matched healthy control subjects.

Extrinsic Factors	Drug Interactions	<p>Include listing of studied DDI studies with mean changes in C_{max} and AUC</p> <p>In Vitro</p> <p>In vitro, abiraterone acetate inhibited P-gp with a 50% inhibitory concentration (IC_{50}) of 10.8 μM, and was a moderate (CYPs 2E1, 2C9, 3A4/5) to potent (CYPs 2C19, 1A2, 2D6) inhibitor effect of several CYP isoforms. The potential for a clinically meaningful drug interaction appears to be unlikely as most plasma concentrations of abiraterone acetate in humans are transient and below the LLOQ of 0.2 ng/mL.</p> <p>In vitro analysis using human liver microsomes showed abiraterone to have no inhibitory effect on CYP2A6 and CYP2E1, a moderate inhibitory effect on CYP2C9, CYP2C19 and CYP3A4/5 ($I/K_i < 0.1$), suggesting that the interaction potential is limited. Abiraterone had a potent inhibitory effect on CYP1A2 and CYP2D6.</p> <p>In Vivo</p> <p>A multiple-dose study was conducted in subjects with mCRPC using dextromethorphan (CYP2D6) and theophylline (CYP1A2) as probe substrates (Study COU-AA-015). The standard dose of 1 g of abiraterone acetate once daily administered in modified-fasted state and 5 mg of prednisone twice daily was used. Mean systemic exposure (AUC) to dextromethorphan, the CYP2D6 probe substrate, was approximately 200% higher when dextromethorphan was co-administered along with abiraterone acetate compared to when dextromethorphan was administered alone. No inhibitory effect was noted for theophylline, the CYP1A2 probe substrate.</p>
	Food Effects	<p>Specify mean changes in C_{max} and AUC and meal type (i.e., high-fat, standard, low-fat)</p> <p>Mean abiraterone C_{max} and AUC values increased by approximately 7- and 5-fold, respectively, when administered with a low-fat meal. Mean abiraterone C_{max} and AUC values increased by approximately 17- and 10-fold, respectively, when administered with a high-fat meal.</p>
Expected High Clinical Exposure	Describe worst case scenario and expected fold-change in C_{max} and AUC. The increase in exposure should be covered by the supra-	

Scenario	<p>therapeutic dose.</p> <p>The expected high risk scenario is a patient taking 1 g daily abiraterone acetate in the presence of high fat food. Three subjects received the supra-therapeutic dose 2 g daily in Study COU-AA-001 without high fat food, and no additional toxicities were observed.</p> <p>Mean abiraterone C_{max} and AUC values increased by approximately 7- and 5-fold, respectively, with low-fat and 17- and 10-fold, respectively, with a high-fat meal.</p> <p>In the popPK model, no food effect was observed, suggesting that patient adherence to the dosing instructions was good.</p> <p>However, to mitigate the risk of a clinical overdose, the proposed label's strict dosing instructions emphasize the need for patients to administer abiraterone acetate without concomitant food.</p>
----------	---

6.2 STUDY ASSESSMENTS

Table of Schedule Events

Evaluation	Treatment Phase												Follow-Up Phase	
	Screening Day -14 to Day -2	Cycle 1 Day -1	Cycle 1 Day 1	Cycle 1 Day 2 and 9	Cycle 1 Day 4 and 7	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 2 Day 2	Cycle 2 and 3 Day 15	Cycle 3, 5, 6, 8, 9, 11, 12 Day 1	Cycle 4, 7, 10 Day 1 and every 3 rd cycle until TX discontinuation ¹	End of Study Treatment Visit ²	Q3 months up to Month 69 ³
Procedures														
Signed consent form ⁴	X													
Medical history, prior prostate therapies	X													
Demographics	X													
Physical exam	X						X	X			X	X	X	
Vital signs ⁵	X	X	X	X	X	X	X	X	X		X	X	X	
ECOG	X	X	X				X	X			X	X	X	
Central Lab ECGs ⁶	X ⁷	X	X					X	X			X	X	
MUGA Scan or Cardiac ECHO ⁸	X												X	
Dosing compliance ¹⁰							X	X			X	X	X	
Concomitant medications	X	X	X				X	X			X	X	X	
Adverse events ⁹		X ¹¹	X				X	X			X	X	X	
Laboratory Assessments														
CBC	X		X					X			X	X	X	
Coagulation Function Tests- PT/PTT (INR)	X												X	
Serum chemistry, electrolytes	X		X				X	X			X	X	X	
Fasting Glucose	X											X	X	
Hemoglobin A1c	X												X	
Serum Lipids	X												X	

Best Available Copy

Table of Schedule Events

Evaluation	Treatment Phase													Follow-Up Phase
	Screening Day -14 to Day -2	Cycle 1 Day -1	Cycle 1 Day 1	Cycle 1 Day 2 and 9	Cycle 1 Day 6 and 7	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 2 Day 1	Cycle 2 Day 2	Cycle 2 and 3 Day 15	Cycle 3, 5, 6, 8, 9, 11, 12 Day 1	Cycle 4, 7, 10 Day 1 and every 3 rd cycle until TX discontinuation ¹	End of Study Treatment Visit ²	Q3 month up to Month 60 ³
Liver Function Tests (AST, ALT, LDH, ALK-P, total Bilirubin)	X									X			X	
PSA ¹⁰	X		X					X			X	X	X	
Serum testosterone	X												X	
Urinalysis (dipstick)	X												X	
Cottroun Stimulation test	X												X ^{11, 18}	
Tumor Assessments														
CT / MRI / other imaging procedure Chest x-ray ^{11, 12}	X											X		
Bone Scan ¹⁷	X											X		
Disease progression assessment												X		
PK Assessments														
Pre-dose PK			X ¹⁴		X	X ¹⁴		X ¹⁴						
0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 hr Post-dose PK			X ¹⁴			X ¹⁴								
1, 2, 4, 6 hr post-dose PK								X ¹⁴						
24 hr post-dose PK				X ¹⁷					X ¹⁶					
Follow-Up Period Assessments														
Follow-Up Assessments														X

- Treatment Discontinuation Visit can occur at any scheduled or unscheduled visit when applicable. At this visit, documentation to confirm progressive disease is required.
- End of Study Visit should be scheduled to collect safety assessments ≥ 3 weeks after last administration of prednisone, and ≤ 4 weeks after last administration of abiraterone acetate. Patients will enter Follow up Phase at that time.
- Written informed consent must be obtained within 30 days prior to Cycle 1 Day 1.
- Vitals include upright sitting blood pressure, heart rate, respiratory rate, and oral or axillary body temperature. On CID-1, CID 1, and C2D1 vital signs will be obtained in conjunction with the ECGs at pre-dose and 1, 2, 4, 6 hours post dose. Weight will be recorded at every visit. Height will be measured at Screening visit only.
- On CID-1, time-matched serial sets of 3 ECGs are obtained at 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours (time-matched on the clock (within 30 minutes) to the time the patient will return for Cycle 1 Day 1 procedures the following day; 24 hours post-dose on Cycle 1 Day -1 is the same as pre-dose on Cycle 1 Day 1). On CID1 serial sets of 3 ECGs are obtained at 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post-dose. On C2D1 serial sets of 3 ECGs are obtained at 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours post-dose. At any other visits, ECGs are obtained at pre-dose. At each collection time, serial sets of three ECGs should be obtained within 5 minutes of each other. The central laboratory machine should be used to acquire all ECGs, and the site personnel must enter the patient ID, study day and timepoint. ECGs should not be obtained when serum potassium is < 3.5mg/dL. Hypokalemia should be corrected prior to ECG collection.
- MUGA scan or ECHO performed up to 28 days prior to Study Day 1 can be used for baseline assessments. A MUGA scan or ECHO should be obtained at baseline and at End of Study visit for all patients.
- Pre-Treatment SAEs should be reported from time patient signs a consent form up to Day 1 treatment administration.
- 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.
- Single 12-lead ECG using local laboratory ECG machine
- If patient undergoes a digital rectal exam (DRE), PSA must be sampled prior to the DRE
- Scan performed up to 28 days prior to Study Day 1 can be used for baseline assessments. If a status of partial or complete response is made, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. If a Chest CT or MRI is performed as part of the imaging evaluation, then the Chest x-ray is optional and may not be performed.
- Bone scans, CT, MRI or other imaging procedures are performed as clinically indicated and as defined in Appendix 2. Assessments should be conducted up to 8 days prior to the indicated visit. Results should be available for review at the Cycles 4, 7, and 10 and every 3rd cycle beyond cycle 10 and Treatment Discontinuation visit.
- Overall survival may be collected by telephone interview or chart review (Subsequent antitumor therapies, with start and stop dates, will be collected)
- PK blood samples collected pre and post dose on Cycle 1 Day 1, Cycle 1 Day 8, and Cycle 2 Day 1. On Cycle 1 Day 8, Cycle 2 Day 1, and Cycle 2 Day 2 patients will be asked to take study treatment following pre-dose sample PK collection.
- 24 hours after the 1st dose and before administration of 2nd dose; 24 hours after the 8th dose and before administration of 9th dose
- At Cycle 1 Day 15 and subsequent visits, dosing compliance check, a count of study treatment tablets, will be conducted during this visit and patient dosing compliance will be assessed. If compliance is ≤ 75% patient should be re-instructed regarding proper dosing procedures. Patients whose dosing compliance is ≤ 75% for 2 consecutive cycles should be discontinued from the study. Patients who have a compliance ≤ 75% secondary to held doses due to toxicities as described in Section 7.6.1 may continue in the study. Source documentation of the compliance check and any patient verbal re-instruction provided should be documented in patient's chart
- To be performed 4 – 8 weeks after the last dose of Abiraterone Acetate
- If patients continue onto a treatment that requires the glucocorticosteroid, this test will not be required
- 24 hours after Cycle 2 Day 1 dose and before administration of Cycle 2 Day 2 dose

Source: Protocol: COU-AA-006

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

/s/

HAO ZHU
03/14/2011

JEFFRY FLORIAN
03/14/2011

SUCHITRA M BALAKRISHNAN
03/14/2011

NORMAN L STOCKBRIDGE
03/14/2011

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Drug Oncology Products

Application Number: NDA 202379

Name of Drug: Zytiga™ (abiraterone acetate) Tablets 250 mg

Applicant: Centocor Ortho Biotech, Inc.

Material Reviewed:

Submission Date: December 18, 2010

Receipt Date: December 20, 2010

Submission Date of Structure Product Labeling (SPL): December 18, 2010

Type of Labeling Reviewed: Word Version

Background and Summary

NDA 202379 Zytiga (Abiraterone Acetate) is an androgen biosynthesis inhibitor, proposed for treatment with prednisone for the treatment of metastatic (b) (4) (b) (4) (b) (4) (castration resistant prostate cancer) in patients who have received prior chemotherapy containing a (b) (4)

This review provides a list of format revisions for the proposed labeling that were conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following deficiencies have been identified in the proposed labeling.

Highlights Section revisions:

1. The following statement should read and be in **bold**, “**See 17 for Patient Counseling Information and FDA-approved patient labeling**” at the end of the Highlights Section.

2. The last sentence in the Dosage and Administration section bullet #2 should read, (b) (4)
3. Insert a horizontal line extending the entire width of the page in between the Full Prescribing Information: Contents and the Full Prescribing Information Sections.
4. Delete the following from the top of each page of the entire product insert: (b) (4)
11-23-10”.

Full Prescribing Information revisions:

4. All the cross-references in the Full Prescribing Information section appear to be in this format: (*see Indications and Usage [1.1]*). Revise all the cross-references to the following format: [*see Indications and Usage (1.1)*].
5. The following identifying characteristics stated in the dosage Forms and Strengths section must also appear under the How Supplied/Storage and Handling section, “TRADENAME™ (abiraterone acetate) 250 mg tablets are white to off-white, oval tablets debossed with AA250 on one side.”
6. The statement “See FDA-approved patient labeling (Patient Information)” should appear at the beginning of Section 17.

Amy Tilley
Regulatory Project Manager

Supervisory Comment/Concurrence:

Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff

Drafted: AT/1-17-11
Revised/Initialed: AT/1-25-11
Finalized: AT/1-25-11
Filename: CSO Labeling Review Template (updated 1-16-07).doc
CSO LABELING REVIEW OF PLR FORMAT

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
02/08/2011

ALICE KACUBA
02/08/2011

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- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Zytiga™ Established/Proper Name: abiraterone acetate Dosage Form: Tablets Strengths: 250 mg		
Applicant: Centocor Ortho Biotech, Inc. Agent for Applicant (if applicable): Cougar Biotechnology, Inc.		
Date of Application: 12-18-10 Date of Receipt: 12-20-10 Date clock started after UN:		
PDUFA Goal Date: 6-20-11	Action Goal Date (if different): 4-29-11	
Filing Date: 2-18-11	Date of Filing Meeting: 1-14-11	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Indicated with prednisone for the treatment of metastatic (b) (4) (b) (4) (b) (4) (castration-resistant prostate cancer) in patients who have received prior chemotherapy containing a (b) (4)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (<i>if OTC product</i>):				
List referenced IND Number(s): 071023				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>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.</i>	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)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ 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			

<u>User Fee Status</u> <i>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.</i>		Payment for this application: <input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>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.</i>		Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
505(b)(2)		YES	NO	NA	Comment
(NDAs/NDA Efficacy Supplements only)					
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?					
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)].					
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)]?					
<i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>					
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.fda.gov/cder/ob/default.htm					
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code		Exclusivity Expiration	
<i>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 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>					
Exclusivity		YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm			X		

<p>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)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i></p>				
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDA/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested: 5 years</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	X			
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDA only</i>)?</p>		X		
<p>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)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>				

Format and Content				
<p><i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i></p>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<p>If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?</p>				
Overall Format/Content	YES	NO	NA	Comment
<p>If electronic submission, does it follow the eCTD guidance?¹ If not, explain (e.g., waiver granted).</p>	X			
<p>Index: Does the submission contain an accurate comprehensive index?</p>	X			
<p>Is the submission complete as required under 21 CFR 314.50 (<i>NDA/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including:</p>	X			

¹

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input type="checkbox"/> pagination <input type="checkbox"/> 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				
<i>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.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
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)?	X			DSI Reviewer has an IR to be sent to sponsor regarding Financial Disclosure mis-match issue.
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				
<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p>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].</p> <p>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...”</p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p>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)</p> <p>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</p>			X	NA since this is a eCTD submission

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p>If yes, date consult sent to the Controlled Substance Staff:</p> <p><u>For non-NMEs:</u> Date of consult sent to Controlled Substance Staff :</p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p>If yes, notify PeRC RPM (PeRC meeting is required)²</p> <p>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.</p>	X			Sponsor is requesting Full Peds Waiver. Notified PeRC by phone 1-6-11. PeRC Docs sent PeRC Mtg is 3-2-11.

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	X			Full Waiver of pediatric studies
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? <i>If no, request in 74-day letter</i>			X	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3) <i>If no, request in 74-day letter</i>	X			
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	X			
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox</i>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request in 74-day letter.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.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? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			Consult sent 1-14-11
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			Consult sent 1-14-11
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			Consult sent 1-14-11
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	X			DMPQ, QT/IRT & DSI QT 1-14-11; DSI 1-13-11
Meeting Minutes/SPAs	YES	NO	NA	Comment

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

End-of Phase 2 meeting(s)? Date(s): 10-4-07; 03-4-08	X			IND 71023
<i>If yes, distribute minutes before filing meeting</i>	X			Sent to team 1-6-11
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): 1-6-10; 12-2-10	X			IND 71023
<i>If yes, distribute minutes before filing meeting</i>				Sent to team 1-6-11
Any Special Protocol Assessments (SPAs)? Date(s): 3-28-08	X			IND 71023
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				Sent to team 1-6-11

ATTACHMENT

MEMO OF FILING MEETING

DATE: 1-14-11

BLA/NDA/Supp #: 202379

PROPRIETARY NAME: Zytiga™

ESTABLISHED/PROPER NAME: abiraterone acetate

DOSAGE FORM/STRENGTH: Tablets

APPLICANT: Centocor Ortho Biotech, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Indicated with prednisone for the treatment of metastatic (b) (4) (b) (4) (b) (4) (castration-resistant prostate cancer) in patients who have received prior chemotherapy containing a (b) (4)

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Amy Tilley	Y
	CPMS/TL:	Alice Kacuba	N
Cross-Discipline Team Leader (CDTL)	Ke Liu		Y
Clinical	Reviewers:	Yang-Min (Max) Ning Paul Kluetz	Y
	TL:	Ke Liu	Y
Social Scientist Review (for OTC products)	Reviewer:		
	TL:		
OTC Labeling Review (for OTC products)	Reviewer:		
	TL:		
Clinical Microbiology (for antimicrobial products)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Elmika Pfuma	Y
	TL:	Jeanne Fourie Zirkelbach	Y
Biostatistics	Reviewer:	Lijun Zhang	Y
	TL:	Shenghui Tang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Robeena Aziz	Y
	TL:	Whitney Helms Robert Dorsam	Y N
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Debasis Ghosh	Y
	TL:	Haripada Sarker	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection (DMPQ)	Reviewer:	Steven Hertz	N
	TL:	Shawn Gould	Y
OSE/DMEPA (proprietary name)	Reviewer:	Jibril Abdus-Samad	N
	TL:	Todd Bridges	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:	Lauren Iacono-Connor	Y
	TL:	Jean Mulinde Tejashri Purohit-Sheth	Y N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	DDMAC	Adam George	Y
		Karen Rulli	N
		Stephanie Victor	N
Pharmacometrics		Nitin Mehrotra	Y
		Christine Garnett	N
Biopharmaceutics		Albert (Tien-Mien) Chen	Y
		Angelica Dorantes	N
Other attendees	DRISK	Mary Dempsey	Y

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(1) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: Unable to navigate the CRFs in EDR. Initial CRFs are different from the CRFs submitted in NDA. Notify sponsor of possible meeting to discuss how to view the CRFs (prior to orientation meeting). Mtg attendees: Clin & Stat TLs and Primary Reviewers only, others optional (sponsor to bring their own laptop to explain how to view the CRFs?). Possibility that sponsor can explain the CRF issue during their orientation meeting if meeting is moved to January. Sponsor to discuss during 2-25-11 Orientation Meeting.</p>	<input type="checkbox"/> Not Applicable
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE

<p>Comments:</p>	<input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>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</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> 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? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) 	<input type="checkbox"/> YES

needed?	<input checked="" type="checkbox"/> NO
BIostatistics Comments: none	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments: Reproductive Toxicology studies not submitted. Possible PM issue if patient population is changed.	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: none</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments: Requested by CMC</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

CMC Labeling Review	
Comments: None	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Dr. Pazdur	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	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).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	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.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> 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)

	<ul style="list-style-type: none"> • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct PM labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	<p>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 (BLAs/BLA supplements only) [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]</p>
<input type="checkbox"/>	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/

AMY R TILLEY
02/01/2011

DSI CONSULT: Request for Clinical Inspections

Date: 1/12/2011

To: Tejashri Purohit-Sheth, M.D., Branch Chief, GCP 2
Jean M. Mulinde, M.D., Acting Team Leader, GCP 2
Lauren Iacono-Connors, Ph.D., GCP2
Division of Scientific Investigations
Office of Compliance/CDER

Through: Y. Max Ning, MD, PhD, Clinical Reviewer, DDOP
Paul Kluetz, MD, Clinical Reviewer, DDOP
Ke Liu, MD, PhD, CDTL, DDOP
Robert Justice, MD, Division Director, DDOP

From: Amy Tilley, Regulatory Health Project Manager, DDOP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 202379

Ortho Biotech Oncology Research & Development Unit of Cougar Biotechnology,
Inc (Regulatory Contact: Christine M. Woods, BS, MA)
Phone: 310-943-8040, Ext 144
Email: CWoods@ITS.JnJ.com

Drug Proprietary Name: Zytiga (abiraterone acetate)
NME or Original BLA (Yes/No): Yes
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: For the treatment of patients with metastatic (b) (4) (b) (4) (b) (4)
(castration-resistant prostate cancer) who have received prior chemotherapy containing a (b) (4)

Letter Date: 12/20/2010
PDUFA: 6/20/2011
Action Goal Date: 5/30/2011
Inspection Summary Goal Date: 4/30/2011

II. Protocol/Site Identification**Protocol: COU-AA-301, entitled “A Phase 3, Randomized, Double-blind, Placebo-Controlled Study of Abiraterone Acetate (CB7630) Plus Prednisone in Patients with Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy”**

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Median OS at Site (Range)
Site #139 Christopher J Logothetis, M.D. Cancer Center Dept. of Genitourinary Medical Oncology, 1155 Pressler St., Unit 1374 Houston, TX 77030 Phone: 713-563-7210 Fax: 713-745-9101 Email: clogothe@mdanderson.org	COU-AA-301	48	433 days (87, 529+)
Site #159 Mansoor Saleh, M.D. 1835 Savoy Drive Suite 300 Atlanta, GA 30341 Phone: 770-496-9403 Fax: 770-496-9497 Email: mansoor.saleh@gacancer.com	COU-AA-301	15	267 days (60, 432+)
Site #600 Johann de Bono, M.D.* Royal Marsden Hospital NHS Foundation Trust, Downs Road, Sutton, Surrey, SM2 5PT United Kingdom Phone: 44 2087224028 Fax: 44 2086427979 Email: jdebono@icr.ac.uk	COU-AA-301	49	433 days (2+, 529+)

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Median OS at Site (Range)
Site #601 Stephen Harland, M.D. MB BX, FRCP 18 NE (55, 459+) 13 6 University College Hospital 1st Floor Central, Oncology 250 Euston road, London NW1 2PQ United Kingdom Phone: 44 207 380 9287 Fax: 44 207 380 9055 Email: stephen.harland@uclh.nhs.uk	COU-AA-301	18	NE (55, 459+)
Site #701 Cora Sternberg, M.D. Hospital San amillo Forlanini O.U. Medical Oncology New pavilions, 4th floor Circonvallazione Gianicolense 87 Rome, 00152 Italy Phone: 39 06 58704262 Fax: 39 06 663 0771 Email: csternberg@scamilloforlanini.rm.it	COU-AA-301	17	500 (45, 500)

*Dr de Bono also served as a coordinating investigator for the overall study
 +: denotes censoring at the time of collection

III. Site Selection/Rationale

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects (Site #139)
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making (Sites #139, #159)
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): Assessment of adequacy of re-monitoring process at sites not audited by sponsor/applicant (Site #159, Saleh)

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data (Site #600 high enroller UK)
- Significant primary efficacy results pertinent to decision-making(Sites #600, #601, #701)
- 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.
- Other (specify): Assessment of adequacy of re-monitoring process at sites not audited by sponsor/applicant. In addition, number of protocol violations and/or serious adverse reactions reported from sites chosen were well below study mean raising concern with adequacy of monitoring (Site #601, Dr. Harland; Site #701, Dr. Sternberg)

Five or More Inspection Sites (delete this if it does not apply):

We have requested these sites for inspection (international and/or domestic) because of the following reasons:

Regulatory decision for this application will depend solely on the results from a single study halted prior to completion by the IDMC for significantly improved overall survival in patients who received abiraterone as compared to placebo. In addition, the Applicant identified that original site monitoring was inadequate, which then necessitated their undertaking an extensive re-monitoring program to ensure the reliability of data submitted. Confirmation of data reliability is deemed essential to support approval and appropriate labeling of abiraterone for the proposed indication.

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact Amy Tilley at 301-796-3994 or Max Ning at 301-796-2321.

Concurrence: (as needed)

Dr. Liu, Cross-Discipline Team Leader
Drs. Ning and Kluetz, Medical Reviewers
Dr. Justice, Division Director (for foreign inspection requests or requests for 5 or more sites)

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
01/13/2011

ROBERT L JUSTICE
01/13/2011