

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202379Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

**PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation and Composition)
and/or Method of Use**

NDA NUMBER

202379

NAME OF APPLICANT/NDA HOLDER

Centocor Ortho Biotech Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)

ZYTIGA (proposed)

ACTIVE INGREDIENT(S)

Abiraterone Acetate

STRENGTH(S)

250 mg

DOSAGE FORM

Tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number 5,604,213	b. Issue Date of Patent February 18, 1997	c. Expiration Date of Patent February 18, 2014
d. Name of Patent Owner BTG International Ltd, formerly British Technology Group Ltd	Address (of Patent Owner) 5 Fleet Place	
	City/State London, UK	
	ZIP Code EC4M 7RD	FAX Number (if available)
	Telephone Number 44 (0)20 7575 0000	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) Dr Leonard C. Mitchard, Nixon & Vanderhye P.C.	Address (of agent or representative named in 1.e.) 901 North Glebe Road, 11th Floor	
	City/State Arlington, VA	
	ZIP Code 22203	FAX Number (if available) 703-816-4100
	Telephone Number 703-816-4005	E-Mail Address (if available) lcm@nixonvan.com
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?		<input type="checkbox"/> Yes <input type="checkbox"/> No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No
- 2.6 Does the patent claim only an intermediate? Yes No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No
- 3.2 Does the patent claim only an intermediate? Yes No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 for each method of using the pending drug product for which approval is being sought that is claimed by the patent. For each pending method of use claimed by the patent, provide the following information:

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No
- 4.2 Patent Claim Number(s) (as listed in the patent) 2, 16, 18, 19, 20, 21 Does (Do) the patent claim(s) referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the proposed labeling.) (b) (4)

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Andrea J. Kamage

Date Signed

December 6, 2010

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Andrea J. Kamage

Address

One Johnson & Johnson Plaza

City/State

New Brunswick, NJ

ZIP Code

08933

Telephone Number

732-524-3957

FAX Number (if available)

E-Mail Address (if available)

akamag12@its.jnj.com

The public reporting burden for this collection of information has been estimated to average 20 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
 Food and Drug Administration
 Office of Chief Information Officer (HFA-710)
 5600 Fishers Lane
 Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXCLUSIVITY SUMMARY

NDA # 202379

SUPPL #

HFD # 150

Trade Name Zytiga

Generic Name abiraterone acetate

Applicant Name Centocor Ortho Biotech, Inc.

Approval Date, If Known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

Investigation #2

!

YES

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====

Name of person completing form: Amy Tilley
Title: Regulatory Project Manager
Date: 3-18-11

Name of Office/Division Director signing form: Robert L. Justice, M.D., M.S.
Title: Director Division of Drug Oncology Products

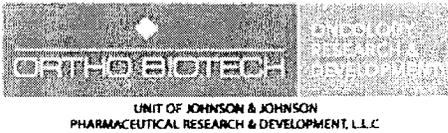
Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

AMY R TILLEY
04/27/2011

ROBERT L JUSTICE
04/28/2011



DEBARMENT CERTIFICATION

ABIRATERONE ACETATE

Johnson & Johnson Pharmaceutical Research & Development, LLC. certifies that we 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.

Robyn B. Sterner, Pharm.D. 1-DEC-2010

Robyn B. Sterner, PharmD
Senior Director
Global Regulatory Affairs Oncology

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 202379 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Zytiga Established/Proper Name: abiraterone acetate Dosage Form: Tablets		Applicant: Centocor Ortho Biotech, Inc. Agent for Applicant (if applicable): Ortho Biotech Oncology Research & Development, Unit of Cougar Biotechnology, Inc.
RPM: Amy Tilley		Division: DDOP
<p>NDA: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check: 4-28-11</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>June 20, 2011</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		<input type="checkbox"/> Received

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics ²	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority</p> <p>Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch</p> <p><input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch</p> <p><input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H BLAs: Subpart E</p> <p><input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41)</p> <p><input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42)</p> <p>Subpart I Subpart H</p> <p><input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR REMS: <input type="checkbox"/> MedGuide</p> <p><input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Communication Plan</p> <p><input type="checkbox"/> Submitted in response to a Pediatric Written Request <input type="checkbox"/> ETASU</p> <p><input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Press Office notified of action (by OEP)	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other BURST

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
---	--

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) AP 4-28-11
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	4-28-11
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	12-20-10
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A

³ Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	4-28-11
<ul style="list-style-type: none"> Original applicant-proposed labeling 	12-20-11
<ul style="list-style-type: none"> Example of class labeling, if applicable 	N/A
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent draft labeling 	4-28-11
❖ Proprietary Name <ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) 	3-14-11 3-14-11; 4-13-11
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> RPM 2-8-11 <input checked="" type="checkbox"/> DMEPA 4-13-11; 4-26-11 <input checked="" type="checkbox"/> DRISK 4-19-11 <input checked="" type="checkbox"/> DDMAC 4-18-11 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews CMC 4-26-11
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	2-1-11
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>3-2-11</u> If PeRC review not necessary, explain: _____ Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	Included

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Internal memoranda, telecons, etc.	4-6-11; 4-26-11
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 11-24-09; 11-9-10
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg 9-27-07; 3-7-08
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	1-31-08; 9-17-08; 5-26-10; 12-3-10
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4-28-11
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4-27-11
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 4-27-11
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 4 PMRs
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	4-27-11
• Clinical review(s) (<i>indicate date for each review</i>)	4-27-11
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See MO Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None 3-14-11; 4-14-11
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> • REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) • REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) • Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input type="checkbox"/> None requested 4-15-11; (2) 4-26-11

⁵ Filing reviews should be filed with the discipline reviews.

Clinical Microbiology		<input checked="" type="checkbox"/> None
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
Biostatistics		<input type="checkbox"/> None
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None 4-14-11
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None 4-14-11
Statistical Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None 4-13-11
Clinical Pharmacology		<input type="checkbox"/> None
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None 4-20-11
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None 4-20-11
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None 4-20-11
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)		<input checked="" type="checkbox"/> None
Nonclinical		<input type="checkbox"/> None
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None 4-19-11
• Supervisory Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None 4-19-11
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)		<input type="checkbox"/> None 4-20-11
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)		<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting		<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)		<input checked="" type="checkbox"/> None requested
Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None 4-8-11
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None 3-31-11
• Product quality review(s) including ONDQA biopharmaceutics reviews (<i>indicate date for each review</i>)		<input type="checkbox"/> None 3-31-11
❖ Microbiology Reviews		<input checked="" type="checkbox"/> Not needed
<input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>)		
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) (<i>indicate date of each review</i>)		
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>)		<input checked="" type="checkbox"/> None

❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	11-15-10
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	N/A
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	N/A
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶</i>)	Date completed: 4-4-11 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input checked="" type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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/s/

AMY R TILLEY
04/28/2011

Tilley, Amy

From: Tilley, Amy
Sent: Thursday, April 28, 2011 10:43 AM
To: 'Woods, Christine [REDACTED] (b) (4)'
Cc: 'Johnson Reid, Kelly [REDACTED] (b) (4)'
Subject: ****TIME SENSITIVE**** Zytiga FDA Revised PPI

Importance: High

Attachments: FDA Revised PPI 4-28-11.doc

Christine,

Attached is the FDA revised PPI for Zytiga.



FDA Revised PPI
4-28-11.doc (8...

Respond back **no later than 11:30 am today EDT** should you have any further revisions to the PPI .

May I remind you that the division is attempting to take an action **as early as possible** this week.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology Products, CDER,
FDA

10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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this page

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/s/

AMY R TILLEY
04/28/2011

From: Tilley, Amy
Sent: Thursday, April 28, 2011 9:16 AM
To: Woods, Christine [CGRUS] cwoods@its.jnj.com
Cc: 'Johnson Reid, Kelly [ORDUS]' kjohnso6@its.jnj.com
Subject: Zytiga logo found acceptable

Importance: High
[Christine,](#)

With regard to your question during our phone conversation late yesterday regarding the use of the logo, I received confirmation from DMEPA and ONDQA see below.

The logo is acceptable.

...ONDQA has reviewed the revised container label with the logo and have found the container label acceptable as we have.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology
Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
04/28/2011

Tilley, Amy

From: Tilley, Amy
nt: Wednesday, April 27, 2011 4:51 PM
o: Woods, Christine [CGRUS]
Cc: 'Johnson Reid, Kelly [ORDUS]'
Subject: NDA 202379 Zytiga - FDA Revised PI & PPI sent 4-27-11

Follow Up Flag: Follow up
Due By: Thursday, April 28, 2011 12:00 AM
Flag Status: Flagged

Attachments: FDA Revised PI 4-27-11.doc; FDA Revised PPI 4-27-11.doc

Christine,

Below are the FDA Revised PI & PPI for Zytiga.



FDA Revised PI
4-27-11.doc (26...



FDA Revised PPI
4-27-11.doc (8...

Your response is requested **no later than 9 am on 4-28-11.**

Kind Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology Products, CDER,
FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
04/27/2011

From: Tilley, Amy
Sent: Monday, April 25, 2011 10:25 AM
To: 'Woods, Christine [CGRUS]'
Cc: Johnson Reid, Kelly [ORDUS]
Subject: NDA 202379 Zytiga - Action sometime this week

Importance: High
Christine,

I have been instructed by management to let you know that we are planning on taking an action as soon as possible this week.

Kind Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology
Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993

 301.796.3994 (phone) • 301.796.9845 (fax) |  amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
04/25/2011

Tilley, Amy

From: Tilley, Amy
Sent: Monday, April 25, 2011 6:16 PM
To: Woods, Christine [CGRUS]
Cc: 'Johnson Reid, Kelly [ORDUS]'
Subject: NDA 202379 Zytiga - FDA Revised PI & PPI sent 4-25-11

Attachments: FDA revised PI 4-25-11.doc; 11 0419 ZYTIGA DRISK PPI Final Review.doc

Christine,

Attached are the Agency's revised PI & PPI for your concurrence.



FDA revised PI
4-25-11.doc (29...



11 0419 ZYTIGA
DRISK PPI Final...

Please respond back **no later than 3 pm Tuesday 4-26-11.**

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology Products, CDER,
FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
04/25/2011

MEMORANDUM OF TELECON

DATE: April 25, 2011

APPLICATION NUMBER: NDA 202379

BETWEEN:

Name: Kelly Johnson Reid
Phone: 908-927-3137
Representing: Centocor Ortho Biotech

AND

Name: Amy Tilley
Division of Drug Oncology Products (DDOP), HFD-150

SUBJECT: On April 22, 2011, the Sponsor requested a teleconference with DDOP and the appropriate representatives from the Division of Drug Marketing, Advertising, and Communications (DDMAC) for Question 1, to discuss the four questions listed below.

(b) (4)

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

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/s/

AMY R TILLEY
04/26/2011

From: Tilley, Amy
Sent: Friday, April 22, 2011 6:24 PM
To: 'Woods, Christine [CGRUS]'
Cc: 'Johnson Reid, Kelly [ORDUS]'
Subject: NDA 202379 Zytiga - SPON TCON 4-25-11
Christine,

As discussed we have scheduled the TCON with you on Monday, April 25, 2011 from 3:30 - 4:00 pm.

It is possible that we could call in to the TCON earlier than 3:30 pm if our pre-meeting from 3 - 3:30 does not take the entire half hour.

Please send us the call in information.

Thank you.

Amy

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology
Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
04/22/2011

From: Tilley, Amy
Sent: Monday, April 18, 2011 10:27 AM
To: 'Woods, Christine [CGRUS]'
Cc: 'Johnson Reid, Kelly [ORDUS]'
Subject: **TIME SENSITIVE** NDA 202379 Zytiga - Clinical Information Request sent 4-18-11

Importance: High

Follow Up Flag: Follow up
Due By: Tuesday, April 19, 2011 4:00 PM
Flag Status: Flagged

Christine,

Below is an Information Request from the Clinical Team.

We note that there is a cohort of patients with secondary malignancies reported in the integrated safety database that favors the abiraterone acetate arm. Please provide your analysis of secondary malignancies from the integrated safety population with case narratives or locations of these narratives in the NDA submission for each of the cases contained in the following table in addition to any other cases you are aware of in the integrated safety population as soon as possible, but no later than COB on Tuesday, 4-19-11.

COU-AA-002-163-046	Basal cell carcinoma
COU-AA-002-163-048	Squamous cell carcinoma
COU-AA-003-157-201	Squamous cell carcinoma
COU-AA-004-176-036	Bladder transitional cell carcinoma
COU-AA-301_104-0001	Squamous cell carcinoma of skin
COU-AA-301_114-0009	Squamous cell carcinoma
COU-AA-301_122-0021	Colon cancer
COU-AA-301_158-0020	Lung neoplasm malignant
COU-AA-301_174-0002	Basal cell carcinoma
COU-AA-301_175-0001	Basal cell carcinoma
COU-AA-301_604-0022	Basal cell carcinoma
COU-AA-301_902-0005	Basal cell carcinoma
COU-AA-301_902-0005	Malignant melanoma
COU-AA-301_907-0004	Squamous cell carcinoma of skin

Kindly respond as soon as possible, but no later than COB on Tuesday, 4-19-11.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993

 301.796.3994 (phone) • 301.796.9845 (fax) |  amy.tilley@fda.hhs.gov

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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
04/18/2011

From: Tilley, Amy
Sent: Monday, April 18, 2011 3:43 PM
To: 'Woods, Christine [CGRUS]' cwoods@its.inj.com
Cc: 'Johnson Reid, Kelly [ORDUS]' kjohnso6@its.inj.com
Subject: NDA 202379 Zytiga - FDA Revised PI & DMEPA Container Revisions sent 4-18-11

Importance: High

Follow Up Flag: Follow up
Due By: Monday, April 25, 2011 12:00 PM
Flag Status: Flagged

Attachments: FDA Revised USPI PPI 4-18-11.doc; DMEPA response to Warning statement_04152011.doc

Christine,

Attached is the FDA Revised PI and DMEPA's latest container revisions. Note we have not completed our review of the PPI and will send the revisions at a later date.



FDA Revised USPI
PPI 4-18-11.d...



DMEPA response to
Warning stat...

Additional Revisions to be made by Sponsor:

- 1. Only place the TM symbol after ZYTIGATM during the first usage of the name in Highlights. Thereafter simply use ZYTIGA.**
- 2. Revise the formatting to include: all fonts, line spacing's, and indentations for sub-headings.**
- 3. Check that all the cross-references are in the following format: [see *Indications and Usage (1.1)*].**
- 4. Check the Highlights section and revise the Table of Contents to be consistent with edits made.**
- 4. 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.**
- 5. Delete the following from the top of each page of the entire product insert:** (b) (4)
- 6. Insert a horizontal line extending the entire width of the page in between the "Full Prescribing Information: Contents" and the "Full Prescribing Information" sections.**
- 7. The statement "See FDA-approved patient labeling (Patient Information)" should appear at the beginning of Section 17.**

Please respond both officially and via email to the above revised FDA PI and DMEPA's container revisions **no later than Noon on Monday, 4-25-11.**

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology
Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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

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/s/

AMY R TILLEY
04/18/2011

From: Tilley, Amy
Sent: Monday, April 18, 2011 4:09 PM
To: 'Woods, Christine [CGRUS]'
Cc: 'Johnson Reid, Kelly [ORDUS]'
Subject: RE: NDA 202379 Zytiga - Minor Correction to FDA Revised PI & DMEPA Container Revisions sent 4-18-11

Importance: High
Christine,

Please note one change to the **Additional Revisions to be made by Sponsor:** regarding #2 in my previous email.

Do not indent the subheadings.

Regards.

Amy

From: Tilley, Amy
Sent: Monday, April 18, 2011 3:43 PM
To: 'Woods, Christine [CGRUS]'
Cc: 'Johnson Reid, Kelly [ORDUS]'
Subject: NDA 202379 Zytiga - FDA Revised PI & DMEPA Container Revisions sent 4-18-11
Importance: High

Christine,

Attached is the FDA Revised PI and DMEPA's latest container revisions. Note we have not completed our review of the PPI and will send the revisions at a later date.

<< File: FDA Revised USPI PPI 4-18-11.doc >> << File: DMEPA response to Warning statement_04152011.doc >>

Additional Revisions to be made by Sponsor:

- 1. Only place the TM symbol after ZYTIGATM during the first usage of the name in Highlights. Thereafter simply use ZYTIGA.**
- 2. Revise the formatting to include: all fonts, line spacing's, and indentations for sub-headings.**
- 3. Check that all the cross-references are in the following format: [see *Indications and Usage (1.1)*].**
- 4. Check the Highlights section and revise the Table of Contents to be consistent with edits made.**

4. 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.
5. Delete the following from the top of each page of the entire product insert: (b) (4)
6. Insert a horizontal line extending the entire width of the page in between the "Full Prescribing Information: Contents" and the "Full Prescribing Information" sections.
7. The statement “See FDA-approved patient labeling (Patient Information)” should appear at the beginning of Section 17.

Please respond both officially and via email to the above revised FDA PI and DMEPA's container revisions **no later than Noon on Monday, 4-25-11.**

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology
Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
04/18/2011

From: Pfuma, Elimika
Sent: Thursday, April 14, 2011 11:57 AM
To: Tilley, Amy; Liu, Ke; Ning, Yang-Min (Max); Kluetz, Paul; Fourie Zirkelbach, Jeanne; Garnett, Christine; Mehrotra, Nitin
Cc: Justice, Robert; Ibrahim, Amna
Subject: RE: Correction to CSR re: QTcF Successfully Processed eCTD: nda202379 in DARRTS

Hello team,
Below is the email from a QT/IRT reviewer stating that this submission does not affect their conclusions or recommendations. Thank you.

Hi, Elimika,

Thank you for sharing the information. The error in the sponsor's report does not 1.) affect the overall conclusion for the QT study, or 2.) our recommendations on label.

In fact, our independent analysis was based on QTcI, not QTcF. So the sponsor's reporting error on QTcF does not affect our results.

Hao

-----Original Message-----

From: Pfuma, Elimika
Sent: Thursday, April 14, 2011 11:16 AM
To: Zhu, Hao; Fourie Zirkelbach, Jeanne
Subject: FW: Correction to CSR re: QTcF Successfully Processed eCTD: nda202379 in DARRTS
Importance: High

Hi Hao,
the following was submitted by the sponsor to update a sentence written incorrectly in the study report for the TQT study you reviewed. Please inform us whether or not it will impact your recommendations. Thanks.

-----Original Message-----

From: Tilley, Amy
Sent: Thursday, April 14, 2011 11:12 AM
To: Liu, Ke; Ning, Yang-Min (Max); Kluetz, Paul; Fourie Zirkelbach, Jeanne; Pfuma, Elimika
Cc: Justice, Robert; Ibrahim, Amna
Subject: FW: Correction to CSR re: QTcF Successfully Processed eCTD: nda202379 in DARRTS
Importance: High

Review Team,

This submission contains a "Correction to COU-AA-006 Clinical Study Report".

"The company recently discovered an inaccuracy in the clinical study report (CSR) for Study COU-AA-006 that was included in our original NDA submission. The following sentence appearing on page 50 of the CSR (Section 7.3.1 Analysis of QTcF) was incorrect: "The mean QTcF change ranged from"

Amy

-----Original Message-----

From: asr-dontreply@fda.hhs.gov [mailto:asr-dontreply@fda.hhs.gov]
Sent: Wednesday, April 13, 2011 2:49 PM
To: Tilley, Amy; CDER-OND-DDOP-EDRNOTIFY; CDER-EDR_ASR_Document_Coordinators;
CDER-EDRSTAFF; CDER-EDRADMIN; CDER ESUB; Khalsa, Gurminders J; Livermore,
Russell J; Thompson, Douglas L. *; CDER-EDRSTAFF
Subject: Successfully Processed eCTD: nda202379 in DARRTS

Successfully Processed eCTD: nda202379 in DARRTS. Details below:

EDR Location: \\CDSESUB1\EVSPROD\NDA202379\202379.enx

For Document Room Staff Use:

Application Type/Number: nda202379
Incoming Document Category/Sub Category: Electronic_Gateway
Supporting Document Number: 20
eCTD Sequence Number: 0019
Letter Date: 04/13/2011
Stamp Date: 4/13/2011

Receipt Date/Time from Notification: 04-13-2011, 14:32:53
Origination Date/Time from Notification: 04-13-2011, 14:31:06
DOCUMENT ID: 4481904

356H Form: \\CDSESUB1\EVSPROD\NDA202379\0019\m1\us\356h.pdf

Cover Letter: \\CDSESUB1\EVSPROD\NDA202379\0019\m1\us\cover-letter.pdf

3397 Form: NOT FOUND

3674 Form: NOT FOUND

For EDR Staff Use:

The submission has already been processed. The following information
is provided if verification is required. No additional action is
required on your part

EDR Location: \\CDSESUB1\EVSPROD\NDA202379\0019
Submission Size: 279191
Gateway Location:
\\chdc9681\cderesub\inbound\ectd\ci1302719466226.178119@llnap31_te

Copy to EDR Status: Good-1

For CDER Project Manager Use:

The following submission received through the Electronic Submission Gateway
has been processed using the following information. This information will be
updated once Document Room personnel have been able to verify the content of
the submission.

Application Type/Number: nda202379
Incoming Document Category/Sub Category: Electronic_Gateway
Supporting Document Number: 20
eCTD Sequence Number: 0019
Letter Date: 04/13/2011

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/s/

AMY R TILLEY
04/14/2011

From: Tilley, Amy
Sent: Wednesday, April 13, 2011 11:11 AM
To: 'Woods, Christine [CGRUS]' cwoods@its.jnj.com
Cc: Johnson Reid, Kelly [ORDUS] kjohnso6@its.jnj.com
Subject: RE: NDA 202379 Zytiga – PMRs and Milestone Dates
Christine,

The review team finds your revised proposed date below for the severe hepatic impairment trial acceptable.

Please submit this information officially to this NDA and also send me a courtesy email once the information is submitted.

Thank you.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology
Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



consider the environment before printing this e-mail

From: Woods, Christine [CGRUS] [<mailto:CWoods@ITS.JNJ.com>]
Sent: Tuesday, April 12, 2011 7:50 PM
To: Tilley, Amy
Cc: Johnson Reid, Kelly [ORDUS]
Subject: RE: NDA 202379 Zytiga - PMRs and Milestone Dates
Importance: High

Amy~

The PMRs and the corresponding proposed milestone dates are acceptable to us, except where noted below for Study 1748-2.

Please let me know if the revised timing for Study 1748-2 is acceptable to the Division.

Many thanks and all the best!

Christine

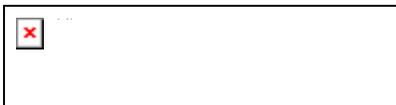
1748-1 Perform an <i>in vitro</i> screen to determine if abiraterone is an inhibitor of human CYP2C8. Based on results from the <i>in vitro</i> screen, a clinical drug-
--

	drug interaction trial may be needed.
	Final Protocol Submission: N/A
	Study Completion: January 2012
	Final Report Submission: June 2012
1748-2	<p>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.</p> <p>Final Protocol Submission: (b) (4) October 2011</p> <p>Trial Completion: (b) (4) October 2013</p> <p>Final Report Submission: (b) (4) April 2014</p>
1748-3	<p>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.</p> <p>Final Protocol Submission: October 2011</p> <p>Trial Completion: April 2013</p> <p>Final Report Submission: November 2013</p>
1748-4	<p>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.</p> <p>Final Protocol Submission: October 2011</p> <p>Trial Completion: April 2013</p> <p>Final Report Submission: November 2013</p>

(b) (4)

Christine M. Woods, BS, MA

No. American Regulatory Affairs, Abiraterone Acetate
CWoods@ITS.JnJ.com



Ortho Biotech Oncology Research & Development

Unit of Cougar Biotechnology, Inc.
 10990 Wilshire Blvd., Suite #1200
 Los Angeles, CA 90024-3913 USA
 310-943-8040 ext. 144 phone
 310-943-8059 fax

From: Tilley, Amy [Amy.Tilley@FDA.HHS.gov]
Sent: Monday, April 11, 2011 2:01 PM
To: Woods, Christine [CGRUS]
Cc: Johnson Reid, Kelly [ORDUS]
Subject: NDA 202379 Zytiga - PMRs and Milestone Dates
Importance: High

Christine,

Below are the PMRs and Milestone dates for NDA 202379 Zytiga.

1748-1 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.

Final Protocol Submission:	N/A
Study Completion:	January 2012
Final Report Submission:	June 2012

1748-2 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.

Final Protocol Submission:	July 2011
Trial Completion:	July 2013

Final Report Submission: January 2014

1748-3 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.

Final Protocol Submission: October 2011
Trial Completion: April 2013
Final Report Submission: November 2013

1748-4 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.

Final Protocol Submission: October 2011
Trial Completion: April 2013
Final Report Submission: November 2013

Please review and respond back by **no later than 1 pm on Wednesday 4-13-11**, with your acceptance of the Milestone dates.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology
Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) |
✉ Amy.Tilley@FDA.HHS.gov



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/s/

AMY R TILLEY
04/13/2011

From: Tilley, Amy
Sent: Monday, April 11, 2011 5:01 PM
To: 'Woods, Christine [CGRUS]' cwoods@its.inj.com
Cc: 'Johnson Reid, Kelly [ORDUS]' kjohnso6@its.inj.com
Subject: NDA 202379 Zytiga - PMRs and Milestone Dates

Importance: High

Follow Up Flag: Follow up
Due By: Wednesday, April 13, 2011 1:00 PM
Flag Status: Flagged
[Christine,](#)

[Below are the PMRs and Milestone dates for NDA 202379 Zytiga.](#)

1748-1 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.

Final Protocol Submission: N/A
Study Completion: January 2012
Final Report Submission: June 2012

1748-2 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.

Final Protocol Submission: July 2011
Trial Completion: July 2013
Final Report Submission: January 2014

1748-3 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.

Final Protocol Submission: October 2011
Trial Completion: April 2013
Final Report Submission: November 2013

1748-4 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.

Final Protocol Submission: October 2011
Trial Completion: April 2013
Final Report Submission: November 2013

Please review and respond back by **no later than 1 pm on Wednesday 4-13-11**, with your acceptance of the Milestone dates.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology
Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
04/11/2011

From: Tilley, Amy
Sent: Friday, April 08, 2011 8:30 AM
To: 'Woods, Christine [CGRUS]' cwoods@its.jnj.com
Cc: Johnson Reid, Kelly [ORDUS] kjohnso6@its.jnj.com
Subject: NDA 202379 Zytiga - FDA response to Spons rationale for PI revs to Sect 2.2 & 8.6

Importance: High

Follow Up Flag: Follow up
Due By: Friday, April 15, 2011 12:00 AM
Flag Status: Flagged

Attachments: Picture (Metafile)
[Christine,](#)

The Clinical Pharmacology Team has the following responses to your rationale for revisions to Sections 2.2 and 8.6.

SPONSORS RATIONALE FOR REVISIONS TO SECTION 2.2



FDA Response:

Using a power model to test dose proportionality from the data submitted for study COU-AA-016, the PK of abiraterone appears to have no major deviations from dose proportionality. The results suggested that the slope for the power model on logarithmic scale for AUC is 0.80 with a 90% confidence interval of (0.69, 0.92), which is overlapped with the confidence interval of (0.8, 1.25). Although the analysis of dose proportionality is confounded due to the presence of large inter-individual variability in exposure, there does not appear to be a major deviation from dose proportionality (Figure 1).

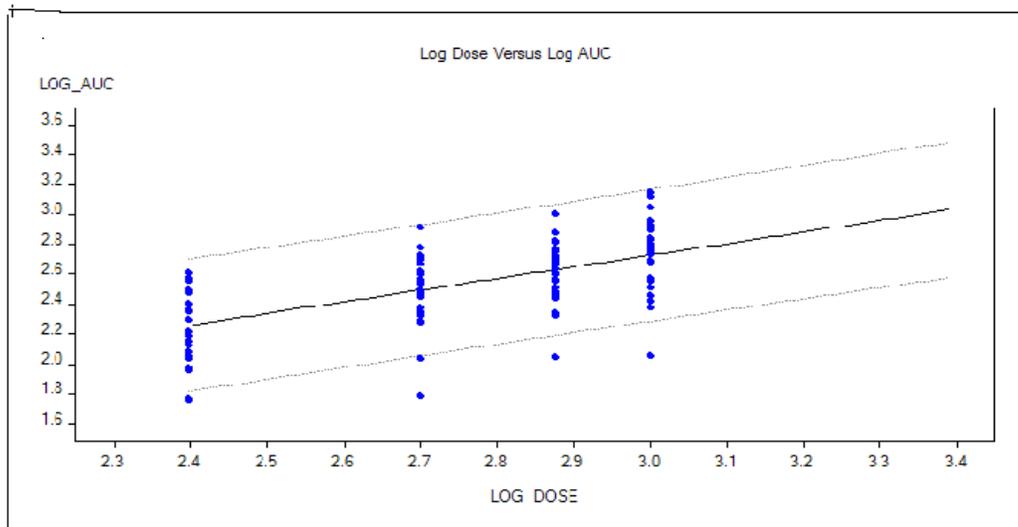
In addition, you used a linear fixed effects model to assess dose proportionality. We generally use the lowest dose tested in the dose ranging study as the reference. Table 1 below shows the results using a linear fixed effects model with the dose of 250 mg as the reference. The test to reference ratio was within the 80 – 125% confidence interval limits for C_{max} at 500, 750 and 1000 mg and for AUC at 500 mg. The 90% confidence intervals did not fall into the 80 – 125% range for the AUC at 750 and 1000 mg although some overlap could be seen. Inter-subject variability was relatively high, with CVs ranging from 49.8 to 63.4% for C_{max} and from 42.0 to 55.8% for the AUCs. Intra-subject variability for most subjects was approximately 31% for AUC_∞ and 42% for C_{max}.

Since it does not appear that the PK of abiraterone has major deviations from dose

proportionality, the single dose PK should be able to predict multiple dose PK. Please refer to the guidance for industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf> for more information.

In addition, in patients with moderate hepatic impairment ALT, AST and bilirubin will be monitored prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. If elevations in ALT and/or AST > 5 x ULN or total bilirubin > 3 x ULN occur in patients with baseline moderate hepatic impairment, abiraterone acetate will be discontinued and patients will not be re-treated. This frequent monitoring and the stopping rules will allow for treatment of patients with moderate hepatic impairment at the reduced dose of 250 mg and we recommend that these recommendations stay in the label to allow for the treatment of this patient population.

Figure 1: Log AUC (ng*hr/mL) Plotted Against Log of Dose (mg) in the Dose Proportionality Study COU-AA-016 in the Dose Range of 250 to 1000 mg.



The dotted lines indicate the confidence interval around the estimates

Table 1: Statistical Analysis of Dose-Normalized Pharmacokinetic Parameters Estimated After Single Doses of Abiraterone Acetate Ranging from 250 – 1000 mg in Healthy Fasting Subjects in Study COU-AA-016.

PK Parameter	Dose	LS Mean (normalized to 250 mg)	Test/Reference Ratio (%)	90% CI
Cmax (ng/mL)	250 (Reference)	31.33		
	500	29.83	95.23	(79.02, 114.77)
	750	26.12	83.39	(69.20, 100.49)

	1000	25.68	81.98	(68.02, 98.80)
AUC_∞ (hr*ng/mL)	250	181.16		
	500	160.54	88.62	(77.00, 102.00)
	750	139.85	77.20	(67.09, 88.83)
	1000	140.36	77.48	(67.32, 89.17)

Should you have further comments and/or revisions please respond to this email as soon as possible.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology
Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
04/08/2011



NDA 202379

CONFIRMATION OF ISSUES DISCUSSED

Cougar Biotechnology, Inc.

On behalf of Centocor Ortho Biotech, Inc.

Attention: Christine M. Woods, BS, MA

Associate Director, Regulatory Affairs

10990 Wilshire Blvd., Suite #1200

Los Angeles, CA 90024

Dear Ms. Woods:

Please refer to your New Drug Application (NDA) submitted on December 20, 2010, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zytiga™ (abiraterone acetate) Tablets 250 mg.

We also refer to your submissions dated March 21, 2011, and March 31, 2011.

As discussed in the teleconference on March 29, 2011, between the FDA and Centocor Ortho Biotechnology, Inc., teleconference attendees and agreements reached are listed below:

Attendees:

FDA

Deborah Mesmer, M.S., Regulatory Health Project Manager-
Quality

Patrick J. Marroum, Ph.D., Biopharmaceutics Lead

Tien-Mien Chen, Ph.D., Biopharmaceutics Reviewer

Centocor Ortho Biotechnology, Inc.

Robert Ghadimian, CMC Regulatory Affairs

Hans Vermeersch, CMC Leader

Mark Pilato, CMC Regulatory Affairs

Robert Charnas, Global Regulatory Affairs Leader

Christine Woods, No. American Regulatory Affairs

Vinny Dhopeswarkar, Pharmaceutical Development

Susan Lerke, Analytical Development

Areti Manola, Statistics

Milind Acharya, Biopharmaceutics / Clinical Pharmacology Leader

Discussion:

FDA stated that the recommended dissolution specification for the drug product is $Q = \text{(b) (4)}$ at 30 minutes. FDA recommended that this specification be implemented immediately in the NDA. FDA also confirmed that the recommended specification can be reassessed following approval, at the Applicant's discretion and in conformance with all applicable regulations. The Applicant confirmed that they would consider this proposal and respond by March 31, 2011.

We also acknowledge your submission dated March 31, 2011, proposing a revised drug product specification for dissolution:

Q is (b) (4) at 30 min.

We acknowledge that you intend to re-evaluate the proposed specification after one year. We want to remind you that if the regulatory specification needs to be changed after approval, you will need to submit a supplement to the NDA. Please see, *Guidance to Industry: Changes to an Approved NDA or ANDA*.

If you have any questions, call Deborah Mesmer, Regulatory Health Project Manager, at 301-796-4023

Sincerely,

{See appended electronic signature page}

Sarah Pope Miksinski, Ph.D.
Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

SARAH P MIKSINSKI
04/08/2011

From: Tilley, Amy
Sent: Thursday, April 07, 2011 9:56 AM
To: 'Woods, Christine [CGRUS]' cwoods@its.jnj.com
Cc: Johnson Reid, Kelly [ORDUS] kjohnso6@its.jnj.com
Subject: RE: NDA 202379 Zytiga – Clinical IR sent 4-6-11

Importance: High
Christine.

Yes we will need this information to be sent in officially to the NDA and/or IND if applicable. Please include a copy of the specific requested Information Request when responding.

Just send me a courtesy email when the official submission is sent.

Thanks.

Amy

From: Woods, Christine [CGRUS] [<mailto:CWoods@ITS.JNJ.com>]
Sent: Wednesday, April 06, 2011 6:03 PM
To: Tilley, Amy
Cc: Johnson Reid, Kelly [ORDUS]
Subject: RE: NDA 202379 Zytiga - Clinical IR sent 4-6-11
Importance: High

Amy~

The reversed column headings for causality in the DSI Listings did affect all sites, not just the 5 referenced sites (#139, 159, 600, 601 and 701).

Do you need me to amend the NDA with this response and/or with the remaining corrected DSI Listings?

Thank you!

Christine

Christine M. Woods, BS, MA
No. American Regulatory Affairs, Abiraterone Acetate
CWoods@ITS.JnJ.com



Ortho Biotech Oncology Research & Development

Unit of Cougar Biotechnology, Inc.
10990 Wilshire Blvd., Suite #1200
Los Angeles, CA 90024-3913 USA
310-943-8040 ext. 144 phone
310-943-8059 fax

From: Tilley, Amy [Amy.Tilley@FDA.HHS.gov]
Sent: Wednesday, April 06, 2011 1:23 PM
To: Woods, Christine [CGRUS]
Cc: Johnson Reid, Kelly [ORDUS]
Subject: NDA 202379 Zytiga - Clinical IR sent 4-6-11
Importance: High

Christine,

Below is an additional Clinical Information Request.

We acknowledge your submission to IND #071023 S/N 0876 and NDA #202379 amendment 0016. Your responses to our information request sent on 4-1-2011 are acceptable. However, please clarify the scope of the reversed column headings for causality. We would like to confirm that this error occurred only for the AE listings of the referenced 5 sites (#139, 159, 600, 601 and 701) and not to other sites.

Please respond to the above information request [no later than Friday, April 8, 2011.](#)

Thank you.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology
Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) |
✉ Amy.Tilley@FDA.HHS.gov



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/s/

AMY R TILLEY
04/07/2011

From: Tilley, Amy
Sent: Wednesday, April 06, 2011 4:23 PM
To: 'Woods, Christine [CGRUS]' cwoods@its.inj.com
Cc: Johnson Reid, Kelly [ORDUS] kjohnso@its.inj.com
Subject: NDA 202379 Zytiga - Clinical IR sent 4-6-11

Importance: High

Follow Up Flag: Follow up
Due By: Friday, April 08, 2011 12:00 AM
Flag Status: Flagged

[Christine,](#)

[Below is an additional Clinical Information Request.](#)

We acknowledge your submission to IND #071023 S/N 0876 and NDA #202379 amendment 0016. Your responses to our information request sent on 4-1-2011 are acceptable. However, please clarify the scope of the reversed column headings for causality. We would like to confirm that this error occurred only for the AE listings of the referenced 5 sites (#139, 159, 600, 601 and 701) and not to other sites.

[Please respond to the above information request no later than Friday, April 8, 2011.](#)

Thank you.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology
Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993

 301.796.3994 (phone) • 301.796.9845 (fax) |  amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
04/06/2011

From: Tilley, Amy
Sent: Wednesday, April 06, 2011 1:56 PM
To: 'Woods, Christine [CGRUS]'
Cc: Johnson Reid, Kelly [ORDUS]
Subject: NDA 202379 Zytiga - DMEPA Container Revision sent 4-6-11

Importance: High

Follow Up Flag: Follow up
Due By: Tuesday, April 12, 2011 12:00 AM
Flag Status: Flagged

Christine,

Below is an Information Request from DMEPA regarding the Container label.

DMEPA recommends including a warning on the container label that is consistent with the handling instructions located in Section 16 - How Supplied /Storage and Handling of the insert label. Currently, the instruction reads:

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

Please revise your container label with the above information and resubmit officially to the NDA and as a courtesy email to me **no later than Tuesday, April 12, 2011**.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology
Products, CDER, FDA

10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
04/06/2011

From: Tilley, Amy
Sent: Tuesday, April 05, 2011 6:16 PM
To: 'Woods, Christine [CGRUS]' cwoods@its.jnj.com
Cc: Johnson Reid, Kelly [ORDUS] kjohnso6@its.jnj.com
Subject: NDA 202379 Zytiga - FDA Revised PI Sections 12.3 - 12.4

Importance: High

Follow Up Flag: Follow up
Due By: Friday, April 08, 2011 12:00 PM
Flag Status: Flagged

Attachments: FDA Revised PI Sections 12 3 - 12 4 sent 4-5-11.doc

Christine,

Attached is a Word version with track changes on, of the FDA Revised PI Sections 12.3 & 12.4 [only](#).

Please review and/or revise these sections of the PI [in this Word version only](#). Do not revise any other sections of the PI or send any other document back to us to review. You may revise the Word document below and send it back to me via email. At this time you are not required to submit the Word document officially.



FDA Revised PI
Sections 12 3 -...

Please respond to the above inquiry by Noon on Friday, April 8, 2011.

We reiterate do not revise any other sections of the PI or send back any other document except the Word version attached above.

If you have questions please contact me at the information listed below.

Your strict adherence to this request is greatly appreciated.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology
Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
04/05/2011

From: Tilley, Amy
Sent: Friday, April 01, 2011 12:54 PM
To: 'Woods, Christine [CGRUS]' cwoods@its.inj.com
Cc: 'Johnson Reid, Kelly [ORDUS]' kjohnso6@its.inj.com
Subject: RE: NDA 202379 Zytiga - Update to Clinical Information Request sent 3-31-11

Importance: High

Follow Up Flag: Follow up
Due By: Wednesday, April 06, 2011 12:00 AM
Flag Status: Red

[Christine,](#)

[Below is an update to our Clinical Information Request sent 3-31-11.](#)

We acknowledge your communication sent via email on 3-30-11 containing data listings for sites # 139, 159, 600, 601 and 6701 with your corrections to the previously reversed column headings *Causality (Abiraterone)* and *Causality (Prednisone/Prednisolone)*. We are in the process of reviewing them against NDA data listings. However, all other items in the IR sent to you on 3-31-11 still apply

[Please respond to this Information Request as soon as possible.](#)

[Regards.](#)

[Amy Tilley](#)

[Amy Tilley | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA](#)
[10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993](#)
[301.796.3994 \(phone\) • 301.796.9845 \(fax\) | !\[\]\(20d484b78cd20b354bf70b727e7c3d79_img.jpg\) amy.tilley@fda.hhs.gov](#)



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From: Tilley, Amy
Sent: Thursday, March 31, 2011 4:15 PM
To: 'Woods, Christine [CGRUS]'
Cc: Johnson Reid, Kelly [ORDUS]
Subject: NDA 202379 Zytiga - Clinical Information Request
Importance: High

[Christine,](#)

[Below is an Information Request from the Clinical Review Team.](#)

During FDA inspections of site #600 at Royal Marsden Hospital (Dr. de Bono PI) and site #601 at University College Hospital (Dr. Harland PI), it was noted that the data with respect to adverse event reporting and causality attribution as recorded in source documentation and Case Report Forms for all subject records reviewed did

not match the respective data listings submitted to the NDA for Study COU-AA-301.

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

Please respond officially as soon as possible.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology
Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
04/01/2011

From: Tilley, Amy
Sent: Thursday, March 31, 2011 4:15 PM
To: 'Woods, Christine [CGRUS]' cwoods@its.jnj.com
Cc: Johnson Reid, Kelly [ORDUS] kjohnso6@its.jnj.com
Subject: NDA 202379 Zytiga - Clinical Information Request

Importance: High

Follow Up Flag: Follow up
Due By: Monday, April 04, 2011 12:00 AM
Flag Status: Flagged

[Christine,](#)

[Below is an Information Request from the Clinical Review Team.](#)

During FDA inspections of site #600 at Royal Marsden Hospital (Dr. de Bono PI) and site #601 at University College Hospital (Dr. Harland PI), it was noted that the data with respect to adverse event reporting and causality attribution as recorded in source documentation and Case Report Forms for all subject records reviewed did not match the respective data listings submitted to the NDA for Study COU-AA-301.

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

[Please respond officially as soon as possible.](#)

[Regards.](#)

[Amy Tilley](#)

[Amy Tilley | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA](#)
[10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD](#)
[20993](#)

[301.796.3994 \(phone\)](tel:301.796.3994) • [301.796.9845 \(fax\)](tel:301.796.9845) | [✉ amy.tilley@fda.hhs.gov](mailto:amy.tilley@fda.hhs.gov)



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/s/

AMY R TILLEY
03/31/2011

Tilley, Amy

From: Tilley, Amy
nt: Wednesday, March 30, 2011 5:29 PM
o: 'Woods, Christine [CGRUS]'
Cc: Johnson Reid, Kelly [ORDUS]
Subject: NDA 202379 Zytiga - FDA Revised PI sects 2.2, 7 - 8, 12.1 - 12.2 & 13

Importance: High

Follow Up Flag: Follow up
Due By: Monday, April 04, 2011 11:00 AM
Flag Status: Red

Attachments: FDA Revised PI Sects 2-2 7 - 8 12-1 - 12-2 13 sent 3-30-11.doc

Christine,

Attached is a Word version with track changes on, of the FDA Revised PI sects 2.2, 7 - 8, 12.1 - 12.2 & 13 only.

Please review and/or revise these sections of the PI in this Word version only. Do not revise any other sections of the PI or send any other document back to us to review. You may revise the Word document below and send it back to me via email. At this time you are not required to submit the Word document officially.



FDA Revised PI
Sects 2-2 7 - 8...

Please respond to the above inquiry by Noon on Monday, April 4, 2011.

We reiterate do not revise any other sections of the PI or send back any other document except the Word version attached above.

If you have questions please contact me at the information listed below.

Your strict adherence to this request is greatly appreciated.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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/s/

AMY R TILLEY
03/30/2011

MEMORANDUM OF TELECONFERENCE

MEETING DATE: March 29, 2011
TIME: 3:00 pm ET
LOCATION: White Oak
APPLICATION: NDA 202379
DRUG NAME: abiraterone acetate tablets, 250 mg
TYPE OF MEETING: TCON

MEETING CHAIR: Patrick J. Marroum, Ph.D., Biopharmaceutics Lead

MEETING RECORDER: Deborah Mesmer, M.S., Regulatory Health Project Manager-Quality

ATTENDEES:

CDER/ONDQA

Deborah Mesmer, M.S., Regulatory Health Project Manager-Quality

Patrick J. Marroum, Ph.D., Biopharmaceutics Lead

Tien-Mien Chen, Ph.D., Biopharmaceutics

Centocor Ortho Biotech, Inc.

Robert Ghadimian, CMC Regulatory Affairs

Hans Vermeersch, CMC Leader

Mark Pilato, CMC Regulatory Affairs

Robert Charnas, Global Regulatory Affairs Leader

Christine Woods, No. American Regulatory Affairs

Vinny Dhopeshwarkar, Pharmaceutical Development

Susan Lerke, Analytical Development

Areti Manola, Statistics

Milind Acharya, Biopharmaceutics / Clinical Pharmacology Leader

BACKGROUND:

Refer to FDA Biopharmaceutics information request dated March 15, 2011. Refer also to applicant responses dated March 21, 2011 and March 31, 2011.

MEETING OBJECTIVES:

To reach agreement on dissolution specifications.

DISCUSSION POINTS:

FDA stated that the dissolution specification for the drug product should be tightened to $Q = \text{(b) (4)}$ at 30 minutes. Applicant referred to release and stability data and stated that a high percentage of batches evaluated require at least Stage 2 (S2) testing for $Q = \text{(b) (4)}$ at 30 minutes, so $Q = \text{(b) (4)}$ would have a high failure rate looking at individuals. Applicant proposes $Q = \text{(b) (4)}$ at

30 minutes because a “normal” specification should not have to go to S2 or S3. Q = (b) (4) places additional analytical burden on the company and could impact shelf life.

FDA clarified that FDA policy is to set the specification based on the mean value, not on individual value to pass S1 or S2. To protect the consumer, Q = (b) (4) minimizes the chance to deliver a dose that is less than (b) (4) of the intended dose. FDA standard is no more than (b) (4) difference in dose. FDA stated that the applicant’s data support Q = (b) (4) at 30 minutes. FDA proposed this could be an interim specification to be reassessed in 1 year.

Applicant requested a written commitment from FDA regarding the interim amendment. FDA committed to provide a written correspondence. Applicant responded that they would like to consider this proposal internally and would respond by March 31, 2011.

DECISIONS (AGREEMENTS) REACHED:

Applicant responded that they would consider this proposal and respond by March 31, 2011.

Post-meeting note: Applicant submitted on March 31, 2011, the revised the drug product specifications for dissolution:

Q = (b) (4) at 30 minutes, to be reassessed in 1 year. Drug product batches currently on stability will be assessed in accordance with this new interim dissolution specification.

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/s/

DEBORAH M MESMER
04/05/2011

PATRICK J MARROUM
04/06/2011

From: Tilley, Amy
Sent: Monday, March 28, 2011 2:58 PM
To: 'Woods, Christine [CGRUS]' cwoods@its.inj.com
Cc: 'Johnson Reid, Kelly [ORDUS]' kjohnso6@its.inj.com
Subject: ** TIME SENSITIVE ** NDA 202379 Zytiga - Clinical/Safety Information
Request
Importance: High
Follow Up Flag: Follow up
Due By: Wednesday, March 30, 2011 4:00 PM
Flag Status: Flagged
[Christine](#),

The Clinical Review Team has the following Information Request (IR).

During our analysis we have found two discrepancies that require clarification:

1. We have been able to reproduce table #5 in the summary of clinical safety based on the DOSEMOD dataset. However, when querying the AE dataset, only 19 patients (rather than 28) are listed as having had dose reductions (AEACNA=2). The following patients who had a dose reduction based on the DOSEMOD dataset were not found in the AE dataset.

COU-AA-301:

116-0001
118-0009
124-0007
127-0003
135-0003
158-0002
158-0011
158-0012
609-0007
617-0003

Please clarify what led to the dose reductions in the 11 patients whom are missing dose reduction (AEACNA=2) categorization in the AE dataset.

2. We also note that there is a discrepancy between the EX dataset and your table #5 in the summary of clinical safety. There are more maximum dose reductions to 750mg noted in your table than in your EX dataset. Based on the EX dataset, 16 patients had maximum dose reductions to 750mg while 11 patients got dose reduced to 500mg. Furthermore, there was one patient who got dose reduced to 250mg. Please clarify.

A brief summary of the differences between the EX dataset, AE dataset and DOSEMOD datasets which may explain discrepancies such as the above would be helpful.

Please respond to the above Clinical IR [no later than COB 3-30-11](#) both officially to the NDA and as a courtesy email.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology
Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD

20993

 301.796.3994 (phone) • 301.796.9845 (fax) |  amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
03/28/2011

From: Tilley, Amy
Sent: Wednesday, March 23, 2011 4:51 PM
To: 'Woods, Christine [CGRUS]' cwoods@its.inj.com
Cc: Johnson Reid, Kelly [ORDUS] kjohnso6@its.inj.com
Subject: NDA 202379 Zytiga - Additional Container Information Request

Follow Up Flag: Follow up
Due By: Friday, March 25, 2011 12:00 AM
Flag Status: Flagged

Attachments: Picture (Enhanced Metafile)
[Christine,](#)

Below are additional container revisions from the DMEPA and ONDQA Review Teams.

Container Label, 250 mg tablet

1. Delete the graphic located on the left-side of the proprietary name.
2. Increase the prominence of the strength, *250 mg*.
3. Relocate the statement, *Each tablet contains: abiraterone acetate 250 mg*, lower, toward the bottom of the label.

(b) (4)

Your prompt response is greatly appreciated.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology
Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD

20993

 301.796.3994 (phone) • 301.796.9845 (fax) |  amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
03/23/2011

From: Tilley, Amy
Sent: Wednesday, March 23, 2011 4:44 PM
To: Woods, Christine [CGRUS] cwoods@its.inj.com
Cc: Johnson Reid, Kelly [ORDUS] kjohnso6@its.inj.com
Subject: NDA 202379 Zytiga - Additional Clinical Information Request

Importance: High

Follow Up Flag: Follow up
Due By: Friday, March 25, 2011 12:00 AM
Flag Status: Flagged

[Christine,](#)

[Below is an additional request from the Clinical Review Team.](#)

We note that two patients in the phase 3 trial and 3 patients in the pooled phase 1/2 safety data experienced adrenal insufficiency. We have been unable to locate the narratives for these events. Please direct us to these narratives or submit narratives if they do not exist.

**COU-AA-301 914-005
COU-AA-301 153-001
COU-AA-002-176-055
COU-AA-003-160-105
COU-AA-003-600-033**

[As always, please respond to this request officially as soon as possible and as a courtesy email.](#)

[Kind Regards.](#)

[Amy Tilley](#)

[Amy Tilley](#) | [Regulatory Project Manager](#) | [Division of Drug Oncology Products, CDER, FDA](#)
[10903 New Hampshire Avenue, Room 2177](#) | [Silver Spring, MD 20993](#)

[☎ 301.796.3994 \(phone\)](tel:301.796.3994) • [301.796.9845 \(fax\)](tel:301.796.9845) | [✉ amy.tilley@fda.hhs.gov](mailto:amy.tilley@fda.hhs.gov)



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/s/

AMY R TILLEY
03/23/2011

From: Tilley, Amy
Sent: Wednesday, March 23, 2011 2:50 PM
To: 'Woods, Christine [CGRUS]'
Cc: Johnson Reid, Kelly [ORDUS]
Subject: NDA 202379 Zytiga - Clinical Information Requests

Importance: High

Follow Up Flag: Follow up
Due By: Friday, April 01, 2011 12:00 AM
Flag Status: Flagged

[Christine,](#)

[Below are the Clinical Team's Information Requests.](#)

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

For Study Subject 116-0005, the reported total dose of previous docetaxel use was 58492 mg in the CRF and Dataset CONMED. That dose seems implausible for the patient based on his BSA of 2.23 M² and the documented docetaxel treatment period between 2/21/06-2/5/08. The reviewer estimated that the total docetaxel dose might be 5849.2 mg. Please clarify what was the total docetaxel dose the patient actually received before enrollment.

[To facilitate our review of this application, please officially submit your response as soon as possible. Also, send me a courtesy email containing your official response.](#)

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology
Products, CDER, FDA

10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
03/23/2011

From: Tilley, Amy

Sent: Tuesday, March 22, 2011 12:46 PM

To: 'Woods, Christine [CGRUS]' <CWoods@ITS.JNJ.com>

Subject: RE: NDA 202379 Zytiga – Information Request re: 4 Month Safety Update Report

Importance: High
Christine,

The Clinical Team has a response to your email below regarding your proposal of the 4 mo Safety Update Report.

Your 2% threshold for reporting increases in adverse events of any grade is acceptable.

In addition, provide an analysis and summary of ANY increase in grade ≥ 3 adverse events and ANY increase in serious and unexpected adverse events.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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Tilley, Amy

From: Woods, Christine [CGRUS] [CWoods@ITS.JNJ.com]
Sent: Monday, March 21, 2011 6:50 PM
To: Tilley, Amy
Subject: RE: NDA 202379 Zyliga - Information Request re: 4 Month Safety Update Report
Attachments: emfinfo.txt

Amy:

In response to FDA Request #2 in the e-mail below, we propose to summarize the AE preferred terms if the observed frequency difference between the abiraterone acetate groups in the original NDA versus the 120-day safety update, or between the placebo groups in the original NDA versus the 120-day safety update is at least 2%. Similarly, for severity, we propose to summarize if the difference in the incidence of Grade 3 or 4 events is at least 2%. I've included an example table below for your reference.

Reference ID: 2921797

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

3/22/2011

310-943-8059 fax

From: Tilley, Amy [Amy.Tilley@FDA.HHS.gov]

Sent: Tuesday, March 15, 2011 7:52 AM

To: Woods, Christine [CGRUS]

Cc: Johnson Reid, Kelly [ORDUS]

Subject: NDA 202379 Zyiga - Information Request re: 4 Month Safety Update Report

Importance: High

Christine,

Please include the following in addition to your 4 month safety update:

1. Analyses, summary and tabulations of the following AEs determined to be of special interest:

- Hypokalemia
- Peripheral edema
- Hypertension
- AST, ALT and Bilirubin
- Cardiac events including:
 - Arrhythmia, Myocardial infarction and Congestive heart failure
- Muscle discomfort to include:
 - Musculoskeletal pain, myalgia, muscle spasms, muscular weakness
- Joint discomfort to include:
 - Arthritis, arthralgia, joint swelling, joint stiffness
- Urinary tract infection
- Diarrhea
- Dry mouth
- Dyspepsia
- Hypophosphatemia
- Hyperglycemia
- Hypertriglyceridemia

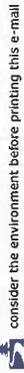
2. Prepare an analysis of unexpected AEs or any increase in the frequency or severity of adverse events reported in the original submission.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993

301.796.3994 (phone) • 301.796.9845 (fax) | ✉ Amy.Tilley@FDA.HHS.gov



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/s/

AMY R TILLEY
03/22/2011

Tilley, Amy

From: Tilley, Amy
Sent: Monday, March 21, 2011 1:36 PM
To: 'Woods, Christine [CGRUS]'
Subject: RE: NDA 202379 Request for Proprietary Name Review
Importance: High
Attachments: NDA 202379 Prop Name Granted Ltr.pdf

Christine,

Attached is a copy of the Proprietary Name Request Letter which was signed on 3-14-11.

The Document Room mails the official letters out so perhaps you will receive the official letter within the next few days.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology Products,
 CDER, FDA
 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
 ☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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From: Woods, Christine [CGRUS] [mailto:CWoods@ITS.JNJ.com]
Sent: Monday, March 21, 2011 11:38 AM
To: Tilley, Amy
Subject: RE: NDA 202379 Request for Proprietary Name Review
Importance: High

Amy~

I didn't receive a "read receipt" for the message below, so I wanted to be sure it reached you. Should we expect to hear something on our proposed tradename today, since the PDUFA date was yesterday?

Thanks for your help!

Christine

From: Woods, Christine [CGRUS]
Sent: Friday, March 18, 2011 11:54 AM
To: Tilley, Amy
Subject: RE: NDA 202379 Request for Proprietary Name Review

Amy~

The PDUFA date for our NDA Request for Proprietary Name Review is this Sunday, 20 MAR 2011. Should we expect to hear something on our proposed tradename today?

Thank you and have a wonderful weekend!

Christine

From: Tilley, Amy [Amy.Tilley@FDA.HHS.gov]
Sent: Wednesday, February 16, 2011 7:50 AM
To: Woods, Christine [CGRUS]
Subject: RE: NDA 202379 Request for Proprietary Name Review
Importance: High

Christine,

The OSE PDUFA date for review of the tradename for this application is 3/20/11. You should expect to hear a response regarding your proposed tradename, Zytiga, by that date.

This is consistent with the 90-day clock for all NDA proprietary name requests.

Regards.

Amy

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
 10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
 ☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ Amy.Tilley@FDA.HHS.gov

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From: Woods, Christine [CGRUS] [CWoods@ITS.JnJ.com]
Sent: Tuesday, February 15, 2011 6:58 PM
To: Tilley, Amy
Subject: NDA 202379 Request for Proprietary Name Review

Amy~

We are approaching the 60-day mark for the AA NDA Request for Proprietary Name Review, which I believe is Friday, 18 FEB 2011. Are you able to provide me an update on where we currently stand in the DMEPA queue and when we might expect some feedback? Our team has been working with Sarah Simon and Sammie Beam in DMEPA. Any update is appreciated.

Many thanks & all the best!!

Christine

Christine M. Woods, BS, MA
 Associate Director, Regulatory Affairs
 No. American Regulatory Lead, Abiraterone Acetate
CWoods@ITS.JnJ.com

Ortho Biotech Oncology Research & Development
Unit of Cougar Biotechnology, Inc.
10990 Wilshire Blvd., Suite #1200
Los Angeles, CA 90024-3913 USA
310-943-8040 ext. 144 phone
310-943-8059 fax



NDA 202379

INFORMATION REQUEST

Ortho Biotech Oncology Research & Development
Unit of Cougar Biotechnology, Inc.
On behalf of Centocor Ortho Biotech, Inc.
Attention: Christine M. Woods, BS, MA
Associate Director, Regulatory Affairs
10990 Wilshire Blvd., Suite #1200
Los Angeles, CA 90024

Dear Ms. Woods:

Please refer to your New Drug Application (NDA) submitted on December 20, 2010, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zytiga™ (abiraterone acetate) Tablets 250 mg.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments. We request a written response no later than March 21, 2011, in order to continue our evaluation of your NDA.

Your proposed dissolution method as shown below is acceptable.

Apparatus: USP 2 (Paddle) at 50 rpm
Medium: Phosphate buffer (pH 4.5) 900 mL containing 0.25% SLS, at 37°C

However, a mean of (b) (4) of Zytiga immediate release tablet dissolved in 30 min, therefore, your proposed dissolution specifications need to be tightened as follows.

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

Revise and implement the proposed dissolution specifications.

If you have any questions, call Deborah Mesmer, Regulatory Health Project Manager, at 301-796-4023.

Sincerely,

{See appended electronic signature page}

Sarah Pope Miksinski, Ph.D.
Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

SARAH P MIKSINSKI
03/15/2011

From: Tilley, Amy
Sent: Tuesday, March 15, 2011 10:52 AM
To: 'Woods, Christine [CGRUS]'
Cc: Johnson Reid, Kelly [ORDUS]
Subject: NDA 202379 Zytiga - Information Request re: 4 Month Safety Update Report

Importance: High
[Christine,](#)

Please include the following in addition to your 4 month safety update:

1. Analyses, summary and tabulations of the following AEs determined to be of special interest:

Hypokalemia

Peripheral edema

Hypertension

AST, ALT and Bilirubin

Cardiac events including:

Arrhythmia, Myocardial infarction and Congestive heart failure

Muscle discomfort to include:

Musculoskeletal pain, myalgia, muscle spasms, muscular weakness

Joint discomfort to include:

Arthritis, arthralgia, joint swelling, joint stiffness

Urinary tract infection

Diarrhea

Dry mouth

Dyspepsia

Hypophosphatemia

Hyperglycemia

Hypertriglyceridemia

2. Prepare an analysis of unexpected AEs or any increase in the frequency or severity of adverse events reported in the original submission.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology
Products, CDER, FDA

10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
03/15/2011



NDA 202379

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Centocor Ortho Biotech, Inc.
c/o:
Ortho Biotech Oncology Research & Development
Unit of Cougar Biotechnology, Inc.
10990 Wilshire Blvd., Suite #1200
Los Angeles, California 90024-3913

ATTENTION: Christine M. Woods
Associate Director, Regulatory Affairs

Dear Ms. Woods:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abiraterone Acetate Oral Tablets, 250 mg.

We also refer to your December 20, 2010, correspondence, received December 20, 2010, requesting review of your proposed proprietary name, Zytiga. We have completed our review of the proposed proprietary name, Zytiga and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your December 20, 2010, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, call Sarah Simon, Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5205. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Alberta Davis-Warren at 301-796-3908.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
03/14/2011

From: Tilley, Amy
Sent: Friday, March 11, 2011 12:38 PM
To: 'Woods, Christine [CGRUS]' CWoods@ITS.JNJ.com
Cc: Johnson Reid, Kelly [ORDUS] kjohnso6@its.jnj.com
Subject: RE: NDA #202379 4-Mo Safety Update
[Christine,](#)

(b) (4)

Your proposed submission date of 4-18-11 for the 4mo safety report update is acceptable.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology
Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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From: Woods, Christine [CGRUS] [<mailto:CWoods@ITS.JNJ.com>]
Sent: Thursday, March 10, 2011 6:23 PM
To: Tilley, Amy
Cc: Johnson Reid, Kelly [ORDUS]
Subject: RE: NDA #202379 4-Mo Safety Update

Amy~

(b) (4)

(b) (4) If not, does the Division agree to the proposal above?

Thank you!

Christine

From: Tilley, Amy [Amy.Tilley@FDA.HHS.gov]
Sent: Thursday, March 10, 2011 7:05 AM
To: Woods, Christine [CGRUS]
Cc: Johnson Reid, Kelly [ORDUS]
Subject: RE: NDA #202379 4-Mo Safety Update

Christine,

Yes, we need to understand the submission timing before we can answer whether or not the 4 month safety update [REDACTED] (b) (4)

Amy

From: Woods, Christine [CGRUS] [CWoods@ITS.JnJ.com]
Sent: Wednesday, March 09, 2011 7:26 PM
To: Tilley, Amy
Cc: Johnson Reid, Kelly [ORDUS]
Subject: RE: NDA #202379 4-Mo Safety Update

Amy~

I just want to be sure that I understand your response. [REDACTED] (b) (4)

Thanks!

Christine

From: Tilley, Amy [Amy.Tilley@FDA.HHS.gov]
Sent: Wednesday, March 09, 2011 1:11 PM
To: Woods, Christine [CGRUS]
Cc: Johnson Reid, Kelly [ORDUS]
Subject: RE: NDA #202379 4-Mo Safety Update
Importance: High

Christine,

How soon could you submit the 4 month safety report?

Thanks.

Amy

From: Woods, Christine [CGRUS] [CWoods@ITS.JnJ.com]
Sent: Tuesday, March 08, 2011 3:19 PM
To: Tilley, Amy

Cc: Johnson Reid, Kelly [ORDUS]
Subject: NDA #202379 4-Mo Safety Update

Dear Amy~

In the Pre-NDA Meeting correspondence, FDA noted (b) (4) (b) (4) as an expedited review was planned at that time. We later learned that an expedited review was not possible, but we were granted Priority Review Status.

(b) (4)

Thanks!

Christine

Christine M. Woods, BS, MA
No. American Regulatory Affairs, Abiraterone Acetate
CWoods@ITS.JnJ.com

Ortho Biotech Oncology Research & Development
Unit of Cougar Biotechnology, Inc.
10990 Wilshire Blvd., Suite #1200
Los Angeles, CA 90024-3913 USA
310-943-8040 ext. 144 phone
310-943-8059 fax

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/s/

AMY R TILLEY
03/11/2011

From: Woods, Christine [CGRUS] CWoods@ITS.JNJ.com
Sent: Wednesday, March 09, 2011 1:27 PM
To: Tilley, Amy
Cc: Johnson Reid, Kelly [ORDUS] kjohnso6@its.jnj.com
Subject: RE: *** TIME SENSITIVE*** NDA 202379 Zytiga - Updated Information Request
re: ECG Waveforms

Importance: High

Attachments: emfinfo.txt
Amy~

We confirm that the XML files requested on 28 JAN 2011 have been submitted to the ECG Warehouse.

Please note the XML dataset uploaded into the ECG warehouse only contains the ECG records up to and including the Cycle 2 Day 2 visits. This information was analyzed in the Biomedical System expert report and is included in the NDA. However, the SAS dataset included in the NDA submission contains ECG data beyond the Cycle 2 Day 2 visit.

Please note that the descriptors for two visits referenced in the SAS dataset included in the NDA and in the XML file uploaded to the ECG warehouse differ from the visit descriptors used in the medical and statistical report found in Appendix 1.7 of the Clinical Study Report for COU-AA-006 (Module 5.3.5.2) as shown in the table below.

Nomenclature	Cycle 1 Day 1 (24 hours Post Dose) & Cycle 2 Day 1 (24 hours Post Dose)	Cycle 1 Day 2 (24 hours Post Dose) & Cycle 2 Day 2 (24 hours Post Dose)
Medical and statistical report of the ECG analysis found in the COU-AA-006 CSR, Appendix 1.7	✓	
SAS dataset submitted in NDA		✓
XML file in ECG warehouse		✓

These differences in nomenclature do not affect the conclusions of the ECG analysis provided in the NDA.

Please let me know if you have any questions. Thank you!

Christine

Christine M. Woods, BS, MA
No. American Regulatory Affairs, Abiraterone Acetate
CWoods@ITS.JnJ.com

Ortho Biotech Oncology Research & Development
Unit of Cougar Biotechnology, Inc.
10990 Wilshire Blvd., Suite #1200
Los Angeles, CA 90024-3913 USA
310-943-8040 ext. 144 phone
310-943-8059 fax

From: Tilley, Amy [Amy.Tilley@FDA.HHS.gov]
Sent: Wednesday, March 09, 2011 9:26 AM
To: Woods, Christine [CGRUS]
Cc: Johnson Reid, Kelly [ORDUS]
Subject: *** TIME SENSITIVE*** NDA 202379 Zytiga - Updated Information Request re: ECG Waveforms
Importance: High

Christine,

Below is an updated Information Request from the Clinical Pharmacology and QT-IRT Reviewer Team.

We have previously requested in an email dated 1/31/2011 that you submit the ECG waveforms to the ECG warehouse www.ecgwarehouse.com. These should be submitted no later than **11 am on March 16, 2011. The QT-IRT cannot make a conclusion on the effect of abiraterone acetate on the QT/QTc interval without reviewing the waveforms.**

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) |
✉ Amy.Tilley@FDA.HHS.gov
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/s/

AMY R TILLEY
03/09/2011

Tilley, Amy

From: Tilley, Amy
Sent: Tuesday, March 08, 2011 5:06 PM
To: 'Woods, Christine [CGRUS]'
Cc: Johnson Reid, Kelly [ORDUS]
Subject: NDA 202379 Zytiga - FDA Revised PI Sections 11 14 16

Importance: High

Follow Up Flag: Follow up
Due By: Tuesday, March 15, 2011 12:00 AM
Flag Status: Flagged

Attachments: NDA 202379 Zytiga FDA Revisions to Sections 11 14 16.doc

Christine,

Attached is a Word document in Track Changes which contains our revisions to the PI in Sections 11, 14 and 16.



NDA 202379 Zytiga
FDA Revision...

Review and respond back **no later than 9 am on March 15, 2011.**

Please remember to submit your response back to us in Word format with Track Changes on both via email and as an official submission to this NDA.

Kind Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology Products, CDER,
FDA

10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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

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/s/

AMY R TILLEY
03/08/2011



NDA 202379

FILING COMMUNICATION

Centocor Ortho Biotech, Inc.
Ortho Biotech Oncology Research & Development
Unit of Cougar Biotechnology, Inc.
10990 Wilshire Blvd., Suite #1200
Los Angeles, CA 90024

Dear Ms. Woods:

Please refer to your New Drug Application (NDA) dated December 18, 2010, received December 20, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Zytiga™ (abiraterone acetate) Tablets 250 mg.

We also refer to your submission dated January 28, 2011 and two separate submissions dated February 1, 2011.

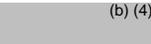
We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is June 20, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by May 30, 2011.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

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, “Discontinue use of TRADENAME™ if patients develop severe hepatotoxicity. (2.2)”
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)
 (b) (4).

Full Prescribing Information revisions:

5. 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)*].
6. 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.”
7. The statement “See FDA-approved patient labeling (Patient Information)” should appear at the beginning of Section 17.

We request that you resubmit labeling that addresses these issues by March 25, 2011. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

REQUIRED PEDIATRIC ASSESSMENTS

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

We reference the waiver granted on March 2, 2011, for the pediatric study requirement for this application.

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

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

ROBERT L JUSTICE
03/03/2011



NDA 202379

INFORMATION REQUEST

Ortho Biotech Oncology Research & Development
Unit of Cougar Biotechnology, Inc.
On behalf of Centocor Ortho Biotech, Inc.
Attention: Christine M. Woods, BS, MA
Associate Director, Regulatory Affairs
10990 Wilshire Blvd., Suite #1200
Los Angeles, CA 90024

Dear Ms. Woods:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zytiga™ (abiraterone acetate) Tablets 250 mg.

We also refer to your submission dated December 18, 2010, received December 20, 2010, the FDA Biopharmaceutics information request dated, January 18, 2011, and your amendment dated January 27, 2010, received January 28, 2010.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a written response no later than March 7, 2011, in order to continue our evaluation of your NDA.

Drug Substance

1. Provide a tabulated summary of side-by-side in-house batch analysis including Certificates of Analysis of all the drug substance intermediate ^{(b) (4)} batches supplied by ^{(b) (4)} and received at the drug substance manufacturing facility at ^{(b) (4)} ^{(b) (4)}. Also provide in-house acceptance criteria and test methods for all quality attributes.

Drug product

^{(b) (4)}

3. We could not find reference to batches CXPG and CNTC (Tables 1 and 2, p. 2) in the response dated January 27, 2011. Indicate where in the application these batches are

referenced or provide the batch size and date and the site of the manufacturing for both batches.

If you have any questions, call Deborah Mesmer, Regulatory Health Project Manager, at 301-796-4023.

Sincerely,

{See appended electronic signature page}

Sarah Pope Miksinski, Ph.D.
Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

SARAH P MIKSINSKI
03/01/2011

From: Tilley, Amy
Sent: Wednesday, February 16, 2011 10:50 AM
To: 'Woods, Christine [CGRUS]', cwoods@its.jnj.com
Subject: RE: NDA 202379 Request for Proprietary Name Review

Importance: High
Christine,

The OSE PDUFA date for review of the tradename for this application is 3/20/11. You should expect to hear a response regarding your proposed tradename, Zytiga, by that date.

This is consistent with the 90-day clock for all NDA proprietary name requests.

Regards.

Amy

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology
Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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From: Woods, Christine [CGRUS] [mailto:CWoods@ITS.JNJ.com]
Sent: Tuesday, February 15, 2011 6:58 PM
To: Tilley, Amy
Subject: NDA 202379 Request for Proprietary Name Review

Amy~

We are approaching the 60-day mark for the AA NDA Request for Proprietary Name Review, which I believe is Friday, 18 FEB 2011. Are you able to provide me an update on where we currently stand in the DMEPA queue and when we might expect some feedback? Our team has been working with Sarah Simon and Sammie Beam in DMEPA. Any update is appreciated.

Many thanks & all the best!

Christine

Christine M. Woods, BS, MA
Associate Director, Regulatory Affairs

No. American Regulatory Lead, Abiraterone Acetate
CWoods@ITS.JnJ.com

Ortho Biotech Oncology Research & Development

Unit of Cougar Biotechnology, Inc.
10990 Wilshire Blvd., Suite #1200
Los Angeles, CA 90024-3913 USA
310-943-8040 ext. 144 phone
310-943-8059 fax

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/s/

AMY R TILLEY
02/16/2011

From: Tilley, Amy
Sent: Wednesday, February 16, 2011 11:03 AM
To: 'Woods, Christine [CGRUS]', cwoods@its.jnj.com
Cc: Johnson Reid, Kelly [ORDUS], kjohnso6@its.jnj.com
Subject: NDA 202379 Abiraterone Acetate - Statistical Information Request

Importance: High

Follow Up Flag: Follow up
Due By: Wednesday, February 23, 2011 12:00 AM
Flag Status: Flagged

[Christine,](#)

[Below is the Statistical Information Request from the Statistical Reviewer.](#)

Please refer to NDA 202379 submitted on December 18, 2010:

1. Your Dataset “FU” contained information collected from 848 study subjects. We understood that there were 276 subjects actively on study at the time of the interim analysis. This means that 71 study subjects who were supposed to be included in Dataset FU had no follow-up information in the dataset after discontinuation of study treatment. Please specify where the follow-up information for the 71 patients can be found in your submission or explain why the information was not submitted or missed.

2. Please provide reasons as to why survival follow-up information was not available for the following 5 subjects who were censored within 2 months after randomization: Subject ID 124-0008, 600-0035, 604-0023, 126-0003, and 615-0002.

Please respond by February 23, 2011.

[As always, respond both via email and with an official submission to the NDA.](#)

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology
Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
02/16/2011

From: Tilley, Amy
Sent: Tuesday, February 15, 2011 3:59 PM
To: 'Woods, Christine [CGRUS]', cwoods@its.inj.com
Cc: Johnson Reid, Kelly [ORDUS], kjohnso6@its.inj.com
Subject: NDA 202379 Abiraterone Acetate - FDA Container Label Revisions

Importance: High

Follow Up Flag: Follow up
Due By: Tuesday, February 22, 2011 12:00 AM
Flag Status: Flagged

Attachments: Zytiga_DMEPA label comments_02152011.doc
Christine,

Attached are the CMC and DMEPA container label revisions.



Zytiga_DMEPA label
comments_02...

Please send your response to these revisions both via email and officially to this NDA.

The Agency respectfully requests your responses no later than February 22, 2011.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology
Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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Zytiga
(abiraterone acetate) tablets
NDA 202379

Container Label, 250 mg tablets

1. Decrease the prominence of the graphic located on the left-side of the proprietary name.
2. Ensure the established name is at least ½ size of the proprietary name. See 21 CFR 201.10(g)(2).
3. 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:

Tradename
(abiraterone acetate) tablets

250 mg

4. Revise the dosage form, tablets, to match the font and weight as the established name.
5. Revise the statement, Dosage: See accompanying product literature, to read:
See package insert for dosing information.
6. Revise your storage statement to reflect the following: “Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [see USP controlled room temperature].”

(b) (4)

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/s/

AMY R TILLEY
02/15/2011

Tilley, Amy

From: Tilley, Amy
Sent: Friday, February 04, 2011 5:05 PM
To: 'Woods, Christine [CGRUS]'
Cc: Johnson Reid, Kelly [ORDUS]
Subject: IND 71023 Abiraterone Acetate, CB7630 - Preliminary Comments

Importance: High

Attachments: IND 71023 Preliminary Comments 2-4-11.pdf

Christine,

Attached are the Preliminary Comments for IND 71023 Abiraterone Acetate, CB7630.



IND 71023
Preliminary Comments

After Cougar reviews the comments please let me know if a face-to-face meeting is still needed and which questions you would like to focus on.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology Products, CDER,
FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD 20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

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February 4, 2011

CLINICAL/STATISTICAL QUESTIONS

QUESTION 1: Extragonadal androgen synthesis is a major biological driver of castration resistance in metastatic prostate cancer independent of previous exposure to hormonal or chemotherapy. (b) (4)

[Redacted]

[Redacted]

FDA Response:

No. [Redacted] (b) (4)

[Redacted] (b) (4)

QUESTION 2: The Sponsor proposes to [Redacted] (b) (4)

[Redacted]

FDA Response:

[Redacted] (b) (4)

QUESTION 3: Despite multiple requests from investigators and ethics committees, the Sponsor plans to maintain the COU-AA-302 study blinded to the project team,

February 4, 2011

investigators, and subjects until the completion of the study or recommendations by the IDMC based on an interim analysis of OS. Does the Agency agree with this response to requests for unblinding from investigators?

FDA Response:

Your response is acceptable. Ultimately the decision to continue blinding or to unblind is your responsibility.

QUESTION 4: [REDACTED] (b) (4)

[REDACTED] does the Agency agree that the unblinding plan submitted by the Sponsor will maintain the integrity of the OS endpoint?

FDA Response:

Unblinding should not affect the endpoint of OS, unless it leads to a large amount of cross-over and post-study use of the product that may reduce the ability to demonstrate an improvement in OS.

QUESTION 5: The Sponsor proposes [REDACTED] (b) (4)

FDA Response:

[REDACTED] (b) (4)

Additional Comment:

We recommend you collect and submit all information on post-study use of abiraterone in addition to a taxane, including docetaxel and cabazitaxel. The submitted information should contain total treatment information including drugs, doses and treatment duration for each drug.

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/s/

AMY R TILLEY
02/04/2011



NDA 202379

PRIORITY REVIEW DESIGNATION

Centocor Ortho Biotech, Inc.
Ortho Biotech Oncology Research & Development
Unit of Cougar Biotechnology, Inc.
10990 Wilshire Blvd., Suite #1200
Los Angeles, CA 90024

Dear Ms. Woods:

Please refer to your New Drug Application (NDA) dated December 18, 2010, received December 20, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Zytiga™ (abiraterone acetate) Tablets 250 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is June 20, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by April 1, 2011.

While conducting our filing review, if we identify potential review issues we will communicate them to you on or before March 4, 2011.

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

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

ROBERT L JUSTICE
02/03/2011

From: Tilley, Amy
Sent: Friday, January 28, 2011 3:12 PM
To: 'Rodriguez, Silvia [CGRUS Non-J&J]'
Cc: 'Woods, Christine [CGRUS]'
Subject: FW: **URGENT REQUEST REPLY NEEDED ASAP** NDA 202379
Abiraterone Acetate - QT Information Request

Importance: High

Follow Up Flag: Follow up
Due By: Monday, January 31, 2011 12:00 AM
Flag Status: Red

Attachments: HighlightsofClinicalPharmacology.doc
Since Christine is having computer issues today, she asked me to forward this email to you.

Please take this urgent IR email to Christine immediately.

Thank you.

Amy

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology
Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov

 consider the environment before printing this e-mail

From: Tilley, Amy
Sent: Friday, January 28, 2011 3:07 PM
To: Woods, Christine [CGRUS]
Subject: **URGENT REQUEST REPLY NEEDED ASAP** NDA 202379 Abiraterone Acetate - QT Information Request
Importance: High

Christine,

The QT Interdisciplinary Review Team has the following urgent Information Request.

Please complete the attached ClinPharm table and submit it to us **ASAP**.

Please submit all related ECG waveforms to the ECG warehouse at www.ecgwarehouse.com.



HighlightsofClinicalP
harmacolo...

Since you stated earlier today that you were having computer problems I will call you to confirm your receipt of this email.

Regards.

Amy

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology
Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
01/28/2011

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
14.	<p>Do there appear to be the requisite number of adequate and well-controlled studies in the application?</p> <p>Pivotal Study #1 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</p> <p>Indication: 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)</p> <p>Pivotal Study #2: None</p> <p style="text-align: center;">Indication:</p>	X			<p>The disease represented an unmet medical need at the time of study initiation.</p> <p>Carbazitaxel, approved recently for use in the same disease setting, relied on the results from one pivotal study.</p>
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	Worldwide patients with 42% of them from the USA
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?				
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?			X	
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?				
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	Waiver Requested
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	41% US accrual with total of 498 patients.
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	Exploratory endpoints included in the key study, with no composite endpoint in support of the efficacy claim.
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse			X	

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	drop-outs) as previously requested by the Division?				
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? X

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Drs. Ning and Kluetz Jan. 07, 2011

 Reviewing Medical Officers Date

Dr. Liu Date

 Clinical Team Leader

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/s/

YANGMIN NING
01/14/2011

PAUL G KLUETZ
01/20/2011

KE LIU
01/20/2011

From: Tilley, Amy
Sent: Wednesday, January 19, 2011 2:45 PM
To: 'Woods, Christine [CGRUS]' cwoods@its.inj.com
Subject: NDA 202379 Abiraterone Acetate - Clinical Information Request - CRF

Importance: High
[Christine,](#)

[Below is an Information Request from the Clinical Review Team.](#)

In the preliminary review of your submission for NDA 202379, we notice that the initial Cougar case report forms (CRFs) are different from the CRF forms that are submitted. This has led to difficulties in finding key information quickly on the submitted CRF forms. We would like the sponsor to help the review team navigate the CRF forms to find the optimal way to access the needed information at the Orientation Meeting on February 25, 2011.

[Please let me know your plans as to how you propose to help us navigate the CRF forms, \(i.e., will you be bringing a computer, etc.\)?](#)

Kind Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology
Products, CDER, FDA

10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993

 301.796.3994 (phone) • 301.796.9845 (fax) |  amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
01/19/2011

From: Tilley, Amy
Sent: Tuesday, January 18, 2011 5:34 PM
To: 'Woods, Christine [CGRUS]' cwoods@its.inj.com
Subject: NDA 202379 Zytiga (Abiraterone Acetate) - Statistical Information Request

Importance: High

Follow Up Flag: Follow up
Due By: Tuesday, February 01, 2011 12:00 AM
Flag Status: Red
[Christine,](#)

Please see below the [Information Request from the Statistical Review Team](#).

Please refer to NDA 202379 submitted on December 18, 2010:

In the Clinical Study Report COU-AA-301 Section 3.11.3.13 "Circulating Tumor Cells", you stated that "additional analyses to explore CTC enumeration as a surrogate for clinical benefit will be provided in a separate report".

Please submit the CTC report and analysis datasets officially by February 1st, 2011.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology
Products, CDER, FDA
10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993
☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
01/18/2011

From: Tilley, Amy
Sent: Tuesday, January 18, 2011 11:27 AM
To: 'Woods, Christine [CGRUS]'
Subject: NDA 202379 Zytiga - Biopharm Information Request

Importance: High

Follow Up Flag: Follow up
Due By: Friday, January 21, 2011 12:00 AM
Flag Status: Flagged
[Christine,](#)

[Below please find an Information Request from the Biopharm Review Team.](#)

Biopharmaceutics Information Request:

Please address the following issues:

1. Under Module 2.7.1 (Clinical Summary; p.9), you indicated that the to-be-marketed (TBM)/commercial formulation tablets will be debossed. It is not clear if the clinically tested Phase-3 tablets were non-debossed. Please clarify.

If the above tablets are indeed different in debossing, an appropriate link between the debossed (commercial; TBM) and non-debossed (clinically tested) tablets will be needed. Please provide to the Agency for review the comparative dissolution data (individual and mean; n=12 tablets/batch) and mean dissolution profiles using your proposed dissolution method.

2. Under Module 3.2.P.5.6 (Justification of Specifications), you provided the mean dissolution profiles of three registration batch, Nos. R0304A001, R0314A001, R0315A001 (Figure 1, p.8). Both batch, Nos. R0304A001 and R0315A001, were also tested clinically.

The individual dissolution data for the above three batches, however, could not be located in the submission. The above information/data are needed to confirm your proposed dissolution methodology and to verify the proposed specifications. If you already submitted the information/data, please provide the Module, Section, Volume, and Page Nos. in the submission. If not yet submitted, please provide the needed information/data for review.

To avoid delay in the review process, please submit the needed information/data for review as soon as possible.

Please submit this information officially to the NDA.

Regards.

Amy Tilley

Amy Tilley | Regulatory Project Manager | Division of Drug Oncology
Products, CDER, FDA

10903 New Hampshire Avenue, Room 2177 | Silver Spring, MD
20993

☎ 301.796.3994 (phone) • 301.796.9845 (fax) | ✉ amy.tilley@fda.hhs.gov



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/s/

AMY R TILLEY
01/18/2011

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/s/

AMY R TILLEY
01/14/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR DDMAC LABELING REVIEW CONSULTATION **Please send immediately following the Filing/Planning meeting**	
TO: CDER-DDMAC-RPM		FROM: (Name/Title, Office/Division/Phone number of requestor) Amy Tilley/RPM, OND/DDOP/301-796-3994	
REQUEST DATE 1-14-11	IND NO.	NDA/BLA NO. 202379	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
NAME OF DRUG Abiraterone Acetate	PRIORITY CONSIDERATION This application may be an Expedited Review	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) 4-8-11 (may be needed prior to this date)
NAME OF FIRM: Centocor Ortho Biotech, Inc. Agent for Applicant: Cougar Biotechnology, Inc.		PDUFA Date: 6-20-11	
TYPE OF LABEL TO REVIEW			
TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input checked="" type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)		TYPE OF APPLICATION/SUBMISSION <input checked="" type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	
		REASON FOR LABELING CONSULT <input checked="" type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION	
EDR link to submission: \\CDSESUB1\EVSPROD\NDA202379\202379.enx			
Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to DDMAC. Once the substantially complete labeling is received, DDMAC will complete its review within 14 calendar days.			
COMMENTS/SPECIAL INSTRUCTIONS: Mid-Cycle Meeting: TBS (DDMAC Reviewer will be invited) Labeling Meetings: TBS (DDMAC Reviewer will be invited) Wrap-Up Meeting: TBS (DDMAC Reviewer will be invited)			
SIGNATURE OF REQUESTER: {See appended electronic signature page}			
SIGNATURE OF RECEIVER:		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> eMAIL <input type="checkbox"/> HAND	

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/s/

AMY R TILLEY
01/14/2011

REQUEST FOR CONSULTATION

TO (Office/Division): **Devi Kozeli**

FROM (Name, Office/Division, and Phone Number of Requestor): **Amy Tilley,
OND/DDOP, 301-796-3994**

DATE
1-14-11

IND NO.

NDA NO.
202379

TYPE OF DOCUMENT

DATE OF DOCUMENT
12-20-10

NAME OF DRUG
Zytiga (Abiraterone Acetate)

PRIORITY CONSIDERATION
Priority

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
**This NDA may be an
Expedited Review**

NAME OF FIRM: **Centocor Ortho Biotech, Inc. (Agent for Applicant: Cougar Biotechnology, Inc.)**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: The Clinical Pharmacology Reviewer requests your review of this application for the QT/QTc prolongation potential of abiraterone acetate. The results of the dedicated QT study (COU-AA-006) are contained in the EDR for NDA 202379. The associated IND # for reference is 71023.

EDR Location: \\CDSesub1\EVSPROD\NDA202379\202379.enx

SIGNATURE OF REQUESTOR
{ See appended electronic signature page }

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

AMY R TILLEY
01/14/2011

From: Tilley, Amy
Sent: Monday, January 03, 2011 3:49 PM
To: Woods, Christine [CGRUS] CWoods@ITS.JNJ.com
Cc: 'SRodri21@ITS.JnJ.com'
Subject: NDA 202379 Zytiga (Abiraterone Acetate) - Statistical Information Request

Importance: High

Follow Up Flag: Follow up
Due By: Friday, January 07, 2011 12:00 PM
Flag Status: Flagged

[Christine,](#)

[Below is an Information Request from the Statistical Reviewer.](#)

Please refer to NDA 202379 submitted on December 18, 2010:

DSMB meeting minutes are required to be included in the NDA submission. If you have submitted, please provide the location in the NDA submission; otherwise, please submit the minutes by January 7th, 2011.

[Regards.](#)

[Amy Tilley](#)

[Amy Tilley](#) | [Regulatory Project Manager](#) | [Division of Drug Oncology Products, CDER, FDA](#)
[10903 New Hampshire Avenue, Room 2177](#) | [Silver Spring, MD 20993](#)
[301.796.3994 \(phone\)](#) • [301.796.9845 \(fax\)](#) | [✉ amy.tilley@fda.hhs.gov](mailto:amy.tilley@fda.hhs.gov)



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/s/

AMY R TILLEY
01/03/2011



NDA 202379

NDA ACKNOWLEDGMENT

Centocor Ortho Biotech, Inc.
Attention: Christine Woods, BS, MA
Ortho Biotech Oncology Research & Development
Unit of Cougar Biotechnology, Inc.
10990 Wilshire Boulevard, Suite 1200
Los Angeles, CA 90024

Dear Ms. Woods:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: ZYTIGA™ (Abiraterone Acetate) 250mg tablets

Date of Application: December 18, 2010

Date of Receipt: December 20, 2010

Our Reference Number: NDA 202379

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 18, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinformo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 202379**, submitted on December 18, 2010, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Oncology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call me, at (301) 796-3994.

Sincerely,

{See appended electronic signature page}

Amy Tilley
Regulatory Health Project Manager
Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

AMY R TILLEY
12/23/2010

MEETING MINUTES

MEETING/TELECON DATE: December 3, 2010 **TIME:** 9 am -10 am

LOCATION: FDA, White Oak Building 22, Conference Room 1309

IND: 071023

Meeting Request Submission Date: October 20, 2010

FDA Response Date: November 10, 2010

Briefing Document Submission Date: November 19, 2010

DRUG: Abiraterone Acetate

SPONSOR/APPLICANT: Cougar Biotechnology, Inc.

TYPE of MEETING: Pre-NDA meeting to discuss the Sponsor's planned NDA submission in eCTD format for treatment of metastatic prostate cancer.

FDA PARTICIPANTS:

Amna Ibrahim, M.D., Deputy Division Director, DDOP

John R. Johnson, M.D., Lead Medical Officer, DDOP

Y. Max Ning, M.D., Ph.D., Medical Officer, DDOP

Jeanne Fourie Zirkelbach, Ph.D., Acting Team Leader Clinical Pharmacology, DCP5

Somesh Chattopadhyay, Ph.D., Mathematical Statistician, DB 5

Lijun Zhang, Ph.D., Mathematical Statistician, DB 5

Jean Mulinde, M.D., Team Leader (Acting), DSI

Winifred A. Meeker-O'Connell, M.S., Consumer Safety Officer, DSI

Leslie Ball, M.D., FAAP, Director, DSI

Alberta E. Davis-Warren, Regulatory Project Manager

INDUSTRY PARTICIPANTS:

Michael Meyers, M.D., Ph.D., Compound Development Team leader,

Robert Charnas, Ph.D., Regulatory Team Leader

Christine Woods, M.A., NA Regulatory Lead

Andrea Masciale, FDA Liaison, Johnson & Johnson

Arturo Molina, M.D., M.S., Clinical Team Leader

Chris Haqq, M.D., Ph.D., Clinical Study Team Leader

Nicole Chieffo, M.B.A., Clinical Operations

Jane Wood, Head R&D QA

John Weisel, Therapeutics Area Clinical QA

Kelly Johnson Reid, M.S., NA Regulatory Lead

Linda Tatem, M.S.J, NA Regulatory Professional

Andrea Masciale, FDA Liaison

Sharon Luzie, Quality Management

Michele Sacman, Quality Management

BACKGROUND: Sponsor is using abiraterone acetate to investigate the treatment of metastatic advanced prostate cancer. On October 20, 2010 Cougar Biotechnology Inc. submitted a meeting request to discuss with the Division of Drug Oncology Products (DDOP) and the Division of Scientific Investigations (DSI) their GCP quality program for study COU-AA-301. The sponsor plans on submitting the NDA in December 2010. The Sponsor submitted a subsequent background package on November 19, 2010. To facilitate the meeting FDA sent preliminary responses by email on December 1, 2010.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Please note that the Sponsor's responses were submitted in the morning of the industry meeting and may not have been reviewed.

QUESTION

Does DDOP or DSI have any comments about the Quality activities undertaken for Study COU-AA-301 or require any additional information prior to review of the NDA submission?

FDA response 12-1-10: Multiple audits and re-audits have been conducted. Please submit the reports that were generated as a result of the audits. In addition please submit a summary of audit findings and provide an analysis of the impact of the findings on data reliability (Cougar and J&J audits).

Sponsor response 12-3-10: As you are aware, we are under no regulatory obligation to provide audit reports. However, we will provide them with the summary analysis as we feel they will help you see the holistic picture of compliance and it is in the interest of transparency, which is why we approached DSI for this meeting in the first case. We are targeting to provide you this information in the next couple of weeks, before the NDA submission.

Meeting discussion 12-3-10: The Sponsor will provide the audit reports as soon as conceivably possible and provide a consolidated summary. However FDA stated that given the time constraints and the lead time required for DSI to conduct their audits, an expedited review as previously suggested will likely not be possible.

Additional Comments from DSI 12-1-10:

Questions related to previously submitted pre-NDA meeting package and current meeting briefing package:

- 1. Was Study COU-AA-301 conducted under IND at all clinical investigator sites?**

Sponsor response 12-3-10: Yes

2. Was Study 2009-0322 (NCT01088529) at MD Anderson Cancer Center conducted under IND? If so, please provide the IND number.

Sponsor response 12-3-10:

Study 2009-0322 was filed to Cougar IND 71023 (Serial #0348) on May 26, 2009 as Cougar Study COU-AA-203. Study number 2009-0322 is the corresponding MD Anderson number for the study.

3. Why was the (b) (4) CRO (original monitor for (b) (4) site management) replaced?

Sponsor response 12-3-10:

(b) (4) was the CRO responsible for site management in the (b) (4) from 2005 to 2008 for the Phase 1 and 2 protocols performed in that country. We carried them through to the Phase 3 trial, but decided during the site initiation phase that we needed to replace them due to concerns with their capacity and ability to implement the trial and to meet the pre-specified trial enrollment plans.

4. What was the root cause(s) for the delay in re-consenting of 250 subjects with the revised ICF developed Feb 2009 (re-consent process completed Aug 2010 per meeting package)?

Sponsor response 12-3-10:

We interpret your question as having 2 parts: A) why did it take us from February 2009 to April 2010 to discover the ICF issue and B) why we did not have re-consenting in place from April 2010 when discovered until August 2010.

A. The root cause has been traced to a deficiency of the written procedures outlining the ICF review and tracking process. An adequate ICF review process was already instituted for the original ICF review during study start up, however, we had to expand that to include any subsequent ICF amendments. The breakdown in process was such that the update to the model ICF and requirement for site ICF revisions could not be found during our routine QA audits and OSQMV visits that occurred during the time period.

As part of the preventative action plan for these studies, the written procedures were revised to ensure a robust process that will prevent such errors from re-occurring. The Regulatory Document Management Plan (a document that governs the conduct of essential documents for the trial) was updated and all sponsor and CRO staff was trained on the new written procedures.

B. The root causes of the delay in re-consenting from discovery April 28, 2010 to August 2010 included the time for identification of the sites and total number of patients affected, the lengthy submission and approval timelines of ethics committee approvals of the revised ICFs, and site scheduling of patients for re-consenting.

5. What triggered the initial decision to conduct on-site Quality Management visits (page 9 of pre-meeting submission, top)? How were the “specific sites” selected?

Sponsor response 12-3-10:

A. High Level View of the Process

The process began with QA auditing and progressed to corrective actions taken by Clinical Development Operations through 2 levels of site remediation (quality visits and remonitoring).

Following due diligence, which utilized an independent audit group, and within the first month of integration, the combined J&J/Cougar GCP audit group reviewed the existing program to evaluate its progress to date.

That process resulted in the development of an updated audit program.

An additional 8 clustered routine site audits (clustered because of rapid enrollment) as well as 2 internal system audits were scheduled: one of Cougar’s Systems and the second of the primary Clinical CRO, (b) (4) (24 routine site, 1 for cause, 1 miscellaneous {Study COU-AA-302 audit ended early and a COU-AA-301 patient was audited}).

Trend results of the clustered 8 audits by QA and the study team led to a decision to initiate corrective actions by the Clinical Development Operations group. These activities began in November 2009 and March 2010. As Study COU-AA-301 ‘Last Patient In’ was in July 2009; there was no additional routine QA auditing performed for COU-AA-301.

B. Initial Remediation Performed by Clinical Development Operations

Involvement by the Quality Management group started with the due diligence efforts prior to Johnson & Johnson (J&J) acquisition of Cougar, which included audits and monitoring visit report reviews from the 3 highest enrolling sites. After the acquisition, the Quality Management Risk methodology was implemented, following the J&J CRO oversight process.

The rationale for selection of each site is documented in the Risk Analysis Plan. Site selection focused on sites that had the highest risk, which was assessed through a risk analysis model using risk indicators such as enrollment, discontinuations, death, serious adverse events, deviations, and delayed query resolution. Additional risk criteria included CRA turnover, feedback on sites by the study team, and at least one site per country was selected.

6. Why did J&J PRD subsequently determine that formal data monitoring was required, and how were sites selected for targeted data re-monitoring?

Sponsor response 12-3-10:

Results from the on-site quality monitoring visits were prioritized as Priority 1 or Priority 2 issues. Priority 1 issues were those relating to source data collection or data entry that were to be investigated and closed prior to database lock. Priority 2 issues were those related to GCP checks or process improvements at the site. The team decided that prior to database lock, additional examination of the critical data points should be performed at sites with Priority 1 findings. The objectives for the re-monitoring effort were as follows: 1) to assure that the key data in the clinical database is accurate and reflects the information captured in the source documentation, and 2) that the correct patient population was enrolled in the study.

Initial site selection for targeted data re-monitoring was based on the sites with Priority 1 data-related findings from the on-site quality visits. Additional sites were also selected due to high enrollment, results from J&J PRD Quality Assurance site audits with critical findings, or concerns with CRA or site staff turnover.

7. Were any of these sites selected for on-site Quality Management visits or formal data re-monitoring previously subject to audit by Cougar and/or J&J PRD?

Sponsor response 12-3-10: Yes, some sites that had been previously audited by Cougar and J&J Pharmaceutical Research and Development (PRD) Quality Assurance were selected for on-site quality visits and re-monitoring.

8. What “improvement[s] of site processes to ensure GCP compliance” were implemented as a result of remonitoring? Were these issues previously identified by CRO monitors or issues first detected on remonitoring?

Sponsor response 12-3-10:

As Michele mentioned, we performed data re-monitoring visits at nearly all the clinical sites participating in the trial (145 of 147 individual centers). The re-monitoring was performed by Cougar and J&J personnel including CRAs and Medical Monitors.

The re-monitoring plan started with a subset of sites identified with OSQMV's Priority 1 data issues and other high enrollers. After review of visits at the initial 26 sites selected (437 patients), we found a trend in under-reporting of non-serious Adverse Events that lead us to targeted re-monitoring for the remaining study centers.

The process improvements at the site level were based on the individual findings from each site re-monitoring visit. Many of these were related to documentation of the informed consent process, eligibility criteria in the source (e.g., ongoing androgen deprivation), process for reviewing and signing lab reports & documentation of clinical significance, and data entry practices to assure that information in source is accurately entered into the database.

Some of the site issues were identified by the CRO monitors and documented for follow up in monitoring visit reports and site follow up letters. However, the targeted

re-monitoring process did discover a trend of un-reported non-serious Adverse Events and restricted medications that the CRO monitors missed.

Retraining sessions have been held for the CRO staff on the source verification process and key site personnel are required to participate in additional GCP training across the study. Following re-monitoring, individual CRAs were required to perform the corrective actions. Cougar and J&J reviewed all improvements requested to ensure we were satisfied with the corrective action plan.

9. What issues were identified as “Major Protocol Deviations” for this study?

Sponsor response 12-3-10:

The study team used the J&J Work Instruction “Handling Protocol Deviations” and considered major deviations to be:

- Subjects who entered the trial but did not satisfy Inclusion/Exclusion Criteria
- Subjects who developed Withdrawal Criteria, but were not withdrawn
- Subjects who received a disallowed concomitant treatment
- Subjects who received the wrong treatment or incorrect dose.

Randomization allocated the subjects who had major deviations in approximately equal percentages to the 2 treatment groups – 8% of subjects in abiraterone acetate and 9% in placebo. The most frequent eligibility deviation was violation of the inclusion criterion requiring no history of prior ketoconazole use (2% of subjects each group). Some subjects appeared to go to some lengths to withhold this information from investigators until after they were randomized when additional source documents were then presented from referring physicians. No other entry criterion was violated in >1% of subjects. The most common major protocol deviation after enrollment and entry criteria deviations was the use of prohibited concurrent medications (5% and 4% of subjects in the abiraterone acetate and placebo groups, respectively). The most frequent category was 5 alpha reductase inhibitors. Since the deviations were equally distributed to the two study arms, the company considers that these deviations have no impact on the interpretation of the study results.

Meeting Discussion 12-3-10: FDA requested that analysis of efficacy be done excluding all patients with major protocol violations as a sensitivity analysis. It is essential that this data be available and be submitted to the NDA so that FDA is able to do its own analysis. The sponsor stated that this analysis may be submitted soon after the initial NDA submission. This was acceptable to the FDA. FDA reminded the sponsor that generally it is expected that the NDA will be complete at initial submission.

10. Was enrollment stopped or placed on hold at any site for any reason by Cougar or J&J PRD during the study?

Sponsor response 12-3-10:

Enrollment was not stopped or placed on hold for any site for this study. However, due to a shortage of drug supply specifically for EU in February 2009, EU sites were asked to slow enrollment of subjects currently in screening until drug availability was improved. The company immediately added a second manufacturer and managed drug supply in EU carefully, so that no patient ongoing on study treatment missed a dose of study medication.

11. Who was responsible for safety case processing for the abiraterone program prior to the selection of (b) (4) in early 2008? Who at Cougar or J&J PRD was responsible for oversight of this vendor, once selected?

Sponsor response 12-3-10:

At the outset of the startup period at Cougar each medical monitor was responsible for identifying and writing safety narratives, which were then submitted. Recognizing that this process lacked scalability and in anticipation of the pivotal studies, Cougar established a dedicated safety and pharmacovigilance group and contracted with (b) (4) at the beginning of Study COU-AA-301. The company managed the vendor until February 2010, when oversight responsibility was transferred to J&J's Global Medical Safety group as part of the integration of the two companies.

Please provide in NDA 12-1-10:

- 1. A Table that describes whose SOPs (Cougar, vendor, or J&J PRD) were followed during what period for key functions (e.g. Data Management, Clinical Monitoring, Safety, Regulatory, Biostatistics).**
- 2. Copies of all versions of clinical and safety monitoring plans; in addition, include a summary describing any deviations from the plans that may have occurred and how such deviations were managed.**
- 3. Copies of the formal data re-monitoring plan, include acceptance criteria (page 9 of pre-meeting submission), pre-specified internal guidelines for making recommendations for site specific actions (page 10 of pre-meeting submission), and any instructions or training provided to the medical reviewers and monitors conducting the re-monitoring visits.**
- 4. A Table that describes, by site, original Cougar monitoring and auditing that occurred, whether site was re-monitored by J&J PRD, and whether site was audited by J&J PRD.**
- 5. Copies all versions of the Data Management Plan, Data Quality Rules, and Data Handling Guidelines; in addition, include a summary describing any deviations from the plans that may have occurred and how such deviations were managed.**
- 6. Copies of all versions of the Data Monitoring Committee Charter and Interim Analysis Plan; in addition, include a summary describing any deviations from the plans that may have occurred and how such deviations were managed.**

7. **Include in the NDA a copy of the data package provided to the Data Monitoring Committee for the August 11, 2010 interim analysis and copies of meeting minutes for the open and closed sessions of the meeting.**
8. **For sites where enrollment was stopped or placed on hold for any reason by Cougar or J&J PRD during the study, a summary of reason(s) enrollment hold was placed, related escalation process that ensued, corrective actions implemented, and outcome of corrective action plan.**
9. **In addition, please see attached documents that request site specific data formatted to facilitate inspection of Clinical Investigator sites (Attachment 1) and generation of a dataset to be used by DDOP and DSI reviewers to assist in selection of Clinical Investigator sites for inspection (Attachment 2).**

Sponsor response 12-3-10:

Our goal is to provide the information necessary to facilitate NDA review. We are within days of making our NDA submission and are initiating the final QC checks for the electronic dossier. To open this process now to include all the requested information would delay the timing of our submission. We can provide most of the requested information that is not already apart of the NDA before submission or as an NDA amendment. Is this acceptable?

Also provided by DSI: (see attached)

Attachment 1: Request for site specific data formatted to facilitate inspection of Clinical Investigator sites.

Attachment 2: Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions.

Attachment 3: Sponsor's handouts

Action items: None

Alberta E. Davis-Warren
Project Manager

Concurrence Chair: John R. Johnson, M.D.
Lead Medical Officer

ATTACHMENT 1

I. Request for general study related information and specific Clinical Investigator information

A. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:

1. Site number
2. Principle investigator
3. Location: Accurate current address (If study records are not located at this address please describe alternate current location)
4. Current contact information (phone, fax, email)

B. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:

1. Number of subjects screened for each site by site
2. Number of subjects randomized for each site by site
3. Number of subjects treated who prematurely discontinued for each site by site

C. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:

1. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
2. List of all vendors performing contracted activities for the study, (e.g. IVRS, central readers, CROs, etc.). Please include current addresses for each entity and describe where study related documents/source data generated by each entity are currently located and would be available for inspection. Include a brief summary of entity's roles and responsibilities in conduct of respective studies.
3. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)

II. Request for Site Level Data

1. For each pivotal trial: Sample blank annotated CRF
2. For each pivotal trial: Site-specific individual subject data ("line") listings from the datasets:
 - a. Line listings for each site listing the subject/number screened and reason for subjects who did not meet eligibility requirements
 - b. Line listings by site and subject, of treatment assignment (randomization)
 - c. Line listings by site and subject, of specific stratification factor(s) used during randomization for subject
 - d. Line listings by site and subject, of drop-outs and discontinued subjects with date and reason
 - e. Line listings by site of evaluable subjects/ non-evaluable subjects and reason not evaluable

- f. Line listings by site and subject, of AEs, SAEs, deaths and dates
- g. Line listings by site and subject, of all protocol deviations.
- h. Line listings by site and subject, of “Major Protocol Deviations”.
- i. Line listings by site and subject, of all protocol violations (if applicable)
- j. Line listings by site and subject, of the primary and secondary endpoint efficacy parameters or events.
- k. Line listings by site and by subject, concomitant medications (as appropriate to the pivotal clinical trials)
- l. Line listings by site and by subject, of laboratory tests performed for safety monitoring

III. Request for Individual Patient Data Listings format:

DSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to the attached document, “Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions” for further information. We request that you provide datasets, as outlined, for each pivotal study submitted in your application (See Attachment 2).

Attachment 2

Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

I. INTRODUCTION

The purpose of this electronic submission of a single new clinical site dataset is to facilitate the timely evaluation of data integrity and selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

II. DESCRIPTION OF THE SUMMARY LEVEL CLINICAL SITE DATASET

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection and are not intended to support evaluation of efficacy. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Variance (TRTEFFV) – the variance of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Variance (SITEEFFV) – the variance of the site-specific efficacy effect size (SITEEFFE)

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- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
 - Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) – the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, “TRTEFFR”.

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the “endpoint” plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1.

III. CREATING AND SUBMITTING THE DATA FILE (SUBMISSION TEMPLATE AND STRUCTURE)

A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt). The file may be submitted electronically through the FDA Electronic Submission Gateway (ESG) referencing the active IND number or via secure CD addressed to the Division of Scientific Investigations point of contact.

Exhibit 1: Summary Level Clinical Site Data Elements

Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
IND	IND Number	Num/Char	6 digit identifier	FDA identification number for investigational new drug	010010
TRIAL	Trial Number	Char	String	Study or Trial identification number	ABC-123
SITEID	Site ID	Num/Char	String	Investigator site identification number	50
ARM	Treatment Arm	Num/Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters)	Active (e.g. 25mg), Comparator drug product name (e.g. Drug x), or Placebo
ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site	20
SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site	100
DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site	5
ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application. (limit 200 characters)	Average increase in blood pressure
ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other)	Continuous
TRTEFFR	Treatment Efficacy Result	Num	Floating Point	The efficacy result for each primary endpoint, by treatment arm	0, 0.25, 1, 100
TRTEFFV	Treatment Efficacy Result Variance	Num	Floating Point	The variance of the efficacy result (TRTEFFR) for each primary endpoint, by treatment arm	0, 0.25, 1, 100
SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	The effect size should be the same representation as reported for the primary efficacy analysis	0, 0.25, 1, 100
SITEEFFV	Site-Specific Efficacy Effect Size Variance	Num	Floating Point	The variance of the site-specific efficacy effect size (SITEEFFE)	0.065
CENSOR	Censored Observations	Num	Integer	The number of censored observations for the given site and treatment	5
NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site. This value should include multiple events per subject.	10
SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site. This value should include multiple events per subject.	5
DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site	1

Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
PROTVIOL	Number of Protocol Violations	Num	Integer	Number of deviations from the protocol noted by the sponsor for a given site. This value should include multiple violations per subject.	20
FINLDISC	Financial Disclosure Amount	Num	Integer	Total financial disclosure amount (\$USD) by the site investigator	50000.00
LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572	Doe
FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572	John
PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator	555-555-5555, 44-555-555-5555
FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator	555-555-5555, 44-555-555-5555
EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator	john.doe@mail.com
COUNTRY	Country	Char	ISO 3166-1-alpha-2	Country in which the site is located	US
STATE	State	Char	String	Unabbreviated state or province in which the site is located	Maryland
CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located	Silver Spring
POSTAL	Postal Code	Char	String	Postal code for the site	20850
STREET	Street Address	Char	String	Street address and office number at which the site is located	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

Exhibit 2: General Structure of Data Submission Template

IND	TRIAL	SITEID	ARM	ENROLL	SCREEN	DISCONT	ENDPOINT	ENDTYPE	TRTEFFR
000001	Study 1	001	Active	26	61	3	Percent Responders	Binary	0.48
000001	Study 1	001	Placebo	25	61	4	Percent Responders	Binary	0.14
000001	Study 1	002	Active	23	54	2	Percent Responders	Binary	0.48
000001	Study 1	002	Placebo	25	54	4	Percent Responders	Binary	0.14
000001	Study 1	003	Active	27	62	3	Percent Responders	Binary	0.54
000001	Study 1	003	Placebo	26	62	5	Percent Responders	Binary	0.19
000001	Study 1	004	Active	26	29	2	Percent Responders	Binary	0.46
000001	Study 1	004	Placebo	27	29	1	Percent Responders	Binary	0.12

TRTEFFV	SITEEFFE	SITEEFFV	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLDISC	LASTNAME	FRSTNAME	PHONE
0.0096	0.34	0.0198	NA	0	2	0	1	0.00	Doe	John	555-123-4567
0.0049	NA	NA	NA	2	2	0	1	0.00	Doe	John	555-123-4567
0.0108	0.33	0.0204	NA	3	2	1	0	45000.00	Washington	George	020-3456-7891
0.0049	NA	NA	NA	0	2	0	3	45000.00	Washington	George	020-3456-7891
0.0092	0.35	0.0210	NA	2	2	0	1	0.00	Jefferson	Thomas	01-89-12-34-56
0.0059	NA	NA	NA	3	6	0	0	0.00	Jefferson	Thomas	01-89-12-34-56
0.0095	0.34	0.0161	NA	4	1	0	0	0.00	Lincoln	Abraham	555-987-6543
0.0038	NA	NA	NA	1	2	0	1	0.00	Lincoln	Abraham	555-987-6543

FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

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/s/

JOHN R JOHNSON
12/20/2010

MEETING MINUTES

MEETING/TELECON DATE: November 9, 2010 **TIME:** 12 pm -1 pm

LOCATION: FDA, White Oak Building 22, Conference Room 1415

IND: 071023

Meeting Request Submission Date: September 3, 2010

FDA Response Date: September 24, 2010

Briefing Document Submission Date: October 11, 2010

DRUG: Abiraterone Acetate

SPONSOR/APPLICANT: Cougar Biotechnology, Inc. /Johnson & Johnson

TYPE of MEETING: Pre-NDA meeting to discuss the Sponsor's planned NDA submission in eCTD format for treatment of metastatic prostate cancer.

FDA PARTICIPANTS:

Richard Pazdur, M.D., Director, OODP

Robert Justice, M.D., M.S., Director DDOP

Amna Ibrahim, M.D., Deputy Division Director, DDOP

John R. Johnson, M.D., Lead Medical Officer, DDOP

Y. Max Ning, M.D., Ph.D., Medical Officer, DDOP

Paul G. Kluetz, M.D., Medical Officer, DDOP

Sarah Pope Miksinski, Ph.D., Branch Chief, ONDQA, Division I, Branch II

Jeanne Fourie Zirkelbach, Ph.D., Acting Team Leader Clinical Pharmacology, DCP5

Elimika Pfuma, Pharm.D., Ph.D., Clinical Pharmacology Reviewer, DCP5

Christine Garnett, Pharm.D., Team Leader Pharmacometrics, OCP

Nitin Mehrotra, Ph.D., Pharmacometrics reviewer, OCP

Shenghui Tang, Ph.D, Team Leader, DB 5

Lijun Zhang, Ph.D., Mathematical Statistician, DB 5

Alberta E. Davis-Warren, Regulatory Project Manager

Theresa Ferrara, Regulatory Project Manager

Yolanda Adkins, Regulatory Project Manager

INDUSTRY PARTICIPANTS:

Michael Meyers, M.D., Ph.D., Compound Development Team leader, Johnson and Johnson

Partha Nandy, Ph.D., Clinical Pharmacology/Modeling & Simulation, Johnson and Johnson

Robert Charnas, Ph.D., Regulatory Team Leader, Cougar Biotechnology, Inc.

Christine Woods, M.A., North American Regulatory Lead, Cougar Biotechnology, Inc.

Andrea Masciale, FDA Liaison, Johnson & Johnson

BACKGROUND: Sponsor is using abiraterone acetate to investigate the treatment of metastatic advanced prostate cancer. On September 3, 2010 Cougar Biotechnology Inc. submitted a meeting request to discuss their planned NDA submission expected in December 2010. The Sponsor submitted a subsequent background package on October 11, 2010. To facilitate the meeting FDA sent preliminary responses by email on November 4, 2010.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. As the Division requested in the 27 AUG 2010 teleconference to facilitate rapid review of the planned NDA, Cougar has attached in **APPENDIX 1** a table listing principal investigators participating in Study COU-AA-301 and the number of patients enrolled at each of their sites. Does the Division anticipate requiring any additional information from Cougar prior to NDA submission to facilitate review of the NDA?

FDA response: The information listed in Appendix 1 is acceptable. Please include this information in Module 1 of your submission.

2. In the 4-month safety update, the company proposes to provide a safety update on the pivotal Study COU-AA-301. Cougar proposes (b) (4)

FDA response: We are currently planning an expedited review and we may waive the 4 month safety update. However, if a safety update is required, you should submit safety narratives if any of the following was observed or reported in the patients:

- 1) Deaths within 30 days of last dose of study drug not due to progressive disease
- 2) Treatment-emergent serious adverse events
- 3) Treatment discontinuation due to adverse events
- 4) Grade 3 or higher adverse events of interest

Meeting Discussion: The Sponsor asked about the timing of the orientation meeting. Based on the planned submission date of December 23, 2010, orientation meeting in the first week of January would be acceptable. FDA commented that inclusion of secondary endpoints in the label may be problematic.

3. Cougar understood from the 27 AUG 2010 teleconference that the Agency wishes to see an updated survival curve. We propose submitting an updated survival curve in the NDA (as of 20 SEP 2010 cut-off date) with approximately 750 death events (~94% of the 797 events specified in the protocol). Given this number

of death events, does the Division agree that it would not require an updated survival curve based on 797 events?

FDA response: It is acceptable to provide survival curves based on 750 death events in the NDA submission.

4. All population PK and PK/PD analysis datasets and codes will be submitted in eCTD format. Therefore, all analysis files will be submitted in “.txt” format only. Analysis datasets will also be made available in “.xpt” format. Is this approach acceptable to the Division?

FDA response: Yes

5. Data from a selected number of studies (COU-AA-008, COU-AA-009 and COU-AA-014) in normal healthy volunteers and data from available patient studies (COU-AA-006 and COU-AA-301) will be used to develop the population pharmacokinetics (pop PK) model. Key elements of the PK-PD relationship modeling in the NDA will include:
 - correlation between drug exposure and disease surrogate marker (PSA) response in the COU-AA-301 patient population and
 - correlation between drug exposure and survival in the COU-AA-301 patient population.

(b) (4)

FDA response: No. Please submit all the updated analyses with your initial NDA submission.

(b) (4)

6. Does the Agency have any comments about our plans for making a tradename available for review?

FDA response: We are currently planning an expedited review. You should submit your tradename as soon as possible. Please refer to the February 2010 FDA Guidance for Industry for a Complete Submission for the Evaluation of Proprietary Names in proposing your trade name.

OTHER FDA COMMENTS:

When will you be able to provide us with your manufacturing sites and when will they be ready for inspection?

Meeting Discussion: The Sponsor indicated that all sites intended for the NDA will be submitted as an IND amendment. The Sponsor also confirmed that all sites are currently ready for inspection.

REGULATORY

1. NDA/sNDA Presentations to CDER's Division of Oncology

The Center for Drug Evaluation and Research's Division of Drug Oncology Products implemented an initiative in which we request an NDA/sNDA applicant to present their NDA/sNDA to Division personnel shortly after NDA/sNDA submission and before the expected NDA/sNDA filing date. This initiative allows the applicant to present an overview of the entire NDA/sNDA to the review team and interested Division personnel.

These presentations are generally expected to last one hour followed by a half-hour question and answer session. The applicant, not consultants, should present important information on each technical aspect (i.e., clinical, statistical, CMC, pre-clinical pharmacology and toxicology, and clinical pharmacology and biopharmaceutics) of the NDA/sNDA. In addition to providing an overview of the NDA/sNDA, the applicant should present their reasons for why the Division or the Office of Drug Evaluation I should approve their NDA/sNDA.

Please contact your Project Manager shortly after NDA/sNDA submission to schedule a date for your presentation. Alternatively, you may provide available dates in the cover letter of your NDA/sNDA and we will try to accommodate them.

2. Financial Disclosure Final Rule

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective and any study in which a single investigator makes a significant contribution to demonstration of safety.

Please refer to the March 20, 2001 “*Guidance for Industry: Financial Disclosure By Clinical Investigators*” (posted on the Internet 3/27/2001) at <http://www.fda.gov/oc/guidance/financialdis.html>.

3. PEDIATRIC RESEARCH EQUITY ACT (PREA)

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

4. PEDIATRIC EXCLUSIVITY

Pediatric studies conducted under the terms of section 505A of the Federal Food, clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

5. DEMOGRAPHICS

In response to a final rule published 2-11-98, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data “by gender, age, and racial subgroups” in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this analysis. To assist you in this regard, the following table is a suggestion for presentation of the numeric patient demographic information. This data, as well as the pertinent analyses, should be provided in the NDA.

Please provide information for each category listed below from the primary safety database excluding PK studies.

CATEGORY		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG
Gender	Males		All Females		Females >50	
Age:	0-#1 Mo.		>1 Mo.-# 2Year		>2-#12	
	12-16		17-64		65	
Race:	White		Black		Asian	
	Other					

6. QT Evaluation

In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Please plan to address this issue early in development.

7. Office of Surveillance and Epidemiology (OSE)

- If the Sponsor and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then the Sponsor is encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).
- For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the following Guidance documents:

Premarketing Risk Assessment: <http://www.fda.gov/cder/guidance/6357fml.htm>

Development and Use of Risk Minimization Action Plans:
<http://www.fda.gov/cder/guidance/6358fml.htm>

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment:
<http://www.fda.gov/cder/guidance/6359OCC.htm>

- **If there is any information on product medication errors from the premarketing clinical experience, OSE requests that this information be submitted with the NDA/BLA application.**
- **The Sponsor is encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.**

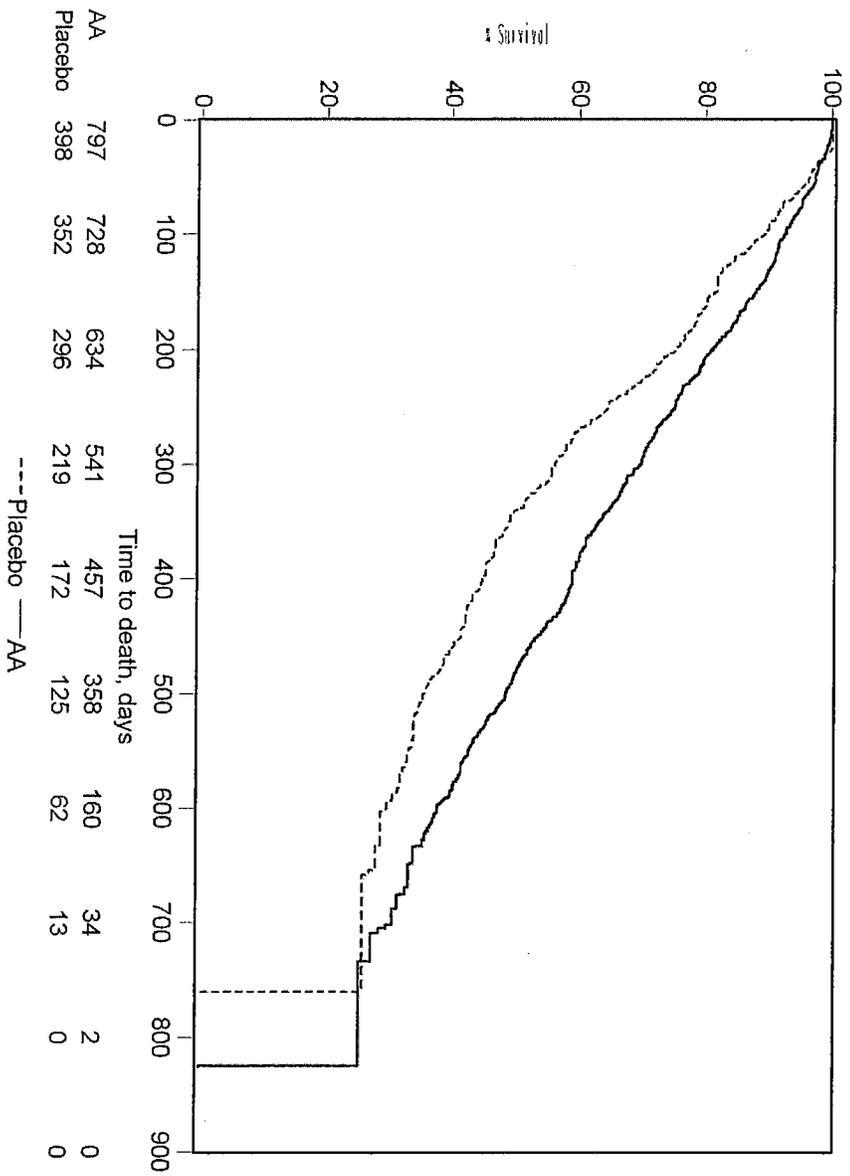
8. Please complete the following table for Study X and submit this with your NDA.

Site Address Point of Contact	# Enrolled	Efficacy Measure	# Gr 3-4 AEs	# Major Protocol Violations

Attachments: Handouts

Alberta E. Davis-Warren
Project Manager

Concurrence Chair: John R. Johnson, M.D.
Medical Team Leader



Date: 27Oct2010

Table TEFF01A : Overall Survival - Stratified Analysis, update at cut-off date (20Sep2010) : Un-cleaned data
(Study COU-AA-301: ITT Population)

	AA (N=797)	Placebo (N=398)
Subjects randomized	797	398
Death	489 (61.4%)	273 (68.6%)
Censored	308 (38.6%)	125 (31.4%)
Overall survival (days) ^a		
Median (95% CI)	483.0 (451.0, 518.0)	341.0 (317.0, 400.0)
p-value ^b	< 0.0001	
Hazard Ratio (95% CI) ^c	0.727 (0.626, 0.845)	

+ = censored observation, NE = not estimable

^aSurvival time is calculated as days from date of randomization to date of death from any cause. Subjects who are not deceased at time of analysis are censored on the last date subject was known to be alive or lost to follow-up.

^bP-value is from a log-rank test stratified by ECOG score (0-1, 2), pain score (absent, present), number of prior chemotherapy regimens (1, 2), and type of progression (PSA only, radiographic).

^cHazard Ratio is from stratified proportional hazards model. Hazard Ratio < 1 favors AA.

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/s/

JOHN R JOHNSON
12/02/2010

MEETING MINUTES

MEETING/TELECON DATE: May 26, 2010 **TIME:** 4 pm – 5 pm
LOCATION: FDA, White Oak Building 22, Conference Room 2376

IND: 071023 **Meeting Request Submission Date:** March 19, 2010
FDA Response Date: April 8, 2010
Briefing Document Submission Date: April 27, 2010

DRUG: Abiraterone Acetate, CB7630

SPONSOR/APPLICANT: Cougar Biotechnology, Inc.

TYPE of MEETING: Type C

FDA PARTICIPANTS:

Anthony Murgo, M.D., M.S., FACP, Associate Director OODP IO, Acting Deputy
Director DDOP
V. Ellen Maher, M.D., Clinical Team Leader, DDOP
Max Ning, M.D., Medical Officer, DDOP
Shenghui Tang, Ph.D, Acting Team Leader, DB 5
Qiang (Casey) Xu, Ph.D., Mathematical Statistician, DB 5
Lijun Zhang, Ph.D., Statistics Reviewer, DB 5
Alberta Davis-Warren, Regulatory Health Project Manager, DDOP

INDUSTRY PARTICIPANTS:

Robert Charnas, Ph.D., Regulatory Team Leader
Christine Woods, M.A., NA Regulatory Lead
Wayne Rackoff, M.D., Head Clinical Oncology
Arturo Molina, M.D., M.S., Clinical Team Leader
Chris Haqq, M.D., Ph.D., Clinical Study Team Leader
Thian Kheoh, Ph.D., Biostatistics Team Leader
Robyn Sterner, Pharm.D., Head NA Oncology Regulatory Affairs
Kelly Johnson Reid, M.S., NA Regulatory Lead
Michael Meyers, M.D., Ph.D., Compound Development Team Leader
Youn Choi Park, Ph.D., Biostatistics
Lindsay Cobbs, Regulatory Liaison Office

BACKGROUND: Sponsor is using Abiraterone Acetate to investigate the treatment of hormone-refractory prostate cancer. On March 19, 2010 Cougar Biotechnology, Inc. submitted a meeting request to discuss the structure and format of their planned NDA which will be in eCTD format. The sponsor submitted a subsequent background package on April 27, 2010. To facilitate the meeting FDA sent preliminary responses by email on May 20, 2010.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Regulatory

Question 1 – The Company proposes to provide Financial Certification and/or Disclosure information (Form FDA 3454/3455) only for investigators who participated in the pivotal study COU-AA-301 and not for any other study. Does the Division agree that this is acceptable?

- **FDA Response (May 20, 2010): This seems acceptable. However, disclosure of financial interests of the investigators involved in other studies should be available upon request. Please see “Guidance for Industry: Financial Disclosure by Clinical Investigators.”**
- **Company Response (May 25, 2010):** We acknowledge the Division’s guidance. No further discussion needed.

Question 2 – The list of principal investigators who participated in studies with abiraterone acetate will contain the investigator’s name, study designation and address. The Company proposes a cut-off of approximately 6 months prior to NDA submission for the list of investigators in ongoing studies. Does the Division agree that this is acceptable?

- **FDA Response (May 20, 2010): Please include their phone number along with the other mentioned geographical information. Please state when the data cutoff will be relative to NDA submission.**

Please complete the following table and include it in Module 1 of your submission.

Investigator Name, Address, Telephone #	# Enrolled	Median OS	# Serious Adverse Events	# Protocol Violations

- **Company Response (May 25, 2010):** We request clarification about what the Agency is requesting with the sentence “Please state when the data cutoff will be relative to NDA submission.” **Does this refer to investigator data or other data (e.g., clinical cut-off)?**

Meeting Discussion (May 26, 2010): Investigator data cut off will be 6 months prior to NDA submission. Patient data cutoff will be 11 months prior to NDA submission (January 2010). This is acceptable.

Does the Division agree with the table format proposed below and its proposed location in Section 1.3.3.1 of Module 1?

Meeting Discussion (May 26, 2010): The sponsor’s proposal is acceptable.

We acknowledge the Division's guidance to provide the table outlined above and a similar table in "Other Comments #8". To satisfy the request above and in Comment #8 below, we propose providing a single table in our submission including information from the pivotal trial only. The proposed table will use the following headings:

Investigator Name Address, Telephone # Point of Contact	# Enrolled	Median OS* (Range)	# SAEs	# Major Protocol Violations

*Based on Kaplan-Meier estimate

The Company wishes to inform the Agency that the median for the primary endpoint, Overall Survival, by investigative site may not be estimable for all sites, because some sites enrolled only a few patients or because the median has not yet been reached. For sites where the median cannot be estimated, the Company will indicate that they are not estimable in the table.

The Company also wishes to clarify that Major Protocol Violations are defined as:

- subjects who entered the trial but did not satisfy the Inclusion/Exclusion criteria,
- subjects who developed pre-specified withdrawal criteria but were not withdrawn,
- subjects who received the wrong treatment or incorrect dose, and
- subjects who received a disallowed concomitant treatment.

Since some patients experienced > 1 violation, for clarity, the number of deviations at each site will be listed (rather than the number of patients with a violation).

Question 3 – For Module 2.7.5 References, citations will be provided based on the Module 2.5 Clinical Overview, Module 2.7.3 Clinical Summary of Efficacy and Module 2.7.4 Summary of Clinical Safety documents. For Module 5.4 Literature References, the Company proposes to provide only published references from Module 2.7.5. Additional citation references will be provided upon request. Does the Division agree that this is acceptable?

- **FDA Response (May 20, 2010): Yes, this is acceptable.**
- Company Response (May 25, 2010): No further discussion needed.

Nonclinical

Question 4 – The Company proposes to provide the non-clinical studies listed in Module 4.2 of the NDA Content Plan (Appendix 1) as part of the NDA. Does the Division agree that the non-clinical studies listed in this appendix are sufficient to support the filing and review of the NDA for the treatment of patients with metastatic advanced prostate cancer who failed chemotherapy?

- **FDA Response (May 20, 2010):** In general, your proposed non-clinical studies appear to be acceptable. You have stated that carcinogenicity studies will not be conducted; however, on April 14, 2010, you submitted a carcinogenicity SPA for abiraterone acetate, basing submission on extended drug therapy for the patient population. Please note that the need for reproductive toxicology studies in different populations/indications is currently under discussion. At this time we agree that as discussed at the EOP2 meeting, reproductive toxicology studies will not be needed for surgically or chemically castrated patients. Reproductive toxicology studies may be needed if the patient population changes. A final decision on the adequacy of nonclinical studies will be made after review of data submitted with the NDA.
- **Company Response (May 25, 2010):** We acknowledge the Division's guidance. We should have specified that carcinogenicity studies will not be conducted for the planned submission of abiraterone acetate for the treatment of patients who have progressed after docetaxel-based chemotherapy.

Clinical/Statistics

Question 5 – Given the differences in the pivotal study and the early phase studies outlined in Section 10.4.4 of this briefing document, the Company proposes no Integrated Summary of Safety (ISS) or Integrated Summary of Efficacy (ISE) for the NDA submission. The results from the studies will each be discussed separately in the Summary of Clinical Efficacy and Summary of Clinical Safety. Does the Division agree that this is acceptable?

- **FDA Response (May 20, 2010):** The listed supportive studies had a total of 321 patients with metastatic CRPC. Safety data from these studies should be pooled and analyzed with that from the pivotal study to evaluate important safety signals that may be related to abiraterone.

Given the primary endpoint and design of the pivotal study, an ISE is not indicated for your submission.

- **Company Response (May 25, 2010):** The Company acknowledges FDA's request to integrate the safety data and would like to clarify that the total number of patients listed in Table 3 of the briefing document is 312. We would like to request consideration of an alternate proposal. We propose to integrate patients who received abiraterone acetate 1000 mg daily on a continuous dosing schedule. This will include approximately 260 patients. **Does the Division agree with the above proposal?**

Meeting Discussion (May 26, 2010): The Sponsor's proposal is acceptable.

Question 6 – Safety narratives will be provided for patients from all studies who meet the following criteria:

- Deaths within 30 days of last dose of study drug not due to progressive disease
- Treatment-related serious adverse events
- Discontinuations due to treatment-related adverse events
- Grade 3 or higher adverse events of interest

Does the Division agree that this is acceptable?

- **FDA response (May 20, 2010): Narratives should be provided for all patients with an SAE or treatment discontinuation, regardless of causality.**
- Company Response (May 25, 2010): *We seek further clarity on the Division's response.*

Meeting Discussion (May 26, 2010): The sponsor will provide narratives for all treatment emergent serious adverse events, all discontinuations due to treatment emergent adverse events and, for the pivotal study, narratives for patients who develop grade 3-4 hypertension, hypokalemia or hepatotoxicity.

Question 7 – The Company proposes to submit Case Report Tabulations (CRTs) only for the pivotal Study COU-AA-301. The Company plans to submit the clinical datasets in CDISC SDTM version 3.1.2 format and the analysis datasets in the NDA. Does the Division agree that this is acceptable?

- **FDA Response (May 20, 2010): This is acceptable.**
- Company Response (May 25, 2010): No further discussion needed.

Question 8 – The Company proposes to submit all electronic Case Report Forms (CRFs) for patients from pivotal Study COU-AA-301 and for patients from all other studies who meet the following criteria:

- Deaths within 30 days of last dose of study drug
- Serious adverse events
- Discontinuations due to adverse events

Does the Division agree that this is acceptable?

- **FDA Response (May 20, 2010): Yes. CRFs should be submitted for all patients who require narratives. The submitted CRFs should be indexed with study subject ID. Additional CRFs should be available upon request.**
- Company Response (May 25, 2010): We acknowledge the Division's guidance. No further discussion needed.

Question 9 – The Company currently uses MedDRA version 11.0 as the coding dictionary in all studies and proposes to use the same version for the NDA submission. Does the Division agree that this is acceptable?

- **FDA Response (May 20, 2010): This is acceptable.**
- Company Response (May 25, 2010): We acknowledge the Division’s guidance. No further discussion needed.

Question 10 – The Company proposes not to include safety data from the ongoing blinded study COU-AA-302 in the NDA. Does the Division agree with this proposal?

- **FDA Response (May 20, 2010): Possibly. Please specify how many patients who have received abiraterone and have been unblinded.**
- Company Response (May 25, 2010): As of May 21, 2010, 1084 patients have been randomized into study COU-AA-302 and 20 patients receiving abiraterone acetate have been unblinded per requirements for safety reporting in the EU. As per company procedures, the unblinding information is restricted to those performing safety reporting and no patient has been unblinded to the Study COU-AA-302 study team.

Meeting Discussion (May 26, 2010): The Sponsor’s proposal is acceptable.

Clinical Pharmacology

Question 11 – Does the Division agree that the clinical pharmacology studies listed in the NDA Content Plan (Appendix 1, Modules 5.3.1.1, 5.3.1.2, 5.3.3.1, 5.3.3.3, 5.3.3.4, 5.3.3.5 and 5.3.5.2 (Study COU-AA-006 only)) are sufficient to support an NDA filing and review of abiraterone acetate for the proposed indication?

- **FDA Response (May 20, 2010): Your proposal appears acceptable; however, the adequacy of the listed studies will be a review determination.**
- Company Response (May 25, 2010): No further discussion needed.

Question 12 – For the studies listed in Appendix 2, the Company plans to submit the datasets in CDISC SDTM version 3.1.2 format. Does the Division agree that this format is acceptable?

- **FDA Response (May 20, 2010): Yes, CDISC format is acceptable.**
- Company Response (May 25, 2010): No further discussion needed.

OTHER FDA COMMENTS:**A. REGULATORY****1. NDA/sNDA Presentations to CDER's Division of Oncology**

The Center for Drug Evaluation and Research's Division of Drug Oncology Products implemented an initiative in which we request an NDA/sNDA applicant to present their NDA/sNDA to Division personnel shortly after NDA/sNDA submission and before the expected NDA/sNDA filing date. This initiative allows the applicant to present an overview of the entire NDA/sNDA to the review team and interested Division personnel.

These presentations are generally expected to last one hour followed by a half-hour question and answer session. The applicant, not consultants, should present important information on each technical aspect (i.e., clinical, statistical, CMC, pre-clinical pharmacology and toxicology, and clinical pharmacology and biopharmaceutics) of the NDA/sNDA. In addition to providing an overview of the NDA/sNDA, the applicant should present their reasons for why the Division or the Office of Drug Evaluation I should approve their NDA/sNDA.

Please contact your Project Manager shortly after NDA/sNDA submission to schedule a date for your presentation. Alternatively, you may provide available dates in the cover letter of your NDA/sNDA and we will try to accommodate them.

Company Response (May 25, 2010): We acknowledge the Division's guidance. No further discussion needed.

2. Financial Disclosure Final Rule

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective and any study in which a single investigator makes a significant contribution to demonstration of safety.

Please refer to the March 20, 2001 "*Guidance for Industry: Financial Disclosure By Clinical Investigators*" (posted on the Internet 3/27/2001) at <http://www.fda.gov/oc/guidance/financialdis.html>.

Company Response (May 25, 2010): We acknowledge the Division's guidance. No further discussion needed.

3. Pediatric Research Equity Act (PREA)

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an

assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

Company Response (May 25, 2010): Reference is made to the September 27, 2007 End of Phase 2 meeting in which the Division stated that an indication of prostate cancer qualifies for a pediatric waiver and thus a pediatric assessment of abiraterone acetate is not required.

Follow-Up Request to FDA (May 25, 2010) – We request confirmation that the Division agrees that an indication of prostate cancer qualifies for a pediatric waiver and thus a pediatric assessment of abiraterone acetate is not required.

Meeting Discussion (May 26, 2010): The final determination will be made by the PREA committee.

4. Pediatric Exclusivity

Pediatric studies conducted under the terms of section 505A of the Federal Food, clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

Company Response (May 25, 2010): We acknowledge the Division's guidance. No further discussion needed.

5. Demographics

In response to a final rule published 2-11-98, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this analysis. To assist you in this regard, the following table is a suggestion for presentation of the numeric patient demographic information. This data, as well as the pertinent analyses, should be provided in the NDA.

Please provide information for each category listed below from the primary safety database excluding PK studies.

CATE GORY		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG
Gen- der	Males		All Females		Females >50	
Age:	0-#1 Mo.		>1 Mo.-# 2Year		>2-#12	
	12-16		17-64		\$65	
Race:	White		Black		Asian	
	Other					

Company Response (May 25, 2010): We acknowledge the Division's guidance. No further discussion needed.

6. QT Evaluation

In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Please plan to address this issue early in development.

Company Response (May 25, 2010): We acknowledge the Division's guidance. No further discussion needed. Please note the following:

Study COU-AA-006, a modified QT study, is currently ongoing. The protocol was initially submitted to IND 71023 on February 02, 2009 (Sequence #260) and the latest amendment (#2) was submitted on March 30, 2009 (Sequence #305). This study was designed in late 2008 by the Company after receiving recommendations about the design of Study COU-AA-002 from the FDA's Interdisciplinary Review Team on January 14, 2008. The final study report will be provided in the NDA.

7. Office of Surveillance and Epidemiology (OSE)

- If the sponsor and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then the

Sponsor is encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).

- For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the following Guidance documents:

Premarketing Risk Assessment: <http://www.fda.gov/cder/guidance/6357fnl.htm>

Development and Use of Risk Minimization Action Plans:
<http://www.fda.gov/cder/guidance/6358fnl.htm>

Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment:
<http://www.fda.gov/cder/guidance/6359OCC.htm>

- If there is any information on product medication errors from the premarketing clinical experience, OSE requests that this information be submitted with the NDA/BLA application.
- The sponsor is encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.

8. Please complete the following table for Study X and submit this with your NDA.

Site Address Point of Contact	# Enrolled	Efficacy Measure	# Gr 3-4 AEs	# Major Protocol Violations

Company Response (May 25, 2010): Please see Response to Sponsor Question #2 above.

Alberta E. Davis-Warren
Project Manager

Concurrence Chair: V. Ellen Maher, M.D.
Clinical Team Leader

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

IND-71023

GI-1

COUGAR
BIOTECHNOLOGY
INC

CB7630 (ABIRATERONE
ACETATE)

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/s/

VIRGINIA E MAHER
06/22/2010



IND 71023

MEETING MINUTES

Cougar Biotechnology, Inc.
Attention: Mark Pilato
Sr. Manager, Regulatory Affairs
10990 Wilshire Blvd., Suite 1200
Los Angeles, CA 90024

Dear Mr. Pilato:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for abiraterone acetate.

We also refer to the meeting between representatives of your firm and the FDA on November 24, 2009. The purpose of the meeting was to discuss Chemistry Manufacturing and Controls (CMC) questions submitted in the Pre-NDA meeting briefing package.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Deborah Mesmer, Regulatory Project Manager at (301) 796-4023.

Sincerely,

{See appended electronic signature page}

Deborah M. Mesmer, M.S.
Regulatory Health Project Manager for Quality
Division of Pre-Marketing Assessment III and
Manufacturing Science
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure:

Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUG QUALITY ASSESSMENT

Sponsor Name:	Cougar Biotechnology, Inc.
Application Number:	IND 071023
Product Name:	Abiraterone Acetate
Meeting Type:	Type B
Meeting Category:	Chemistry, Manufacturing and Controls, Pre-NDA Meeting
Meeting Date and Time:	Tuesday, November 24, 2009, 13:00 – 14:00 ET
Meeting Location:	Food and Drug Administration, White Oak Campus, Silver Spring, MD
Received Briefing Package	October 23, 2009
Meeting Requestor	Mark Pilato, Senior Manager Regulatory Affairs, Cougar Biotechnology
Meeting Chair	Richard Lostritto, Ph.D., Division Director
Meeting Recorder	Deborah Mesmer, M.S., Regulatory Project Manager

FDA ATTENDEES:

CENTER FOR DRUG EVALUATION RESEARCH

Office of New Drug Quality Assessment

Richard T. Lostritto, Ph.D., Division Director
Haripada Sarker, Ph.D., Pharmaceutical Assessment Lead
Debasis Ghosh, Ph.D., Review Chemist
Tapash Ghosh, Ph.D., Biopharmaceutics
Deborah Mesmer, M.S. Regulatory Health Project Manager- Quality

EXTERNAL ATTENDEES:

Cougar Biotechnology Inc.

Robert Charnas, VP, Regulatory Affairs
Wendy Mavroudakos, Sr. Director CMC Regulatory Affairs
Robert Ghadimian, Director Regulatory Affairs

Tracy Lin, Director CMC Regulatory Affairs
Mark Pilato, Senior Manager Regulatory Affairs
Hans Vermeersch, ChemPharm Team Leader
Tom Callewaert, Drug Substance Process Development

1.0 BACKGROUND

Abiraterone Acetate is being developed by Cougar Biotechnology Inc. (Cougar) for the treatment of hormone refractory prostate cancer under IND 071023, currently in Phase 3 trials. Cougar submitted a Type B, CMC Pre-NDA meeting request on June 10, 2009. The meeting request was granted by ONDQA on July 1, 2009. A face-to-face meeting was scheduled for September 11, 2009. Cougar Biotechnology, Inc. was acquired by, and became a wholly-owned subsidiary of, Johnson & Johnson on July 9, 2009. Cougar Biotechnology, Inc. remains the Sponsor of IND 071023 for abiraterone acetate. The meeting was rescheduled to November 24, 2009, at Cougar's request. A meeting briefing package was received on October 23, 2009. FDA preliminary responses were archived and shared with Cougar on November 20, 2009, to promote an efficient discussion at the meeting held on November 24, 2009. The minutes of the meeting discussion follow. The handout that Cougar provided at the meeting to facilitate discussion is attached.

2.0 SPONSOR QUESTIONS, FDA PRELIMINARY RESPONSES, AND MEETING DISCUSSION

2.1 Information for Justifying (b) (4) (b) (4) as the Starting Material

(b) (4)

Meeting Discussion: Cougar stated that the estimated time for their NDA submission has been changed to the end of the third quarter of 2010.

(b) (4)

(b) (4)

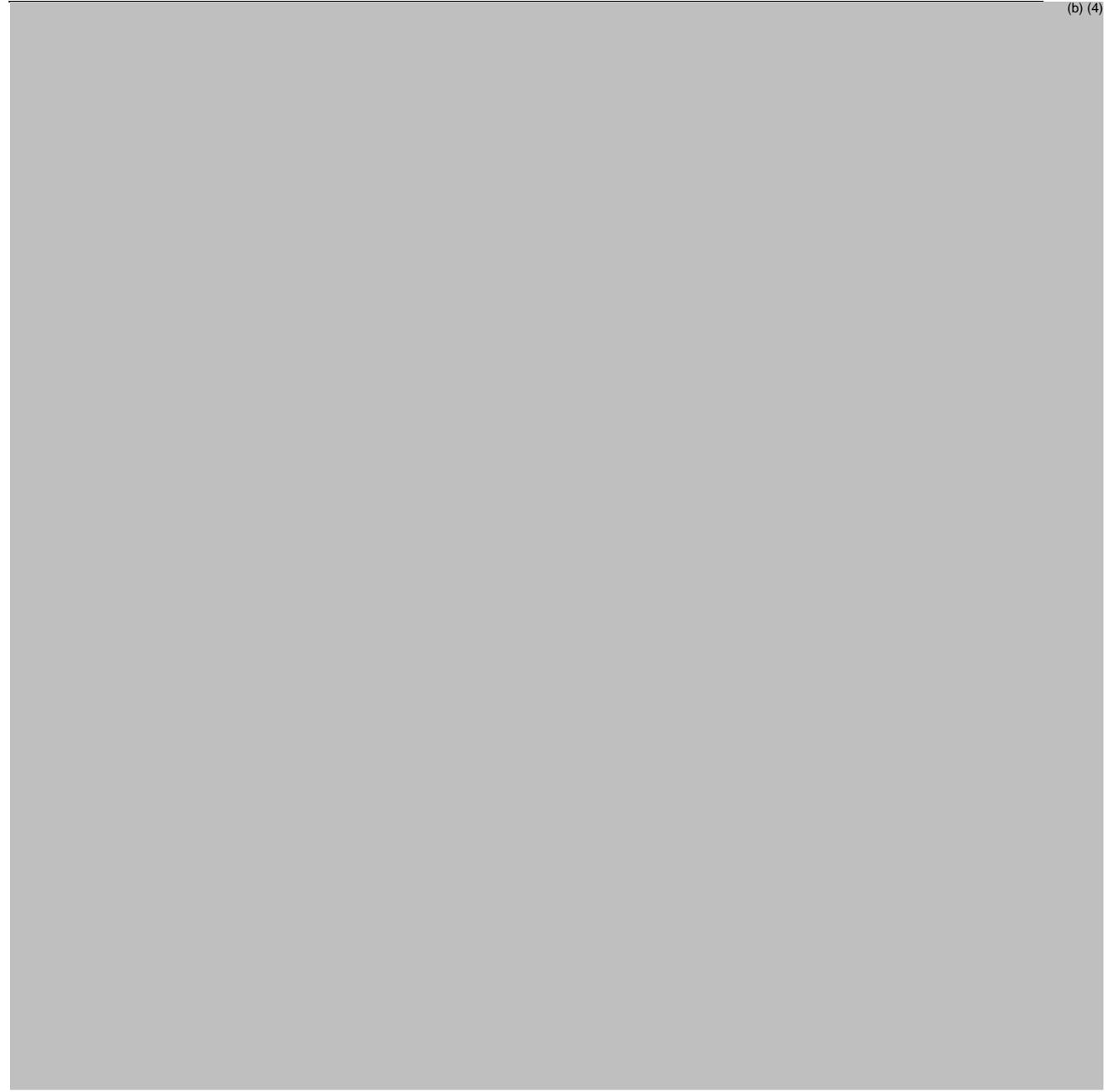
2.2 Comparability Criteria for the DS produced by (b) (4)
(b) (4)

Question 2a: Does the FDA agree that the data that will be generated from (b) (4)

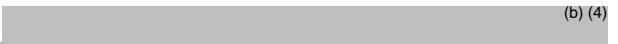
FDA Response: No. (b) (4)

(b) (4)

(b) (4)



2.3 Stability Data needed to File the DS Produced by CML

Question 2b: Does the FDA agree that  (b) (4)



FDA Response: No. See Response to Question 2a.

Meeting Discussion: See Response to Question 2a.

2.4 Change and Transfer of tablet's Manufacturing Process

Question 3: Does the FDA agree that the in vitro data and the results from a BE study indicating equivalency between the DP manufactured using the (b) (4) and DP produced using Patheon's commercial process will fully support and bridge the process changes between the (b) (4) and commercial processes and the site transfer?

FDA Response: Based on the information submitted in this briefing package, the *in vitro* dissolution data appear to be sufficient to bridge the process changes between the (b) (4) and commercial processes and the site transfer. Therefore, the proposed BE study may not be needed. However, the issue will be revisited during NDA review when a final decision will be made based on the acceptance of the dissolution methodology, comparison of dissolution profiles and proposed dissolution specification.

Meeting Discussion: Cougar requested clarification that FDA had reviewed the data submitted. FDA commented that full review of the data will be done upon NDA submission. However, based on preliminary assessment of the data, the approach appears reasonable. FDA stated that Cougar should provide sufficient BA data on the reference formulation which should be the to-be-marketed formulation. Provide the full PK characterization on the reference in the NDA. Then Cougar can bridge across processes and sites via dissolution. Dissolution from a single pH will be a review issue. Provide justification for the single pH to the NDA.

2.5 Stability of the Drug Product

Question 4: Will the 9 months room temperature and 6 months accelerated data for the drug product support the filing of the NDA (Section 11.P.3)?

FDA Response: Sufficient data to support the proposed expiry period should be submitted in the initial NDA submission. Any additional stability data submitted during the review period may or may not be reviewed as time and resources allow. At a minimum, the initial stability data should support a commercially viable product, one considered to have an expiry period of one year or greater. Lack of such data may be a filability issue. The adequacy of the stability information will be determined during the review process.

Meeting Discussion: See Response to Question 2a.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion at this time.

4.0 ACTION ITEMS

There are no specific due dates or time lines for submission of information or other action items. General agreements and commitments are included in the Meeting Discussion Section 2.0 above.

5.0 CONCURRENCE:

{See appended electronic signature page}

Deborah Mesmer
Regulatory Health Project Manager for Quality
Division of Pre-Marketing Assessment III and Manufacturing Science
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

{See appended electronic signature page}

Richard T. Lostritto, Ph.D.
Division Director
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

6.0 ATTACHMENTS AND HANDOUTS

Cougar Biotechnology provided a single page handout at the meeting, *Abiraterone Acetate Synthesis*. The handout is attached.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
IND-71023	GI-1	COUGAR BIOTECHNOLOGY INC	CB7630 (ABIRATERONE ACETATE)

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/s/

DEBORAH M MESMER
01/06/2010

RICHARD T LOSTRITTO
01/06/2010

Clinical Pharmacology Plan Type C meeting

Date: September 17, 2008 at 3:00 pm (EDT; 12:00 pm PDT)

Meeting Minutes

Introduction: Nadia Agopyan

Introduced Attendees:

Cougar:

Arturo Molina, M.D., M.S., Chief Medical Officer, Executive Vice President, Clinical Research and Development

Richard Phillips, Ph.D., Senior Vice President, Regulatory Affairs and Quality Assurance

Thian Kheoh, Ph.D., Biometrics

Chris Haqq, M.D., Ph.D., Clinical Research and Development

Thomas Griffin M.D., Clinical Research and Development

Robert Charnas, Ph.D., Regulatory Affairs

Nicole Chieffo, MBA., Clinical Operations

Nadia Agopyan, Ph.D., RAC Director Regulatory Affairs

Namphuong Tran, M.D. Clinical Research and Development

(b) (4)

FDA Introduction by Alberta Warren Davis

Frank Cross Jr.	Chief, Project Manager	DDOP
Margaret Brower	Pharmacologist	DDOP
Yang-Min (Max) Ning	Medical Officer	DDOP
Michael A. Pacanowski	Pharmacologist	OCP
Amy McKee	Medical Officer	DDOP
Ramzi Dagher	Deputy Director	DDOP
Gene M. Williams	Pharmacologist	OCP
Amna Ibrahim	Lead Medical Officer	DDOP
Haleh Saber	Pharmacologist	DDOP
Jeanne Fourie	Clin Pharm Reviewer	DCP5
Alberta E. Davis-Warren	Regulatory Project Manager	DDOP

Items discussed : Response to questions 6, 7, and comment # 1

Comment # 1

1. Regarding your plan for hepatic and renal impairment we recommend that studies in subjects with organ impairment be performed with a timing that allows them to be submitted in the NDA. The study design (subject population, single/multiple dose, etc.) can be discussed at the time of protocol preparation.

Cougar Response:

- *Cougar thanks the FDA for their response and the offer to discuss this in more detail at the time of protocol preparation.*
- *Cougar is considering single dose studies in hepatically or renally impaired, but otherwise healthy volunteers.*
- *Data from such studies could be available at the time of the NDA.*
- *Multiple dosing would require studies in patients and Cougar is concerned that these data would not be available at the time of the NDA*

Discussion: Cougar requested guidance on the best way to have the discussion on the protocol, such as a meeting request or a protocol submission to the IND.

FDA (Gene Williams) replied that the sponsor is free to seek another meeting and that would be acceptable to the clinical pharmacology group. From the clinical pharmacology group's perspective, the use of healthy volunteers is acceptable. There ensued a discussion within the FDA about the fact that these volunteers have organ impairment and are not healthy. Cougar (b) (4) proposed to follow the FDA guidance on the matter.

Following a period when the FDA went on hold, there was agreement that single dose studies could be performed in volunteers without prostate cancer but with renal or hepatic impairment. The ability to use the population will be a review issue at the time of the protocol submission. The expected concentrations in those volunteers will be of particular interest to the FDA and any information that can be provided about what to expect would be helpful.

FDA informed Cougar that it is a compromise not to perform such studies at steady state, but this is usually satisfactory. However, if a lower dose than that used in the clinic were to be used, then this would be more of a compromise and would suggest that the reason for doing so would lead to a study in patients.

The need to dose patients is clear and the FDA wants data. The argument about taking too long to do was not well received and FDA commented about poor planning on Cougar's part.

Question # 7:

Does the Agency agree with the proposal to investigate the effect of abiraterone acetate on the pharmacokinetics of theophylline (CYPIA2 substrate) and desipramine (CYP2D6 substrate) using a cocktail in healthy volunteers?

FDA response: The proposed study is for a single dose of abiraterone; we recommend that abiraterone be dosed to steady-state prior to administering a single dose of the reference substrate drug(s).

In principle the use of a cocktail is acceptable. However, in practice the lack of appropriate control information usually precludes such an approach. Below is a reproduction from FDA's 2006 draft *Guidance for Industry Drug Interaction Studies Study Design, Data Analysis, and Implications for Dosing and Labeling: Simultaneous administration of a mixture of substrates of CYP enzymes in one study (i.e., a "cocktail approach")* in human volunteers is another way to evaluate a drug's inhibition or induction potential, provided that the study is designed properly and the following factors are present: (1) the substrates are specific for individual CYP enzymes; (2) there are no interactions among these substrates; and (3) the study is conducted in a sufficient number of subjects (see section IV.G). Negative results from a cocktail study can eliminate the need for further evaluation of particular CYP enzymes. However, positive results can indicate the need for further in vivo evaluation to provide quantitative exposure changes (such as *AVC*, *Cmax*), if the initial evaluation only assessed the changes in the urinary parent to metabolite ratios. The data generated from a cocktail study can supplement data from other in vitro and in vivo studies in assessing a drug's potential to inhibit or induce CYP enzymes. If you elect to pursue the cocktail approach we recommend that you submit information to address the above excerpt from the guidance and have it reviewed by the FDA prior to initiating the study.

Cougar Response:

- *Cougar thanks the FDA for the response*

Part 1: healthy volunteers

- *We would like to discuss FDA's recommendation for steady state dosing with respect to Cougar's concern about confounding effects of multiple medications and practical challenges in conducting a non-therapeutic trial in advanced (CRPC) prostate cancer patients (Cougar considers it unacceptable to perform multiple dose studies with abiraterone acetate in healthy volunteers because it would lead to medical castration).*
- *Our proposal was based on the interpretation of the available data in the context of The Guidance cited above.*
- *Cougar considered that performing a single dose study would provide as much information about drug interactions as performing a multiple dose study and measuring at the steady state because in vitro data indicate that abiraterone is a direct inhibitor of the CYP enzymes. Cougar therefore considered that there is no reason to suspect that a delay would be likely in demonstrating the effect in vivo.*

- *If, however, as data from the multiple dose study of the pharmacokinetics of abiraterone acetate and the mass balance testing becomes available, Cougar will re-evaluate this position if required, based on the above considerations for conducting steady state drug interaction.*

Discussion: FDA (Gene Williams) commented that this is not unusual in oncology and that the product in question is not overtly cytotoxic. From FDA's perspective, these studies are mechanistic. The drugs used are reference substrates; a negative result from such studies provides certainty about interactions. While the FDA understands the issue of confounding from the other medicines the patients may be taking and sympathetic to the concern, they recommend that multiple doses be given and the measurement made at steady state.

Following an internal discussion (phone was on mute), the FDA commented that it should be feasible to use a prostate cancer patient population with early stage CRPC. These patients would likely have fewer medications and this could allow the study to proceed. FDA feels "reasonably strongly" about this.

Part 2. Acceptability of the cocktail.

- *A review of the literature indicates the validity of the use of theophylline and desipramine in an in vivo cocktail approach to assessing potential in vivo drug interactions of abiraterone on CYP1A2- and CYP2D6-mediated metabolic reactions.*
- *Desipramine is metabolized to its 2-hydroxy metabolite predominantly by CYP2D6.*
- *Theophylline is metabolized principally by CYP1A2 and CYP2E1. In vivo studies indicate that theophylline metabolism is not affected by the debrisoquine phenotype, the CYP2D6 pathway (Dahlqvist et al. 1984) or by either acute or 2-week repeated-dose pretreatment with desipramine (Kot et al. 2007).*
- *Although in vitro inhibition of desipramine hydroxylation has been observed in vitro at high concentrations of theophylline (von Bahr et al. 1985), similar effects have not been reported in vivo.*
- *Cougar has thought about this in great detail, recognizes the FDA position and will send the protocol to the FDA for review. Cougar requests timely feedback for this protocol. Cougar is currently discussing experiences of "cocktail studies" with CROs to aid the development of the protocol.*

Discussion: FDA (Gene Williams) has rarely seen cocktails in dosing patients. Even though it cannot be ruled out, and this is why it is in the guidance, it is usually found that a cocktail approach doesn't have the appropriate controls in place and doesn't meet regulatory rigor. The FDA mentioned that independent DDI studies are preferred and strongly encouraged Cougar to send the protocol which delineates the dose, excretion etc to get FDA's feedback on the feasibility of the study. If Cougar decides to pursue a

cocktail approach, Cougar was advised to ensure that there is no interaction between the two drugs used in the cocktail.

Question # 6:

Does the Agency agree with the proposal to perform a mass balance study using ¹⁴C labeled abiraterone acetate in healthy volunteers?

FDA response: In principle, yes. We do not know how the decision to sample for 120 hours was arrived at. Is there data that supports that 120 h is likely to be sufficient to capture close to 100% of the administered drug mass?

Cougar: Response:

- *Current data suggests that the half life of abiraterone after 1000 mg dose is approximately 14 - 16 hours.*
- *The 120 hour period was proposed as it would be close to 7 half lives and capture > 97.5% of the administered radioactivity. Cougar thanks the Agency for highlighting this.*
- *We will extend the sampling period to 168 hours.*
- *Does the Agency agree?*

Discussion: FDA agreed that in the absence of data Cougar's proposal sounded reasonable. They requested that if Cougar has human profiling to provide the scientific basis for either 120 hrs or 168 hrs. If no data is acquired by the time the protocol is submitted they requested that Cougar conduct simulations to justify the time chosen.

FDA found Cougar's suggestion acceptable to submit some protocols to the IND and wait for feedback, whereas others would be the subject of a meeting request that would follow the timelines for such an activity.



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUG QUALITY ASSESSMENT

Sponsor Name:	Cougar Biotechnology, Inc.
Application Number:	IND 71,023
Product Name:	Abiraterone Acetate Tablets
Meeting Type:	Type B
Meeting Category:	Chemistry, Manufacturing and Controls (CMC), End of Phase 2 (EOP2) Meeting
Meeting Date and Time:	Friday, March 7, 2008, 1300 – 1400 ET
Meeting Location:	Food and Drug Administration, White Oak Campus, Silver Spring, MD
Received Briefing Package	February 6, 2008

The following consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for **Friday, March 7, 2008**, between **1300 – 1400 ET**, at the **Food and Drug Administration, White Oak Campus, Silver Spring, MD** between **Cougar Biotechnology, Inc.** and the Center for Drug Evaluation and Research/Office of New Drug Quality Assessment. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments. If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, (301) 796-2055). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. **Please note that if there are any major changes to the questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting.** If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager for Quality to discuss the possibility of including these for discussion at the meeting.

1.0 BACKGROUND

Cougar Biotechnology, Inc. (Cougar) submitted IND 71,023 (19 December 2005, Division of Oncology Drug Products; currently in Phase 2) for abiraterone acetate, a solid, 250 mg immediate release tablet. The regimen, in combination with prednisone, is proposed for the treatment of metastatic castration resistant prostate cancer in patients who have failed up to two chemotherapy regimens, one of which contains docetaxel. An End-of-Phase 2 (EOP2) CMC meeting requested on December 26, 2007, granted on January 3, 2008, and scheduled for March 7, 2008, with the Office of New Drug Quality Assessment to review and discuss Cougar's pharmaceutical development strategy related to abiraterone acetate drug substance and drug product intended to support the pivotal Phase 3 study. Proposed discussion topics include 1) evaluate the results of Cougar's pharmaceutical development efforts to date that support the Phase 3 investigational product, 2) review Cougar's developmental plans and technical protocols for abiraterone acetate immediate release tablets that will provide the technical data intended to support a planned marketing application, and 3) identify additional information deemed important to support a marketing application. The corresponding briefing package that provided additional information on discussion topics and final questions was sent by Cougar on February 5, 2008. The following preliminary responses to the questions contained in the briefing package are being archived and shared with Cougar to promote a collaborative and successful discussion at the meeting.

2.0 DISCUSSION

- 2.1 1. The physico-chemical characterization of abiraterone acetate has been extensively evaluated using ¹H NMR, ¹³C NMR, IR, XRPD and DSC and the data are presented in Section 13.1.S.2. Does the Agency agree that the physico-chemical data collected to date are adequate to support a market application?

FDA Preliminary Response: Your approach is generally acceptable. All supporting data will be assessed for adequacy at the time of NDA submission. Additionally, please include the stereochemical purity testing for abiraterone acetate.

- 2.2 2. Representative batch analysis of abiraterone acetate drug substance, including the detected impurities are presented in section 13.1.S.9. The purity of abiraterone acetate active pharmaceutical ingredient (API) is generally > 99.7% with the only major manufacturing impurity being (b) (4) (b) (4). No other major impurities in the drug substance are routinely observed and ICH Q3A(R2) will be followed with respect to the identification and qualification of any new observed manufacturing impurities or degradation products. Does the Agency agree with the approach to impurities in abiraterone acetate drug substance?

FDA Preliminary Response: Your approach to the utilization of ICH Q2(R1) to validate the analytical methods is acceptable with a caveat that the methods should be sufficiently sensitive to quantitate the impurities and degradation products at their proposed thresholds. Additionally, please submit a rationale for establishing impurity acceptance criteria that includes safety considerations (ICH Q3B(R2)). Include a discussion of the impurity profiles observed in the safety and clinical development batches, together with a consideration of the impurity profile of batches manufactured by the proposed commercial process.

Acceptance criteria should be set for each specified identified impurity and any unspecified impurity with an acceptance criterion of no more than the identification threshold as described in ICH Q3B (R2). These criteria should be expressed as “NMT” as a maximal limit. If any structural alerts for genotoxicity are likely to be present, such impurities should be measured and controlled using a sensitive analytical method, keeping in mind that the total daily intake of such impurities is not expected to be more than 1.5 micrograms in the drug product at its proposed maximum daily dose.

- 2.3 3. (b) (4) has been used as the starting material for the synthesis of abiraterone acetate API throughout Phase 1 – 3 of the clinical development process. Detailed specifications for the acceptance of (b) (4) release information on the quality of (b) (4) from different sources, as well as the quality of abiraterone acetate API prepared from (b) (4) (b) (4) from various sources is being developed as described in Section 13.1.5.S.1. While it is recognized that final agreement on the classification of (b) (4) as starting material for abiraterone acetate API will be a review issue, does the Agency agree with the justification provided in Section 13.1.5.S.1 and the approach proposed to provide data to support the classification of (b) (4) (b) (4) as the starting material for the synthesis of abiraterone acetate?

FDA Preliminary Response: The proposed starting material is (b) (4)

(b) (4) Therefore, considering the (b) (4) of the proposed starting material to the drug substance, the acceptability will heavily depend on the submission of a Type II DMF for the proposed starting material from each of its vendors. Your proposed submission of (b) (4) is not acceptable. The DMF(s) should be submitted to justify the choice of the proposed starting material. Alternatively, you may propose the starting material sufficiently (b) (4) (b) (4) (b) (4) and described the details in the NDA. To justify (b) (4) (b) (4) as a choice of starting material, you should also include the following information in the NDA. This information will be reviewed for adequacy at the time of NDA submission:

- An impurity profile for (b) (4) (b) (4) using two complementary analytical methods. .
- A detailed synthetic scheme (either in the NDA or via reference to DMFs).

- A thorough discussion of potential carry-over of impurities that are present in the starting materials to the final drug substance, based on analytical data and a demonstration that any impurity present in the starting material is not carried over into the drug substance at levels above (b) (4) if such an impurity is not a structural alert for genotoxicity. If an impurity in the starting material is a structural alert for genotoxicity, it is not carried over beyond a level that may result in a total daily intake of more than (b) (4) in the drug product.
- Appropriate controls of the proposed starting materials using validated analytical test methods to separate and measure potential impurities.
- Full supplier information from the intended vendors of any proposed starting materials.
- Results from the design of experiments (DoEs) and/or mechanistic approaches, if available, demonstrating the identification of all critical process parameters and their controls in the synthesis of the drug substance.
- Data from purging studies using impurities to demonstrate the ability of the manufacturing process to remove and control the impurities to desired levels.
- Acceptable change control strategies for any potential revisions to the manufacture of the proposed starting materials, including the proposed procedures for the vendor's reporting of any changes in starting material manufacture to you.
- Supportive literature data, as available.

2.4 4. The test, analytical methods, and specification criteria for abiraterone acetate API as established for the Phase 1/2 studies will continue to be used for the Phase 3 clinical trial material. However, the abiraterone acetate API specification has been updated for Phase 3 clinical development. The updates in the API specification include: a tightening of the heavy metals specification from (b) (4) addition of a limit for (b) (4) and a particle size specification. Does the Agency agree that proper the tests are included in the current abiraterone acetate API specification that will allow the collection of data required to assess the API's specification criteria during the NDA review?

FDA Preliminary Response: The approach is generally acceptable. Please consider the comments from the previous questions, especially with regard to the limits for impurities and degradation products. Replace "No other single (b) (4) with "Individual unspecified drug-related impurities: NMT (b) (4)" Any impurity with a limit exceeding qualification threshold needs to be supported by safety information. Therefore, provide data supporting the safety of abiraterone at the proposed level of (b) (4) Also, justify the selection of the chosen limits for particle size distribution, for example, by demonstration of drug product manufacture using the drug substance at the extremes of its proposed particle size distribution. All supporting data will be assessed for adequacy at the time of the NDA submission.

In support of your proposed change in the analytical method for impurities and stability and to develop a harmonized method that is common to both drug substance and the drug product, you propose to bridge the current method with the new method by testing one stability testing time point. Please note that adequate method validation data and data supporting cross-validation of different analytical methods is needed. It is recommended that more than one stability time point be assessed using the old and the new analytical methods.

- 2.5 5. During development scale up, a minor change to the Phase 1/2 formulation was required in order to be able to manufacture abiraterone acetate tablets for the ongoing and planned clinical trials. The quantity of magnesium stearate (Mg stearate) was (b) (4) Mg stearate functions as a (b) (4) in the formulation. As described in Section 13.3.P.1; the impact of this formulation change was evaluated through additional dissolution studies. The results from these studies demonstrated that the (b) (4) Mg stearate from (b) (4) had no meaningful impact on the quality or performance of the formulation. Does the Agency agree that the (b) (4) (b) (4) in the Mg stearate represents a minor change and that the abiraterone acetate 250 mg tablets used in the Phase 1/2 and Phase 3 clinical trials can be considered "equivalent"?

FDA Preliminary Response: Based on the provided data on multi-point dissolution profiles in multiple dissolution media, we agree that the (b) (4) the magnesium stearate represents a minor change and CMC bridging alone may be sufficient to link the Phase 1 /2 versus Phase 3 product. However, additional data on comparability of manufacturing process and formulation development is needed to confirm this assertion. You indicate that since (b) (4) was observed with the formulation containing (b) (4) during product (b) (4); (b) (4), a formulation change to include an additional (b) (4) magnesium stearate and (b) (4) (b) (4) (b) (4) solved this problem. Provide a detailed description of the pharmaceutical development including optimization of (b) (4) times following addition of magnesium stearate, (b) (4) (b) (4) and other pertinent details in the NDA. In addition, provide information on the source (b) (4) of magnesium stearate to be used in the abiraterone acetate drug product.

It is indicated that an average of (b) (4) minutes (b) (4) and a higher tablet (b) (4) was seen with the formulation containing (b) (4); magnesium stearate versus (b) (4) (b) (4) although, it met the proposed specification of $Q = (b) (4)$ at 45 minutes. In view of this observation, we recommend that you submit the dissolution profile data in the NDA for the batches at release and on stability. Also, submit data pertaining to the permeability and an assessment of BCS classification in the NDA. We will assess the suitability of the proposed dissolution specification in light of the product's BCS classification and may consider a (b) (4) dissolution specification, if needed. Also, provide a test for disintegration testing in the drug product specifications.

- 2.6** 6. Pharmaceutical development is ongoing for a commercial immediate release solid oral tablet formulation that can be scaled and commercialized. The optimization studies required to link the Phase 3 formulation and the commercial (market image) formulation will be conducted in parallel with the Phase 3 clinical trial in accordance with the process optimization plan. Does the Agency agree with the formulation and process optimization plan presented in Sections 13.3.P.2.2 and 13.3.P.2.1?

FDA Preliminary Response: You indicate that the formulation optimization for the abiraterone acetate tablet formulation is ongoing and that as of the date of this meeting package, it is not known whether the formulation to be used in the Phase 3 trial will be the same as the market image formulation. You also indicate that PAT and Quality by Design (QbD) approaches are being utilized to optimize the formulation. You seem to have identified many areas to evaluate and optimize the manufacturing process. (b) (4)

Therefore, without knowing the extent of changes likely to happen in the formulation and the process, and rigor with which they will be assessed using PAT and QbD approach, we cannot say whether the formulation and process optimization plan is acceptable to us or not. It should also be noted that the extent of QbD information will dictate how much of CMC bridging and pharmacokinetic bridging will be needed for the proposed changes. It is expected that via your QbD approach, all critical and non-critical process parameters are identified and adequate in-process controls are established for them. It is also expected that the critical quality attributes are preserved during the proposed changes in the formulation and the process. You are free to conduct the comparative study at any time during your development program, but completion of the comparative study prior to beginning the Phase 3 clinical trial is recommended, in order to confirm the equivalence of the clinical and intended commercial formulations.

- 2.7** 7. As explained in Section 13.3.P.2.3, the SUPAC-IR guidance will be used in order to evaluate the changes made during the optimization process. The approach and studies to establish the equivalence of the Phase 3 formulation with the commercial formulation are presented in Section 13.3.P.2.3. Does the Agency agree with the proposed plan to link the Phase 3 formulation and process to the commercial formulation and manufacturing process and the proposed approach to evaluate the changes?

FDA Preliminary Response: The SUPAC guidances are developed for post-approval changes for products with significant body of manufacturing experience. You may use the SUPAC principles but be advised that they may not in themselves be adequate to demonstrate CMC bridging of Phase 3 formulation with the commercial formulation. Therefore, a conservative approach is recommended. Your plan for the assessment of the formulation and process optimization in which up to one level 2 change may be carried out, we recommend that you assess such changes using dissolution testing in multiple media and at multiple time points. However, depending on the type of level 2 change, a bioequivalence bridging may or may not be needed. The data will be assessed for adequacy at the time of NDA submission. Alternatively, if you request a pre-NDA meeting, we could review some of this data and provide a feedback whether a bioequivalence bridging is needed or not.

- 2.8 8. The development plan involves the formulation and manufacturing optimization of the commercial (to-be-marketed) formulation at the current developmental site (b) (4). Upon completion of the formulation and process optimization work at the development site, the commercialization strategy for the NDA is envisioned to involve a "technical transfer" of the optimized formulation/manufacturing process to an alternate commercial site. Does the Agency agree with the proposed plan presented in Section 13.3.P.3 and Figure 3 to qualify the material from the alternative site for commercial use?

FDA Preliminary Response: As indicated above, you may use the principles of SUPAC to support the site change; however, a conservative approach is recommended. Since SUPACs are based on end product testing alone, they may need to be augmented by additional QbD and PAT information that will be gathered during pharmaceutical development and process transfer operations. All supporting CMC information regarding your proposed alternate manufacturing site should be provided in the initial NDA submission. Please also note that as indicated above, if significant formulation and process changes are necessitated by the scale-up and technology transfer, CMC bridging alone may not be adequate and additional human PK bridging may be needed to ensure unchanged quality, safety and efficacy profile. A CMC-specific meeting following formulation and process optimization is recommended.

- 2.9 9. As described in Sections 13.1.S.1, abiraterone acetate API is practically insoluble in water over a wide range of pHs. Significant degradation of the API is also observed at pH (b) (4). The addition of sodium laurel sulfate (SLS) (b) (4) of the abiraterone acetate with the highest solubility obtained between pH 4-5. In aqueous media of pH (b) (4) (b) (4) are not reached even with the addition of SLS. Therefore, pH 4.5 has been chosen as the dissolution medium for the dissolution test as this is the only pH where (b) (4) (b) (4) can be met. For the release of all abiraterone acetate tablets, full dissolution profiles will be obtained during the development phase in aqueous media with (b) (4) SLS and pH 4.5. Does the Agency agree with the justification for the choice of the dissolution method, including its medium, and the planned developmental work on the dissolution test as presented in Section 13.4.P.3.1.

FDA Preliminary Response: Your proposed choice of dissolution method is acceptable with a caveat that the acceptance criteria (i.e. Q and time point) will be assessed upon review of the dissolution profile data in the NDA. Also, as discussed above, depending on the BCS classification information for your product, we may also propose a (b) (4), (b) (4) dissolution specification, if appropriate. Also, establishment of IVIVC is recommended for your product.

- 2.10** 10. ICH Q3BR2 for the reporting, identification, and qualification of the impurities in the finished product is being followed. This guideline will be followed for the impurities that are detected in the room temperature (25°C/60% RH) stability studies to support the recommended storage condition for the drug product. Does the Agency agree with the approach presented in Section 13.6.P.1.1 regarding the identification of impurities detected during the stability studies at 25°C/60% RH?

FDA Preliminary Response: This approach is reasonable if there is no significant change is seen during six months of accelerated stability testing. If any significant change occurs during accelerated stability testing, we recommend that stability studies be conducted at 30°C/65% RH for a minimum of 12 months. The resulting data should be provided in the initial NDA submission.

- 2.11** 11. Stability protocol and data for Phase 1-3 formulations are presented in Section 13.6.P. The stability plan and protocol include the number of lots with their respective size planned for the NDA to support the shelf-life of the commercial product are presented in Table 25. Does the Agency agree with the appropriateness of the stability protocols to support the shelf life of the Phase 3 and commercial formulations including the product from the alternate site?

FDA Preliminary Response: We expect to see primary stability data on three batches of the drug product made using the revised formulation, which contains (b) (4) magnesium stearate. If any other significant changes are made to the formulation and or the manufacturing process, additional stability assessment may be warranted. All primary and supportive stability data will be assessed for adequacy at the time of NDA review. Also, as indicated above, provide the dissolution profiles on stability and assess the need for monitoring tablet hardness and friability on stability.

- 2.12** 12. As describe in Section 13.1.S.9.1, efforts are underway to harmonize the impurity methods for both the API and the drug product. Does the Agency agree with the proposed approach to implement the potential updated impurity test in the ongoing stability studies?

FDA Preliminary Response: In general your approach is reasonable; however, the impurity methods for both the API and the drug product will be assessed for adequacy at the time of submission. If the method change is implemented during the midst of the stability studies, data on adequate bridging of the analytical methods should be provided. As indicated above, this may entail adequate validation/cross-validation of analytical methods and re-analysis of hold samples at multiple time points.

- 2.13 13.** Does the Agency have any other observations or comments that they want to advise Cougar after review of the information package?

FDA Preliminary Response: Please ensure that all manufacturing, testing, labeling and packaging sites are ready for inspection at the time of NDA submission. Provide a listing of all sites, their addresses, and CFN/FEI numbers in the NDA. Include complete addresses and contact information with your FDA Form 356h.

You have the option of implementing a quality-by-design (QbD) approach to pharmaceutical development as outlined in ICH Q8 Guidance on *Pharmaceutical Development*. In view of the above discussion on QbD and PAT approaches, please include QbD-related information and questions in a CMC-specific meeting or request a CMC guidance meeting to discuss your QbD approach during your Phase 3 clinical studies.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion at this time

4.0 CONCURRENCE:

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Regulatory Health Project Manager for Quality
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment

{See appended electronic signature page}

Ravi Harapanhalli, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment III & Manufacturing Science
Office of New Drug Quality Assessment

Linked Applications

Sponsor Name

Drug Name

IND 71023

COUGAR
BIOTECHNOLOGY INC

CB7630 (ABIRATERONE ACETATE)

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/s/

SCOTT N GOLDIE
03/04/2008

RAVI S HARAPANHALLI
03/04/2008

MEETING MINUTES

TELECON DATE: January 31, 2008 **TIME:** 3:30 pm **LOCATION:** 2201

APPLICATION: IND 71,023 **DRUG NAME:** Abiraterone Acetate (CB7630)

TYPE OF MEETING: Guidance

PROPOSED INDICATION: Prostate Cancer

SPONSOR: Cougar Biotechnology, Inc.

Meeting Request Submission Date: December 21, 2007

Meeting Granted Date: January 4, 2008

Briefing Document Submission Date: January 10, 2008

Briefing Document Received Date: January 10, 2008

FDA ATTENDEES:

Ann Farrell, M.D., Deputy Division Director, DDOP

Bhupinder Mann, M.D., Acting Medical Team Leader, DODP (*Meeting Chair*)

Robert White, M.D., Medical Officer, DODP

Rajeshwari Sridhara, Ph.D., Statistical Team Leader, DBI

Sharon Thomas, Consumer Safety Officer, DDOP (*Minutes Recorder*)

SPONSOR ATTENDEES:

Arturo Molina, MD, MS, Sr. Vice President, Clinical Research and Development

Richard Phillips, Ph.D., Vice President, Regulatory Affairs and Quality Assurance

Gloria Lee, MD, PhD, Vice President Clinical Research and Development

Thian Kheoh, Ph.D., Vice President, Biometrics

Chris Haqq, MD, PhD, Senior Director Clinical Research and Development

Nadia Agopyan, PhD, RAC, Director Regulatory Affairs

Nicole Chieffo, MBA, Senior Director, Clinical Development and Operations

Alan Auerbach, Chief Executive Officer, President

MEETING OBJECTIVES:

To discuss the FDA's draft comments sent to the sponsor on January 28, 2008.

BACKGROUND:

On November 5, 2007, the sponsor submitted a request for a Special Protocol Assessment for their study 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."

The FDA issued a non-agreement letter on December 21, 2007. On December 21, 2007, the sponsor submitted a Type A meeting request to discuss the study design and statistical approach for their COU-AA-301 protocol. The FDA provided responses to the sponsor's questions on January 28, 2008. On January 29, 2008 the sponsor decided to proceed with the scheduled industry meeting to obtain clarification on questions 1 and 3. The discussion points are indicated in italics

QUESTIONS for DISCUSSION with FDA RESPONSE AND DECISIONS REACHED:

1. Does the Agency agree that the revised statistical analysis and the stratification factors described above adequately address the concern?

FDA: Yes.

Cougar's Response: Cougar would like to confirm that FDA agreement to Question # 1 is inclusive of the analysis model described in section 3.5.1, of Attachment 1 on page 21 of information package. If so, could the draft FDA responses be amended to clarify that this is what is being agreed to?

FDA: As per your response to our response on page 9, we agree that the primary efficacy OS analysis will be based on stratified log-rank test. The analysis model presented in section 3.5.1 will be considered as supportive analysis

Discussion Point: The sponsor is proposing to conduct a log-rank test as the primary analysis and will also specify in the protocol a method to compute an adjusted p value. The Agency agreed in principle.

2. Does the Agency agree that  (b) (4)

FDA: No.  (b) (4)

 (b) (4)

- 3. Does the Agency agree that the clarifications described above and reflected in attachments 4 and 5 regarding the Concomitant Therapy (permissible medication) as well as changes to sections 5.6 and 5.7 address the concern?

FDA: Yes, except for the second sentence of the third bullet in section 5.6. We are concerned about patients who have their dose of steroid changed or are placed on a more potent steroid because of fatigue. Since fatigue or pain may indicate disease progression or toxicity this may confound study results. Please address this in your protocol.

Cougar's Response: Cougar would like to confirm that the following changes to the COU-AA-301 protocol will address the FDA's concern re fatigue and glucocorticoid use (Q #3). Cougar proposes to address the concern in the protocol by deleting the second sentence of the third bullet in section 5.6 in its entirety. Consequently, both the Concomitant therapy (section 5.6) and the Criteria for discontinuation of study treatment (section 6.8) will be modified to state that an increase in the dose of prednisone or prednisolone or addition of a more potent glucocorticoid, such as dexamethasone, will be considered a disease progression event. The actual modifications, highlighted in yellow, are provided as attachments hereto.

Discussion Point: This appears acceptable.

- 4. Does the Agency agree that the proposed modifications in stratification factor as documentation of disease progression addresses agencies the concern?

FDA: Yes.

- 5. Does the Agency agree with the proposed approach for the [redacted] (b) (4)

FDA: No. [redacted] (b) (4)

6. Does the Agency agree with the [redacted] (b) (4)

FDA: No. [redacted] (b) (4)

[redacted] (b) (4)

7. Does the Agency agree with the proposed wording for the Informed Consent regarding use of prednisone?

FDA: Yes.

8. Does the Agency agree with the proposed plan for more intensive ECG monitoring in the COU-AA-301 trial?

FDA: Yes.

9. Does the Agency agree to this inclusion of [redacted] (b) (4)

FDA: [redacted] (b) (4)

10. Does the FDA agree with the proposal that IDMC members will also monitor the death events along with the safety data every 4 months (instead of every 6 months as currently written in the Charter)?

FDA: Yes.

The meeting concluded at 4:15 pm.

Sharon Thomas
Consumer Safety Officer
Minutes Preparer

Concurrence Chair: _____
Bhupinder Mann, M.D
Medical Team Leader

Linked Applications

Sponsor Name

Drug Name

IND 71023

COUGAR
BIOTECHNOLOGY INC

CB7630 (ABIRATERONE ACETATE)

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/s/

BHUPINDER S MANN
02/05/2008

MEETING MINUTES

TELECON DATE: September 27, 2007 **TIME:** 10:00 am **LOCATION:** 1315

APPLICATION: IND 71,023 **DRUG NAME:** CB7630 (Abiraterone Acetate)

TYPE OF MEETING: End-of-Phase 2

PROPOSED INDICATION: Prostate Cancer

SPONSOR: Cougar Biotechnology, Inc.

Meeting Request Submission Date: June 12, 2007

Meeting Granted Date: June 18, 2007

Briefing Document Submission Date: August 27, 2007

Briefing Document Received Date: August 29, 2007

FDA ATTENDEES:

Robert Justice, M.D., Division Director, DDOP

Ann Farrell, M.D., Deputy Division Director, DDOP

John Johnson, M.D., Medical Team Leader, DODP (*Meeting Chair*)

Robert White, M.D., Medical Officer, DODP

John Leighton, Ph.D., Pharmacologist Team Leader, DODP

Shengui Tang, Ph.D., Statistical Reviewer, DBI

Brian Booth, Ph.D., Clinical Pharmacology Team Leader, DDOP

Christine Garnett, Pharm.D., QT-IRT Reviewer, Pharmacometrics, OCP

Sharon Thomas, Consumer Safety Officer, DDOP (*Minutes Recorder*)

SPONSOR ATTENDEES:

Arturo Molina, MD, MS, Senior Vice President, Clinical Research and Development

Richard Phillips, Ph.D., Vice President, Regulatory Affairs and Quality

Gloria Lee, MD, Ph.D., Vice President Clinical Research and Development

Thian Kheoh, Ph.D., Vice President, Biometrics

Chris Haqq, MD, Ph.D., Senior Director Clinical Research and Development

Nadia Agopyan, Ph.D., RAC, Director Regulatory Affairs

Nicole Chieffo, MBA, Senior Director, Clinical Development and Operation

Arie Belldegrun, MD, Vice Chairman

Johann de Bono, MD, Ph.D., Institute for Cancer Research, Principle Investigator

Howard Scher, MD, Memorial Sloan Kettering, Principle Investigator

MEETING OBJECTIVES:

To discuss the FDA's draft comments sent to the sponsor on September 14, 2007.

BACKGROUND:

The sponsor submitted an End of Phase 2 meeting request on June 12, 2007 to discuss their phase 3 clinical development plan for abiraterone acetate.

The FDA provided responses to the sponsor's questions on September 14, 2007. On September 20, 2007 the sponsor decided to proceed with the scheduled industry meeting for clarification. The discussion points are indicated in italics.

QUESTIONS for DISCUSSION with FDA RESPONSE AND DECISIONS REACHED:

1. Does the Agency agree that the overall design of the pivotal Phase 3 study (COU-AA-301), in addition to data from COU-AA-001, COU-AA-002, COU-AA-003, COU-AA-004, and COU-AA-BE will provide adequate efficacy and safety data for filing and review of a market authorization application for the following indication?

Cougar: Acknowledged and understood.

FDA: Possibly, however the specific wording of the indications section is a review issue.

- a. **For a single randomized trial to support an NDA, the trial should be well designed, well conducted, internally consistent and provide statistically persuasive and clinically meaningful efficacy findings so that a second trial would be ethically or practically impossible to perform. We strongly suggest that you conduct two adequate and well-controlled trials to support the proposed indication.**

Cougar: Acknowledged and understood.

- b. **We strongly recommend that you add the following stratification factors: 1) one versus two prior chemotherapy regimens; 2) PSA progression versus objective progression in soft tissue or bone.**

Cougar: Cougar would like to have further guidance from the Agency on the definition of "chemotherapy regimens". Cougar would also like to understand the Agency's rationale for including "PSA progression versus objective progression in soft tissue or bone" as a stratification factor. Furthermore there is concern that the inclusion of additional stratification factors may impact the efficacy of the trial design. Hence, Cougar would

like to discuss and seek the Agency's agreement on the proposed stratification factors.

DISCUSSION: FDA clarified that these are suggestions for consideration. The FDA recommended a non-stratified log rank test as the primary analysis. The sponsor proposed a stratification by region (US vs Non US). The FDA agreed.

c. We strongly recommend that you only measure PSA at the same time that you obtain objective disease measurements.

Cougar: Cougar would like to discuss this further with the Agency. Although Cougar agrees to specify in the protocol that PSA should only be measured at the same time that objective disease measurements are gathered, it is likely that investigators will obtain PSA measurements as part of patient management outside the pre-specified schedule in the protocol.

DISCUSSION: The sponsor indicated that the protocol specified criteria for discontinuation of study treatment, which would include confirmation of PSA progression and radiographic progression with repeat studies.

d. What evidence do you have that there is activity of this drug in patients with metastatic CRPC after failure of two chemotherapy regimens?

Cougar: Although the majority of patients on the COU-AA-003 study (abiraterone acetate monotherapy) have had only one prior chemotherapy regimen, several patients received two chemotherapy regimens and at least one of these patients had a PSA response lasting six months. Additionally several of these patients have received experimental agents before or after docetaxel prior to entering the study. Demographic and efficacy data from the COU-AA-004 study (abiraterone acetate plus prednisone) are still not available.

2. Does the Agency agree with the clinical and statistical design of the proposed COU-AA-301 protocol appended in Appendix 2 with regard to the primary and secondary endpoints?

FDA: Yes.

Cougar: No comment/discussion.

a. The overall study design and statistical analysis approach including the planned interim and final analysis of OS (the primary endpoint)?

FDA: Yes, in general, your statistical analysis plan appears acceptable. Please pre-specify the stratification factors which will be used in the primary analysis.

Cougar: Based upon the stratification factor discussion and agreement with regard to the FDA's response to Question 1 above, the agreed upon stratification factors to be used in the primary analysis will be pre-specified in the SAP.

- b. The patient population described in the inclusion/exclusion section of the COU-AA-301 protocol (Appendix 2) is supportive of the proposed patient population (Target Product Profile-Appendix 3)?

FDA: Yes.

Cougar: No comment/discussion.

- c. Prednisone 5 mg twice a day (BID) as an appropriate comparator arm for metastatic CRPC after failure of a docetaxel-containing regimen?

FDA: Yes.

Cougar: No comment/discussion.

- d. The dose and schedule of abiraterone acetate 1000 mg once daily (QD) and its use in combination with prednisone 5 mg twice daily (BID) as an appropriate investigational intervention (treatment arm) in the indicated patient population?

FDA: Yes.

Cougar: No comment/discussion.

3. Does the Agency agree that the proposed safety database summarized in Table 1 would provide sufficient patient exposure from the safety perspective to support the filing of a market authorization application for abiraterone acetate?

FDA: Yes.

Cougar: No comment/discussion.

4. Does the Agency agree that the methodology of collecting (b) (4)

FDA:

a. We doubt that the proposed analysis of [REDACTED] (b) (4) will be adequate [REDACTED] (b) (4).

[REDACTED] (b) (4)

[REDACTED] (b) (4)

Cougar: We agree. No comment or discussion.

[REDACTED] (b) (4)

Cougar: Understood. [REDACTED] (b) (4)

DISCUSSION: The sponsor agreed to include time matched blood draws for exposure response analysis.

(b) (4)

Cougar: We agree. (b) (4) (b) (4) (b) (4)
(b) (4) will be utilized.

(b) (4)

DISCUSSION: The FDA recommended that the sponsor submits a formal ECG monitoring plan for review.

5. Does the Agency agree that an indication for abiraterone acetate for the treatment of prostate cancer qualifies for a pediatric waiver and thus a pediatric assessment of abiraterone acetate is not required?

FDA: Yes.

Cougar: No comment/discussion.

6. Does the Agency agree that (b) (4)

FDA: No.

(b) (4)

Cougar: Acknowledged and understood.

(b) (4)

7. Does the Agency agree that abiraterone acetate qualifies for a reproductive and developmental toxicity study waiver as the patients in whom it is intended to be indicated for are surgically and/or chemically castrated?

FDA: Yes, reproductive toxicity studies will not be required for this patient population.

Cougar: No comment/discussion.

8. Does the Agency agree that long term carcinogenicity studies of abiraterone acetate are not due to the life expectancy for the indicated population is less than 5 years?

FDA: Yes, carcinogenicity studies with abiraterone acetate are not required for this patient population.

Cougar: No comment/discussion.

9. Does the Agency agree that the preclinical pharmacology and toxicology/studies data, completed and planned, adequately support the filing of a market authorization application in the proposed indication?

FDA: Six-month repeat dose toxicology studies will need to be completed, as is generally required for long-term hormonal therapy. Additional studies may be needed following review of your recently completed and proposed non-clinical studies. Please also submit your finalized 13-week studies in rats and monkeys ((b) (4) Study # 7777-100, and 7777-101).

Cougar: Acknowledged and understood. Cougar intends to conduct a 6-month repeat-dose toxicology study in rats and a 9-month repeat-dose toxicology study in monkeys with the results to be included in the market authorization application.

The final reports for (b) (4) Study #7777-100 and 7777-101 are currently undergoing peer and QA review and once finalized, will be provided to the Agency.

In addition, if your future development plan includes clinical studies with a longer duration of treatment, in patients likely to have an extended survival, or as adjuvant therapy, reproductive toxicity studies as described by ICH Guidelines (segments A-F), as well as additional studies may be needed.

Cougar: No comment/discussion.

10. Upon review of this information package, including the COU-AA-301 protocol, does the Agency have any other comments or questions to provide to Cougar?

FDA: Yes. See below.

FDA Additional Comments:

- 1. If you plan to submit this protocol for a Special Protocol Assessment, please submit CRF, SAP, and DSMB charter.**

Cougar: The indicated documents (Protocol, CRF, SAP, DSMB Charter) will be provided in the SPA.

2. Do you have any information regarding the reversibility of adrenal suppression?

Cougar: Clinically meaningful adrenal suppression was not observed during the phase 1 and 2 studies. Due to end-of-study patient compliance, lab data on reversibility of adrenal suppression is not available.

3. Please submit your planned and completed clinical pharmacology development program for review and discussion.

Cougar: Acknowledged and understood. Cougar intends to submit human ADME protocols for the Agency's review/feedback by June 2008.

4. We recommend that you screen CB7630 in vitro to determine whether it is a substrate of cytochrome P-450 isozymes. You should also assess whether it is a substrate or inhibitor of P-glycoprotein.

Cougar: No comment/discussion.

5. Genetic polymorphisms in UGT enzymes may alter drug concentrations. Is it known which UGT is responsible for glucuronidation of abiraterone?

Cougar: No comment/discussion.

6. Since both abiraterone acetate and abiraterone are strong inhibitors of P450 CYPs 2C19, 2D6 and 1A2, there is the potential for your drug to exacerbate drug toxicity when given concomitantly with drugs metabolized by these P450 isoenzymes whose therapeutic indices are low. Narrow therapeutic index substrates of CYPs 2C19, 2D6 and 1A2 should be used with caution in all clinical trials, and this information along with a list of the substrates needs to be added to the concomitant medication section of your protocols.

Cougar: No comment/discussion.

7. We recommend the addition of sparse sampling in your phase 3 in order to characterize exposure-response, and exposure-toxicity relationships.

DISCUSSION: *The sponsor agreed to incorporate sparse sampling in the phase 3 trial.*

The meeting concluded at 11:00 am.

Sharon Thomas
Consumer Safety Officer
Minutes Preparer

Concurrence Chair: _____
John Johnson, M.D.
Medical Team Leader

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/s/

John Johnson

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