

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203415Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 203415

SUPPL #

HFD # 150

Trade Name Xtandi

Generic Name enzalutamide

Applicant Name Medivation, Inc.

Approval Date, If Known August 31, 2012

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?

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

Investigation #3 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

Investigation #3 YES NO

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

Name of Office/Division Director signing form: Robert Justice, M.D.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

CHRISTY L COTTRELL
08/31/2012

ROBERT L JUSTICE
08/31/2012

1.3.3 Debarment Certification

Medivation, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Diana Lee Francis
Senior Director, Quality Management
Medivation, Inc.



Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 203415 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Xtandi Established/Proper Name: enzalutamide Dosage Form: Soft Gelatin Capsule		Applicant: Medivation, Inc. Agent for Applicant (if applicable):
RPM: Christy Cottrell		Division: 150
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>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><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>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><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² 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:</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>November 22, 2012</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

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

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ 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 _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p> <input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<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)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> 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 ASCO

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<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 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>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ⁴	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<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) Approval; 8-31-12
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. 	Included; 8-30-12
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	5-22-2012
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A

⁴ Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> ❖ 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. 	Included; 8-30-12
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	5-22-2012
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A
<ul style="list-style-type: none"> ❖ 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 	8-24-2012
<ul style="list-style-type: none"> ❖ 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>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	8-3-2012 8-3-2012
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 8-3-2012 <input checked="" type="checkbox"/> DMEPA 7-11-2012 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 8-30-12 <input checked="" type="checkbox"/> ODPD (DDMAC) 8-29-12 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	8-9-2012
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input checked="" type="checkbox"/> Not a (b)(2) <input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> ❖ 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
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>Full waiver granted on 8/1/12</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
<ul style="list-style-type: none"> ❖ 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

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)	Included: 8/28/12, 8/27/12, 8/17/12 (2), 8/15/12 (2), 8/7/12, 8/6/12, 8/3/12 (2), 8/1/12, 7/27/12, 7/25/12, 7/24/12 (2), 7/17/12, 7/11/12 (2), 7/3/12 (2), 6/29/12, 6/25/12, 6/15/12, 6/14/12, 6/11/12, 6/6/12, 5/25/12
❖ Internal memoranda, telecons, etc.	
❖ 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 3-30-2012
• EOP2 meeting (<i>indicate date of mtg</i>)	<input type="checkbox"/> No mtg see tab
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	see tab
❖ 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 8-31-12
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8-31-12
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 8-19-2012
PMR/PMC Development Templates (<i>indicate total number</i>)	<input type="checkbox"/> None 8-30-12
Clinical Information⁶	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	8-19-2012
• Clinical review(s) (<i>indicate date for each review</i>)	8-19-2012; 8/30/12
• 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>)	8-19-2012; page 17 of clinical review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None 8-13-2012; 8-7-12
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management	
• 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

⁶ Filing reviews should be filed with the discipline reviews.

❖ DSI Clinical Inspection Review Summary(ies) (include copies of DSI letters to investigators)	<input type="checkbox"/> None requested 8-14-2012
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None Concurrence with stat TL memo; 8-20-12
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None 8-20-2012
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 8-15-2012
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None Concurrence with primary clin pharm review; 8-28-12
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None Concurrence with primary clin pharm review; 8-28-12
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 8-28-2012
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of DSI letters)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input type="checkbox"/> None 8-22-2012
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None 8-20-2012
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 8-22-2012
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<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 (include copies of DSI letters)	<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	8-29-2012
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None	8-22-2012
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None	8-22-2012 (X2)
❖ Microbiology Reviews		
<input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed	8-7-2012
<input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/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 type="checkbox"/> None	8-15-2012
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		8-22-2012; page 81 of CMC review
<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) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷)</i>	Date completed: 6-20-2012	<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) (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 checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

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

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

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

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

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

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

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

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

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

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/s/

CHRISTY L COTTRELL
08/31/2012

From: Cottrell, Christy L.
Sent: Tuesday, August 28, 2012 2:09 PM
To: 'Lynn Seely'
Subject: NDA 203415 for Xtandi: FDA-revised labeling

Importance: High

Attachments: 8-28-12 labeling.doc
Lynn,

Please refer to your NDA 203415 for Xtandi. Attached is another round of FDA-revised labeling. We anticipate discussing any remaining labeling disagreements during tomorrow's telecon. If you agree with this labeling and no discussion is needed, we can cancel the telecon.

As I mentioned in my voicemail to you a few minutes ago, the Patient Package Insert is still under review by our Patient Labeling Team. They do not know for certain whether they will be able to accommodate our expedited review timeline. So, in the interest of not delaying action, there is a possibility that we would take action without a finalized PPI. In that case, you could submit a labeling supplement afterwards with the proposed PPI. This is just a back-up plan - there is still a chance that the PPI can be included with this action.

Talk to you tomorrow,
Christy



8-28-12
beling.doc (1 ME)

Christy Cottrell | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
 301.796.4256 (phone) •  301.796.9845 (fax) |  christy.cottrell@fda.hhs.gov



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/s/

CHRISTY L COTTRELL
08/28/2012

From: Cottrell, Christy L.
Sent: Monday, August 27, 2012 2:32 PM
To: 'Lynn Seely'
Subject: NDA 203415 for Xtandi: Response to Medivation information request

Importance: High
 Lynn,

Below is the response provided by our clinical pharmacology team to the information request you submitted last week. Let me know if any further clarification is needed.

In addition, we would like to reserve time for a teleconference to discuss labeling on Wednesday, August 29 at 2:00pm (eastern time). Please confirm whether your team is available and provide a call-in #.

Thanks,
 Christy

Medivation Information Request:

We would like to request a copy of the data used to support the forest plots (Figures 1 and 2) in the Clinical Pharmacology draft label sent to us on August 17th so that we can confirm the information in the label. Specifically, we are requesting the plotted mean values and the confidence intervals.

FDA response: Below please find a summary of the data used to create the forest plots in the label.

Figure 1:

Factor	PK	ratio	lratio	uratio
Strong CYP2C8 inhibitor (Gemfibrozil)
600 mg BID	Cmax	0.84	0.75	0.95
.	AUC	2.17	1.91	2.47
Strong CYP3A4 inhibitor (Itraconazole)
200 mg QD	Cmax	0.97	0.87	1.09
.	AUC	1.28	1.17	1.41
Hepatic Impairment Mild (Child-Pugh A)
.	Cmax	1.23	0.92	1.66
.	AUC	1.13	0.89	1.43
Hepatic Impairment Moderate (Child-Pugh B)
.	Cmax	0.89	0.69	1.15
.	AUC	1.18	0.96	1.45
Food High Fat Meal
.	Cmax	0.7	0.63	0.79
.	AUC	0.99	0.87	1.12
.
.

Figure 2:

Factor	PK	ratio	lratio	uratio
CYP3A4 Substrate, Midazolam 2 mg	Cmax	0.23	0.2	0.27
.	AUC	0.14	0.12	0.17
.
CYP2C9 Substrate, S-warfarin 10 mg	Cmax	0.93	0.86	0.99
.	AUC	0.44	0.41	0.48
.
CYP2C19 Substrate, Omeprazole 20 mg	Cmax	0.38	0.26	0.54
.	AUC	0.3	0.24	0.36
.
CYP2C8 Substrate, Pioglitazone 30 mg	Cmax	0.82	0.67	1.01
.	AUC	1.2	0.98	1.47
.
.

Christy Cottrell | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA
 10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
 ☎ 301.796.4256 (phone) • 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov

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/s/

CHRISTY L COTTRELL
08/27/2012

Kacuba, Alice

From: Bridges, Todd
Sent: Saturday, August 25, 2012 6:18 PM
To: Kacuba, Alice; Chidambaram, Nallaperum; Ghosh, Debasis
Cc: Justice, Robert; Ibrahim, Amna; Maher, Virginia E.; Maher, Virginia E.; Ning, Yang-Min (Max); Pierce, William (CDER); Cottrell, Christy L.; Defronzo, Kimberly
Subject: RE: NDA 203415: Revised Carton and Container Labeling

[These are acceptable from DMEPA's perspective.](#)

From: Kacuba, Alice
Sent: Friday, August 24, 2012 9:18 AM
To: Bridges, Todd; Chidambaram, Nallaperum; Ghosh, Debasis
Cc: Justice, Robert; Ibrahim, Amna; Maher, Virginia E.; Maher, Virginia E.; Ning, Yang-Min (Max); Pierce, William (CDER); Cottrell, Christy L.
Subject: FW: NDA 203415: Revised Carton and Container Labeling
Importance: High

DMEPA and CMC,

The sponsor called about 6 PM Thursday to say that they noticed that they inadvertently left off a statement /part of a statement about storage on the carton and container labels about "excursions (b) (4) ..." so they have resubmitted. Please let me know if these labels are acceptable.

Thank you.

Alice

Alice Kacuba, RN, MSN, RAC
 Chief, Project Management Staff
 Division of Oncology Products 1 (new name for DDOP)
 Office of Hematology and Oncology Products
 OND/CDER/FDA
 301-796-1381
 (f) 301-796-9845
 alice.kacuba@fda.hhs.gov

*Consider setting your email font setting to at least 12 font.

From: Lynn Seely [mailto:Lynn.Seely@medivation.com]
Sent: Friday, August 24, 2012 8:50 AM
To: Kacuba, Alice
Cc: Cottrell, Christy L.
Subject: NDA 203415: Revised Carton and Container Labeling

Dear Alice,

As we discussed by telephone yesterday, please find attached revised carton and container labeling. This revision of the labeling contains temperature excursion information that was not included in the prior carton and container labeling submitted. This information will also be submitted formally via the Electronic Submissions Gateway.

Please let me know if there are any questions or concerns.

Best regards, Lynn
650 315 5020

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/s/

ALICE KACUBA
08/29/2012

Kacuba, Alice

From: Ghosh, Debasis
Sent: Wednesday, August 22, 2012 10:21 AM
To: Kacuba, Alice; Abdus-Samad, Jibril; Bridges, Todd
Cc: Chidambaram, Nallaperum; Maher, Virginia E.; Pierce, William (CDER); Ning, Yang-Min (Max); Cottrell, Christy L.
Subject: RE: NDA 203415

Alice,
From CMC perspective, the container and carton labels are acceptable (received concurrence from BC)
Thanks
Debasis Ghosh
CMC reviewer

From: Kacuba, Alice
Sent: Tuesday, August 21, 2012 6:27 PM
To: Abdus-Samad, Jibril; Bridges, Todd
Cc: Chidambaram, Nallaperum; Ghosh, Debasis; Maher, Virginia E.; Pierce, William (CDER); Ning, Yang-Min (Max); Cottrell, Christy L.
Subject: FW: NDA 203415
Importance: High

Thank you.

Alice

Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Oncology Products 1 (new name for DDOP)
Office of Hematology and Oncology Products
OND/CDER/FDA
301-796-1381
(f) 301-796-9845
alice.kacuba@fda.hhs.gov

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From: Lynn Seely [mailto:Lynn.Seely@medivation.com]
Sent: Tuesday, August 21, 2012 6:20 PM
To: Kacuba, Alice
Cc: Cottrell, Christy L.
Subject: NDA 203415

Dear Alice,

Please find attached the requested revisions to the carton/container labeling.

After you have had a chance to review, I would appreciate it you would let me know if there are any outstanding issues.

There revisions were also formally submitted today via the Electronic Submissions Gateway.

Best, Lynn

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ALICE KACUBA
08/22/2012

Kacuba, Alice

From: Bridges, Todd
Sent: Tuesday, August 21, 2012 7:02 PM
To: Kacuba, Alice; Abdus-Samad, Jibril
Cc: Chidambaram, Nallaperum; Ghosh, Debasis; Maher, Virginia E.; Pierce, William (CDER); Ning, Yang-Min (Max); Cottrell, Christy L.; Defronzo, Kimberly
Subject: RE: NDA 203415

Hi Alice,

These are acceptable from DMEPA's perspective.

Thanks

From: Kacuba, Alice
Sent: Tuesday, August 21, 2012 6:27 PM
To: Abdus-Samad, Jibril; Bridges, Todd
Cc: Chidambaram, Nallaperum; Ghosh, Debasis; Maher, Virginia E.; Pierce, William (CDER); Ning, Yang-Min (Max); Cottrell, Christy L.
Subject: FW: NDA 203415
Importance: High

Thank you.

Alice

Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Oncology Products 1 (new name for DDOP)
Office of Hematology and Oncology Products
OND/CDER/FDA
301-796-1381
(f) 301-796-9845
alice.kacuba@fda.hhs.gov

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From: Lynn Seely [mailto:Lynn.Seely@medivation.com]
Sent: Tuesday, August 21, 2012 6:20 PM
To: Kacuba, Alice
Cc: Cottrell, Christy L.
Subject: NDA 203415

Dear Alice,

Please find attached the requested revisions to the carton/container labeling.

After you have had a chance to review, I would appreciate it you would let me know

if there are any outstanding issues.

There revisions were also formally submitted today via the Electronic Submissions Gateway.

Best, Lynn

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ALICE KACUBA
08/22/2012

Kacuba, Alice

From: Cottrell, Christy L.
Sent: Friday, August 17, 2012 11:08 AM
To: Lynn Seely
Cc: Kacuba, Alice
Subject: NDA 203415 for Xtandi: Clinical Pharmacology revisions to the labeling

Attachments: 8-17-12 FDA revised clinical pharmacology labeling.doc

Lynn,

Attached is a document outlining our proposed changes to the Clinical Pharmacology sections of the labeling (as well as other outstanding sections such as Geriatric Use).

I wanted to go ahead and send these edits to you now so your team can begin reviewing them. I will insert these sections into the counterproposal document that you sent to us the other day, so that when we send everything back to you (after discussing some items further in today's telecon and more work on the labeling internally), these changes will be in the document already.

I will be on vacation next week, as will our clinical team leader, so I don't anticipate much labeling negotiation taking place next week. But, if you send in your counterproposals to these Clinical Pharmacology changes sometime next week, please cc: Alice Kacuba so she can at least forward to the team in my absence.

Regards,
Christy



8-17-12 FDA
vised clinical p

Christy Cottrell | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
☎ 301.796.4256 (phone) • 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov



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ALICE KACUBA
08/22/2012

Kacuba, Alice

From: Kacuba, Alice
Sent: Friday, August 17, 2012 2:41 PM
To: Lynn Seely
Cc: Cottrell, Christy L.
Subject: NDA 203415 carton and container Request

Importance: High

Hi,

Container and Carton:

To help ensure that the graphic to the left of the name doesn't cause confusion with the proprietary name, reduce the prominence of the graphic and change the font color to a color other than the color utilized for the proprietary name.

Please resubmit asap (email and official submission).

Please include me on emails while Christy is on leave.

Thank you.

Alice

Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Oncology Products 1 (new name for DDOP)
Office of Hematology and Oncology Products

OND/CDER/FDA

301-796-1381

(f) 301-796-9845

alice.kacuba@fda.hhs.gov

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ALICE KACUBA
08/17/2012

Kacuba, Alice

From: Kacuba, Alice
Sent: Wednesday, August 15, 2012 5:37 PM
To: Lynn Seely
Cc: Cottrell, Christy L.
Subject: NDA 203415 Clinical IR (Labeling)

Importance: High

Hi,

We have the following Information Request from Clinical on labeling.

Please provide the patient ID numbers used to calculate the incidence rates in Table 1 of the full prescribing information for "asthenic conditions" and for "lower respiratory (b) (4) and lung infections".

Please reply expeditiously so that we can finish the labeling and send back to you.

I may be covering Thursday as well so please continue to have both Christy and I on emails.

I left you a VM in response to your VM earlier today. I am in office until 8 pm tonight so you can still call or email me the questions that you have.

Thank you.

Alice

Alice Kacuba, RN, MSN, RAC
Chief, Project Management Staff
Division of Oncology Products 1 (new name for DDOP)
Office of Hematology and Oncology Products
OND/CDER/FDA
301-796-1381
(f) 301-796-9845
alice.kacuba@fda.hhs.gov

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ALICE KACUBA
08/22/2012

Kacuba, Alice

From: Kacuba, Alice
Sent: Wednesday, August 15, 2012 6:09 PM
To: Kacuba, Alice
Subject: RE: NDA 203415 Clinical IR (Labeling)

At 5:45 Dr. Seely called me and asked the following questions:

1. Are the container and carton labels submitted today acceptable. I replied that I will look at them and assure they are reviewed by appropriate staff. They wanted to print them before the action. I said that we can not give her an official approval of the carton and container labels until she has received a signed action letter from Dr. Pazdur on the entire application. If they choose to print prior to receiving the action letter it is a business decision and done at their own risk.
2. She inquired about whether there would be any more PMC/R requests? I told her I'd check and if so, we'd communicate to her.
3. She asked about what our target date for action was. I said, "Technically, we have 6 months, but the review is progressing well" and left it there. She said that she understood.

Thank you.

Alice

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Chief, Project Management Staff
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alice.kacuba@fda.hhs.gov

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From: Kacuba, Alice
Sent: Wednesday, August 15, 2012 5:37 PM
To: Lynn Seely
Cc: Cottrell, Christy L.
Subject: NDA 203415 Clinical IR (Labeling)
Importance: High

Hi,

We have the following Information Request from Clinical on labeling.

Please provide the patient ID numbers used to calculate the incidence rates in Table 1 of the full prescribing information for "asthenic conditions" and for "lower respiratory (b) (4) and lung infections".

Please reply expeditiously so that we can finish the labeling and send back to you.

I may be covering Thursday as well so please continue to have both Christy and I on emails.

I left you a VM in response to your VM earlier today. I am in office until 8 pm tonight so you can still call or email me the questions that you have.

Thank you.

Alice

Alice Kacuba, RN, MSN, RAC

Chief, Project Management Staff

Division of Oncology Products 1 (new name for DDOP)

Office of Hematology and Oncology Products

OND/CDER/FDA

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(f) 301-796-9845

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ALICE KACUBA
08/15/2012

From: Cottrell, Christy L.
Sent: Tuesday, August 07, 2012 2:28 PM
To: 'Lynn Seely'
Cc: 'Cheryl Madsen'
Subject: NDA 203415 for MDV3100: Clinical Pharmacology PMRs

Importance: High
Lynn,

Please refer to your pending NDA 203415 for MDV3100. See below for the PMRs identified by the Clinical Pharmacology team. We will need you to fill in the milestone dates and return to us via e-mail. Once you have determined the milestone dates for these PMRs (as well as the clinical PMR sent to you previously by Dr. Maher), please submit a general correspondence to the NDA providing your commitment to these PMRs.

1. Conduct a clinical trial in patients with normal hepatic function and patients with pre-existing severe hepatic impairment to assess the effect of severe hepatic impairment on the pharmacokinetics of enzalutamide and N-desmethyl enzalutamide. The proposed protocol must be submitted for review prior to trial initiation.

Milestones:	Final Protocol Submission:	MM/DD/YYYY Y
	Trial Completion:	MM/DD/YYYY Y
	Final Report Submission:	MM/DD/YYYY Y
	Other : _____	MM/DD/YYYY Y

2. Conduct a drug interaction trial to evaluate the effect of rifampin (a strong CYP3A inducer and a moderate CYP2C8 inducer) on the pharmacokinetics of enzalutamide and N-desmethyl enzalutamide. The proposed trial protocol must be submitted for review prior to trial initiation.

Milestones:	Final Protocol Submission:	MM/DD/YYYY Y
	Study Completion:	MM/DD/YYYY Y
	Final Report Submission:	MM/DD/YYYY Y
	Other : _____	MM/DD/YYYY Y

- Conduct drug interaction trials to evaluate the effect of enzalutamide at steady state on the pharmacokinetics of CYP2D6 and CYP1A2 substrates. The proposed trial protocols must be submitted for review prior to initiation of the trials.

Milestones:	Final Protocol Submission:	MM/DD/YYYY Y
	Study Completion:	MM/DD/YYYY Y
	Final Report Submission:	MM/DD/YYYY Y
	Other :	MM/DD/YYYY Y

- Perform an in vitro screen to determine if N-desmethyl enzalutamide is metabolized by the major human CYP450 isozymes. Based on results from the in vitro screen, clinical drug-drug interaction trials may be needed.

Milestones:	Final Protocol Submission:	MM/DD/YYYY Y
	Study Completion:	MM/DD/YYYY Y
	Final Report Submission:	MM/DD/YYYY Y
	Other :	MM/DD/YYYY Y

Feel free to contact me with any questions.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993

 301.796.4256 (phone) • 301.796.9845 (fax) |  christy.cottrell@fda.hhs.gov

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/s/

CHRISTY L COTTRELL
08/07/2012

From: Maher, Virginia E.
Sent: Monday, August 06, 2012 9:50 AM
To: 'Cheryl Madsen'; Lynn Seely
Cc: Cottrell, Christy L.
Subject: Enzalutamide PMR

Ms. Madsen and Ms. Seely,

We have a few clarification in the e-mail that I sent on Friday that may help.

Ellen

V. Ellen Maher, M.D.

TL GU Oncology

Because patients at increased risk of seizure were excluded from the randomized clinical trial, convene a panel of experts in oncology and neurology to obtain recommendations regarding which patients at increased risk of seizure it is appropriate to study in a postmarketing safety trial, e.g. patients with a history of seizure (taking/not taking anti-convulsants), loss of consciousness, TIA or CVA, AVM in the CNS, head trauma with loss of consciousness, treated brain metastases, use of medications which may increase the seizure threshold, or other risk factors for the development of seizures. Following the panel's recommendations, conduct a single-arm safety trial to assess the risk of seizure with enzalutamide 160 mg/day in at least 350 patients with metastatic castrate-resistant prostate cancer who are at increased risk for seizure. The primary endpoint should be the incidence of seizure. With 350 patients the trial has 85% power to detect an increase in seizures from ~1% as seen in the CRPC2 study to 3%. Patients should remain on study until disease progression, development of a seizure, or the development of an unacceptable adverse event. The protocol should contain stopping rules for an excessive incidence of seizures.

Please provide the following milestones for this post-marketing requirement by August 8, 2012.

Expert panel recommendations:

Final protocol submission:

Trial completion date

Final report submission:

If you would like clarification or are unable to provide the timelines by August 8, please contact Christy Cottrell to arrange a teleconference.

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/s/

CHRISTY L COTTRELL
08/07/2012



NDA 203415

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Medivation, Inc.
201 Spear Street
Third Floor
San Francisco, CA 94105

ATTENTION: Lynn Seely, MD
Chief Medical Officer

Dear Dr. Seely:

Please refer to your New Drug Application (NDA) dated May 21, 2012, received May 22, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Enzalutamide Capsules, 40 mg.

We also refer to your May 21, 2012, correspondence, received May 22, 2012, requesting review of your proposed proprietary name, Xtandi. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

If **any** of the proposed product characteristics as stated in your May 21, 2012, 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, contact Frances Fahnbulleh, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0942. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Christy Cottrell at (301) 796-4256.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh

Director

Division of Medication Error Prevention and Analysis

Office of Medication Error Prevention and Risk Management

Office of Surveillance and Epidemiology

Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
08/03/2012

From: Maher, Virginia E.
Sent: Friday, August 03, 2012 3:59 PM
To: cheryl.madsen@medivation.com
Cc: Cottrell, Christy L.
Subject: NDA 203415

Ms. Madsen,

We are concerned about the absence of information concerning the risk of seizure with enzalutamide in patients who are at high-risk for seizure and have determined that that a clinical trial exploring this issue should be conducted as a post-marketing requirement.

Convene a panel of experts to assess the risk and benefit of enzalutamide in patients with CRPC who are at high risk for seizures. In evaluating the risk factors for seizure, the panel should consider whether enzalutamide should be studied in patients with a history of the following: seizure (taking/not taking anti-convulsants), loss of consciousness, TIA or CVA, AVM in the CNS, head trauma with loss of consciousness, and treated brain metastases. The panel should also consider whether enzalutamide should be evaluated in patients using medications which may increase the seizure threshold (as outlined in # 17 of Section 9.3.2 of your CRPC2 protocol). The panel may also want to consider other risk factors for the development of seizures.

Following the panel's recommendations, conduct a single-arm safety trial to assess the risk of seizure with enzalutamide 160 mg/d in at least 350 patients with castrate-resistant prostate cancer who are at high risk for seizure. The primary endpoint should be the incidence of seizure. Patients should remain on study until disease progression, development of a seizure, or the development of an unacceptable adverse event.

Please note that with 350 patients the trial has 85% power to detect an increase in seizures from ~1% (as seen in the CRPC2 study) to 3%.

Please provide the following milestones for this post-marketing requirement by August 8, 2012.

Expert panel recommendations:
Final protocol submission:
Trial completion date
Final report submission:

If you would like clarification or are unable to provide the timelines by August 8, please contact Christy Cottrell to arrange a teleconference.

Thank you for your help.

Ellen
V. Ellen Maher, M.D.
Team Leader, GU Oncology
DOP1/OHOP/CDER/FDA

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/s/

CHRISTY L COTTRELL
08/07/2012

From: [David, Jeannie C](#)
To: ["Lynn Seely"](#)
Cc: [Mesmer, Deborah](#); [Cottrell, Christy L.](#)
Subject: NDA 203415 CMC IR 8/1/12
Date: Wednesday, August 01, 2012 4:50:40 PM
Importance: High

Dear Dr. Seely,

We have the following additional CMC requests for information. We kindly request response by **COB this Friday, August 3, 2012**. An email copy by that date with a formal follow up submission of the same information will be fine.

Drug Substance:

Provide certificate of analysis for Impurity (b) and Impurity (b)(4), which were used as reference analytical standards of the drug substance MDV3100.

Drug Product:

Provide drug product container closure system performance testing as per USP<671> to verify the tightness of the container closure system with respect to moisture permeability.

If there is any delay, please notify me and you may respond to the two information requests separately.

Best regards,

Jeannie

Jeannie David, M.S.
Regulatory Health Project Manager
Food and Drug Administration
Phone: (301) 796-4247

From: David, Jeannie C
Sent: Monday, July 23, 2012 10:36 PM
To: Lynn.Seely@medivation.com
Cc: Cottrell, Christy L.; Mesmer, Deborah
Subject: Re: NDA 203415 CMC IR 7/17/12

Dear Dr. Seely,

Thank you for your notification and for the courtesy electronic copy of the response to IR. This email is to confirm receipt.

Best regards,

Jeannie

From: Lynn Seely [<mailto:Lynn.Seely@medivation.com>]
Sent: Monday, July 23, 2012 6:36 PM

To: David, Jeannie C
Cc: Cottrell, Christy L.; Mesmer, Deborah
Subject: RE: NDA 203415 CMC IR 7/17/12

Dear Jeannie,

Please find attached to this email our response to the CMC IR 7/17/12.
This response was also submitted via the electronic submissions gateway today.

Best, Lynn

From: Mesmer, Deborah [mailto:Deborah.Mesmer@fda.hhs.gov]
Sent: Friday, July 20, 2012 1:50 PM
To: Lynn Seely
Cc: David, Jeannie C; Cottrell, Christy L.
Subject: FW: NDA 203415 CMC IR 7/17/12

Dear Dr. Seeley,

I just saw your read receipt come across for this information request below; however, per our phone conversation just now, I am forwarding the IR again.

Please acknowledge receipt of this email.

Please provide a courtesy copy of your response to Jeannie David (copied on this message). I will be out of the office from July 23- August 3, 2012.

Sincerely,

Debbie

From: Mesmer, Deborah
Sent: Tuesday, July 17, 2012 3:23 PM
To: 'Lynn Seely'
Cc: Cottrell, Christy L.; David, Jeannie C
Subject: NDA 203415 CMC IR 7/17/12

Dear Dr. Seely,

Please find attached a courtesy copy of a CMC Information Request dated July 17, 2012. We are requesting that your response be submitted to your application by COB on Thursday, July 19, 2012. Please also send me a courtesy copy of your response.

I will be out of the office from July 23- August 3, 2012. During this time Ms. Jeannie David will be covering for me. I have copied Ms. David on this message so you will have her email address.

Please acknowledge receipt of this message.

Sincerely,

Debbie Mesmer

Deborah Mesmer

Regulatory Project Manager for Quality

Office of New Drug Quality Assessment (ONDQA)

Division of New Drug Quality Assessment (DNDQA1)

Food and Drug Administration

White Oak Building 21, Rm 1627

10903 New Hampshire Avenue

Silver Spring, MD 20993-0002

(301) 796-4023

deborah.mesmer@fda.hhs.gov

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/s/

JEANNIE C DAVID
08/01/2012



NDA 203415

**METHODS VALIDATION
MATERIALS RECEIVED**

Medivation, Inc.
Attention: Lynn Seely, M.D.
Chief Medical Officer
525 Market Street
36th floor
San Francisco, CA 94105

Dear Lynn Seely:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Enzalutamide liquid filled soft gelatin capsules, 40 mg and to our June 29, 2012, letter requesting sample materials for methods validation testing.

We acknowledge receipt on July 31, 2012, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
07/31/2012

From: Lynn Seely [Lynn.Seely@medivation.com]
Sent: Wednesday, July 25, 2012 1:21 PM
To: Pierce, William (CDER)
Cc: Maher, Virginia E.; Cottrell, Christy L.
Subject: RE: Quick question: ID #s for patients who stopped therapy due to fall AEs
Dear Bill,

We can confirm that there was only one patient (#9785-CL-011B-E00201) who permanently discontinued study drug due to fall.
In addition, one patient in CRPC2 (CRPC-356-10) temporarily discontinued study drug briefly after a fall (from 04-23-2011 until 04-26-2011).
You are correct that these are the two cases referred to in the summary of clinical safety. We are not aware of any other cases of fall resulting in study drug dose modification.

We are working on updating the table of falls as requested in your second email and will forward that as soon as it is available.

Best, Lynn

From: Pierce, William (CDER) [mailto:William.Pierce@fda.hhs.gov]
Sent: Tuesday, July 24, 2012 7:30 AM
To: Lynn Seely
Cc: Maher, Virginia E.
Subject: Quick question: ID #s for patients who stopped therapy due to fall AEs

Greetings Lynn,

I have a quick question related to the numbers of patients who discontinued therapy due to falls that I want to clarify for my review. On page 106 of the Summary of Clinical Safety, it states that two MDV3100 patients discontinued MDV3100 due to fall AEs. Can you provide the patient ID #s for these and any others? Please also clarify if these were permanent discontinuations, temporary discontinuations, or if there were any dose modifications for fall AEs. In the datasets, I found one patient (#9785-CL-011B-E00201) who permanently discontinued and one patient (CRPC-356-10) who temporarily discontinued MDV3100, but I wasn't sure if these are the two cases that are referred to in the summary of clinical safety, or if there are others.

Thank you in advance,

Bill Pierce

Senior Clinical Analyst
Genitourinary (GU) Cancer Team
Division of Oncology Products 1 (DOP1)
Office of Hematology & Oncology Products (OHOP)
Center for Drug Evaluation and Research (CDER)
Food and Drug Administration (FDA)

WK: (301) 796-0521
FAX: (301) 796-9849
EMAIL: william.pierce@fda.hhs.gov

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/s/

CHRISTY L COTTRELL
07/25/2012

From: Cottrell, Christy L.
Sent: Tuesday, July 24, 2012 10:40 AM
To: 'Lynn Seely'
Subject: NDA 203415 for MDV3100: Clinical and Statistical Information Request

Importance: High

Attachments: 7-24-12 clinical and stat IR.pdf
Lynn,

Please refer to your NDA 203415 for MDV3100. See attached for an information request from the clinical and statistical review teams. Response requested by August 2, 2012.

Regards,
Christy



7-24-12 clinical
and stat IR.p...

Christy Cottrell | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
 301.796.4256 (phone) •  301.796.9845 (fax) |  christy.cottrell@fda.hhs.gov



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Date: 07/20/2012

The FDA review teams have the following five inquiries for the applicant of NDA 203415 to address. Please respond by August 2, 2012.

1) For 645 patients reported to have radiographic progression who were included in your rPFS analysis, as shown on Page 95 of the CSR, please provide a new dataset with the same cut-off date of 2011-09-25 to include the following columns:

- Study ID
- Treatment Arm
- USUBJID
- Confirmation Scans Performed (Yes vs No: only for disease progression detected at Week 13 or before)
- Confirmation Scan Dates (in both numeric and character formats)
- Confirmation Bone Scan Performed (Yes vs No)
- Confirmation Bone Scan Dates (in both numeric and character formats)
- Confirmation Soft Tissue Scan Performed (Yes vs No)
- Confirmation Soft Tissue Scan Dates (in both numeric and character formats)
- Disease Progression Determination by Scan (Bone Scan, CT/MRI, or Both)
- Scans Performed During Protocol-Specified Time Periods (Yes vs No)
- Missing Scan by Scheduled Assessment Weeks (13, 25, 37, 49, 61, 73, and 85: use 7 individual columns)
- Reasons for Missing Scans (description)
- Subsequent Treatments Initiated before Last Scans (Yes vs No)
- Subsequent Treatment Initiation Date (in both numeric and character formats)
- Pathological SREs (Yes vs No)
- Pathological SRE Date (in both numeric and character formats)
- Non-Pathological SREs (Yes vs No)
- Non-Pathological SRE Date (in both numeric and character formats)
- Surgical or Radiation Therapy for CRPC or Involving Bone (Yes vs No)
- Surgical or Radiation Therapy for CRPC or Involving Bone (in both numeric and character formats)
- Reassessed Radiographic Progression (Yes vs No: see Inquiry 2 for censoring)
- Censoring (Yes vs No)
- Reassessed Radiographic Progression Date (in both numeric and character)
- Previously Reported PFS Date (PFSEVDT from Dataset ADIPFS)
- Difference in Time between the Reassessed and Previously Reported PFS Dates

2) Please submit a new rPFS analysis based on information contained in the above new dataset along with relevant information contained in the previously submitted Dataset ADIPFS. Please use the following censoring criteria for radiographic progression (rPD) events **occurring on or before the previously reported overall rPD dates**:

- Censoring to the last scans without evidence of disease progression for rPD events required to confirm per the protocol but not confirmed or with no documented confirmation scans for any reasons. This censoring rule should also apply to patients whose confirmation scans occurred after new treatment initiation, incidence of SREs, or surgical or radiation therapy for prostate cancer or disorders involving bone during the trial (see below).
- Censoring to the last bone scan without evidence of disease progression for pathological SREs or non-pathological SREs because of the impact of the SRE events on bone scan interpretation.
- Censoring to the last scans without evidence of disease progression for patients whose new treatment started before study treatment discontinuation or before the previously reported overall progression dates.
- Censoring to the last scans without evidence of disease progression for patients who had surgical or radiation therapy performed for prostate cancer related lesions or other disorders that most likely affected bone scan interpretation.

3) Specify your rationale for excluding 9 patients whose study treatment was discontinued for radiographic disease progression from your original primary rPFS analysis as shown on Page 95 of your CSR. The 9 patients had the following ID numbers:

CRPC2-103-06
CRPC2-250-03
CRPC2-303-17
CRPC2-308-02
CRPC2-310-05
CRPC2-456-01
CRPC2-600-04
CRPC2-603-04
CRPC2-659-04

4) Please clarify why 243 of the 645 patients reported with rPD had their RPRSCHDT dates occurring prior to the randomization. What was the role of this variable in the rPFS analysis shown on Page 95 of your CSR? Note that RPRSCHDT refers to “the scheduled scan date prior to where first reported PD occurred” in Dataset ADIPFS.

5) Please provide scan compliance analyses as requested in the table on next page.

	MDV3100 (N=800)							Placebo (N=399)						
	Number of scans, n(%)							Number of scans, n(%)						
		CT/MRI		Bone		Missing (both CT/MRI and bone scan)	Missing (either CT/MRI or bone scan)		CT/MRI		Bone		Missing (both CT/MRI and bone scan)	Missing (either CT/MRI or bone scan)
Timing of assessment	Expected	Received	Missing	Received	Missing			Expected	Received	Missing	Received	Missing		
Wk13														
Wk25														
Wk37														
Wk49														
Wk61														
Wk73														
Wk85														

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CHRISTY L COTTRELL
07/24/2012

From: Cottrell, Christy L.
Sent: Tuesday, July 24, 2012 2:06 PM
To: 'Lynn Seely'
Subject: NDA 203415 for MDV3100: Clinical Information request

Importance: High
 Dr. Seely,

Please refer to your pending NDA 203415 for MDV3100. See below for an information request from clinical safety reviewer.

The attached is a table of the number of patients with abnormal laboratory values on CRPC2. The way in which these values are derived is presented above the table. Our numbers differ from those in the CSR. Please explain why. **Reply requested by Friday, July 27th.**

Feel free to contact me with any questions.

Regards,
 Christy

1. Used adlb.xpt from amendment 12, received 7-20-12
2. Selected STUDYID = CRPC2
3. Removed ABLFL = Y
4. Removed VISIT = LFU2, SCREENING, SFU
5. Still have 2,308 rows for WEEK 1, ADY varies from -39 to 8
6. Removed all ADY = negative or 1
7. Used ATOXGRL or ATOXGRH
8. Highlighted # are # in CSR
9. Tried looking at TRTEMFL = Y, but some of the TRTEMFL = N are for WEEK 13, WEEK 21, etc. Don't see why these are not treatment emergent.

On Study Laboratories				
	Enzalutamide N = 797		Placebo N = 395	
Hematology	Gr 1-4	Gr 3-4	Gr 1-4	Gr 3-4
Neutropenia	121 (15%)	9 (1%)	24 (6%) 25	0
Lymphopenia	285 (36%) 288	67 (8%) 71	148 (37%) 157	45 (11%) 47
Low Hemoglobin	629 (79%) 633	32 (4%) 36	320 (81%) 321	20 (5%) 21
Thrombocytopenia	58 (7%) 64	4 (0.5%)	27 (7%) ¹ 28	3 (0.8%) ¹ 4
	Enzalutamide N = 797		Placebo N = 396	
Chemistry	Gr 1-4	Gr 3-4	Gr 1-4	Gr 3-4

AST	178 (22%) 186	3 (0.4%)	146 (37%) 149	4 (1%)
ALT	79 (10%) 81	2 (0.3%)	67 (17%) 72	2 (0.5%)
Bilirubin	23 (3%)	2 (0.3%)	6 (2%) 7	0 1
Creatinine	76 (10%) 77	0	44 (11%) 49	1 (0.3%)
Hyperglycemia	715 (90%) 720	17 (2%) 18	336 (85%) 342	10 (3%)
Hypoglycemia	39 (5%) 40	0	12 (3%) 13	0
Hyperkalemia	27 (3%) 28	2 (0.3%)	18 (5%) 19	3 (0.8%)
Hypokalemia	28 (4%) 29	6 (0.8%)	21 (5%) 22	3 (0.8%) 4
Hypermagnesemia	68 (9%)	0	44 (11%) 43	1 (0.3%)
Hypercalcemia	25 (3%)	1 (0.1%)	12 (3%)	0
Hypocalcemia	71 (9%) 77	13 (2%)	44 (11%) 46	12 (3%) 15
Hypophosphatemia	93 (12%) 96	21 (3%) 23	36 (9%) 37	11 (3%) 10

N = 394

Data Cutoff 1-31-12

Christy Cottrell | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
☎ 301.796.4256 (phone) • 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov



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/s/

CHRISTY L COTTRELL
07/24/2012



NDA 203415

INFORMATION REQUEST

Medivation, Inc.
Attention: Lynn Seely, MD
Chief Medical Officer
201 Spear St., Third Floor
San Francisco, CA 94105

Dear Dr. Seely,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Enzalutamide (code: MDV3100) Capsules, 40 mg.

Please refer the FDA Information Request dated July 3, 2012, and your submission dated July 11, 2012, received July 12, 2012.

We have the following request for information. We request a prompt written response no later than close of business on Thursday, July 19, 2012, in order to continue our evaluation of your NDA.

In the Response dated July 11, 2012, (and received by email on July 6, 2012), to the CMC Information Request of July 3, 2012, you provided as requested the genotoxic impurity levels of the drug substance lots intended to be used for the manufacturing of commercial drug product. However, the batch analyses of the corresponding lots were not included in your NDA submission. Provide the complete MDV3100 drug substance batch analysis of lots# 09120028, 09120029 and 09120030.

If you have any questions, call Deborah Mesmer, Regulatory 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/

JANICE T BROWN

07/17/2012

Janice Brown for Sarah Pope Miksinski, Ph.D.

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR PATIENT LABELING REVIEW CONSULTATION	
TO: CDER-DMPP-PatientLabelingTeam		FROM: (Name/Title, Office/Division/Phone number of requestor) Division of Oncology Products 1 Christy Cottrell, RPM	
REQUEST DATE: July 12, 2012	NDA/BLA NO.: NDA 203415	TYPE OF DOCUMENTS: (PLEASE CHECK OFF BELOW) New NDA – Patient Labeling	
NAME OF DRUG: Enzalutamide (MDV3100)	PRIORITY CONSIDERATION: High	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE (Generally 2 Weeks after receiving substantially complete labeling) August 24, 2012
SPONSOR: Medivation, Inc.		PDUFA Date: November 22, 2012 (EXPEDITED REVIEW: Action goal date is August 31, 2012)	
TYPE OF LABEL TO REVIEW			
TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <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"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> MANUFACTURING (CMC) 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: EDR Location: \\CDSESUB1\EVSPROD\NDA203415\203415.enx			
Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.			
COMMENTS/SPECIAL INSTRUCTIONS: Filing/Planning Meeting: Already occurred Mid-Cycle Meeting: Already occurred Labeling Meetings: July 23, 27, 30, and 31; August 2, 7, 8, 13, 14, and 15 Wrap-Up Meeting: TBD			
SIGNATURE OF REQUESTER Christy Cottrell			
SIGNATURE OF RECEIVER		METHOD OF DELIVERY (Check one) <input type="checkbox"/> eMAIL (BLAs Only) <input checked="" type="checkbox"/> DARRTS	

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CHRISTY L COTTRELL
07/12/2012

From: Cottrell, Christy L.
Sent: Wednesday, July 11, 2012 1:11 PM
To: 'Lynn Seely'
Subject: NDA 203415 for MDV3100: Clinical Pharmacology Information Request

Importance: High
Lynn,

Please refer to your pending NDA 203415 for MDV3100. See below for an information request from the Clinical Pharmacology team.

- You state that your drug is an inducer of (b) (4) (see below). Could you please indicate which study is the source of these data, and where it may be found in the submission. I was not able to find these data in trial 9785-CL-0007 as referenced in the labeling language below. Are these data based on literature findings from (b) (4)?

Induction Effects

Clinical data indicate that TRADENAME is a moderate inducer of CYP2C9 and CYP2C19 and a strong inducer of

CYP3A4 (Figure 1); (b) (4) may be induced as well. These results suggest that TRADENAME causes enzyme

induction via activation of the nuclear pregnane X receptor (PXR). Co-administration of TRADENAME with substrates

of CYP2C9, CYP2C19, CYP3A4, or (b) (4) may reduce the oral bioavailability and/or increase the clearance of these

substrates, resulting in decreased exposure [*see Drug Interactions (7.1)*].

9785-CL-0007 Section 8.3, (b) (4) 2010

We are hoping that you can provide a response by COB today.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993

☎ 301.796.4256 (phone) • 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov



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/s/

CHRISTY L COTTRELL
07/11/2012



NDA 203415

INFORMATION REQUEST

Medivation, Inc.
Attention: Lynn Seely, MD
Chief Medical Officer
201 Spear St., Third Floor
San Francisco, CA 94105

Dear Dr. Seely,

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Enzalutamide (code: MDV3100) Capsules, 40 mg.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response no later than, July 16, 2012, in order to continue our evaluation of your NDA.

1. Based upon the dissolution data submitted in the NDA, your proposed dissolution acceptance criterion of $Q = (b)(4)$ at $(b)(4)$ mins $(b)(4)$. Revise the dissolution acceptance criterion to $Q = (b)(4)$ at 15 mins. Update and submit the drug product specifications to reflect this dissolution criterion.
2. Your proposed submission date for a complete response to the July 3, 2012, CMC Information Request is unacceptable. Submit your complete response to your application by no later than July 16, 2012.

If you have any questions, call Deborah Mesmer, Regulatory 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/

JANICE T BROWN

07/11/2012

Janice Brown for Sarah Pope Miksinski, Ph.D.

Fahnbulleh, Frances

From: Bridges, Todd
Sent: Tuesday, July 03, 2012 2:09 PM
To: Fahnbulleh, Frances
Cc: Defronzo, Kimberly
Subject: FW: NDA 203415 Xtandi

Hey Frances,

Please upload this email to the record in AIMS.

Thanks.

From: Defronzo, Kimberly
Sent: Tuesday, July 03, 2012 1:32 PM
To: Cottrell, Christy L.; Bridges, Todd
Cc: Fahnbulleh, Frances
Subject: RE: NDA 203415 Xtandi

Great thank you Christy for your help! Happy July 4th to all !

From: Cottrell, Christy L.
Sent: Tuesday, July 03, 2012 1:30 PM
To: Bridges, Todd
Cc: Defronzo, Kimberly; Fahnbulleh, Frances
Subject: RE: NDA 203415 Xtandi

Here is the company's response:

I wanted to confirm for you and the Division of Medication Error and Prevention Analysis that the imprint "MDV" to be used on the enzalutamide capsules will be a unique imprint and will not be used on any other product by Medivation.

From: Bridges, Todd
Sent: Sunday, July 01, 2012 7:20 PM
To: Cottrell, Christy L.
Cc: Bridges, Todd; Defronzo, Kimberly; Fahnbulleh, Frances
Subject: NDA 203415 Xtandi

Hi Christy,

In the insert labeling for this product, the Applicant indicates that the capsules will contain the imprint "MDV" (please see below). I'm assuming this is an abbreviation for Medivation.

Can you contact the Applicant and determine if they plan to use this "MDV" imprint on capsules for other products they may develop in the future - or is the "MDV" imprint going to be unique to Xtandi?

Please let me know if you have any questions and thanks for your help.

Todd

TRADENAME (enzalutamide) 40 mg capsules are supplied as white to off-white oblong soft gelatin capsules

imprinted in black ink with MDV.

Todd Bridges, RPh
Team Leader
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology

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/s/

FRANCES G FAHNBULLEH
07/03/2012



NDA 203415

INFORMATION REQUEST

Medivation, Inc.
Attention: Lynn Seeley, MD
Chief Medical Officer
201 Spear St., Third Floor
San Francisco, CA 94105

Dear Dr. Seeley

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Enzalutamide (code: MDV3100) Capsules, 40 mg.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response in no later than, July 6, 2012 in order to continue our evaluation of your NDA.

Drug Substance

1. The description of drug substance manufacturing process as presented in section 3.2.S.2.2 does not adequately describe the manufacturing process. The description of the manufacturing process in the NDA is your commitment on how you will routinely manufacture the drug substance. The use of terms such as: “not more than, not less than or at less than, as needed, approximately or until approximately, about, below, up to, and at least” are vague and do not specify the operating range that is normally used during routine manufacturing. Revise the manufacturing process description and include normal operating ranges or scientifically justified ranges for all process variables including process parameters reagent quantities, reaction and process temperatures, solvent volumes for reaction, etc.
2. The regulatory flexibility statement in “Sec 3.2.S.2.2.2.1 General Information for All Steps” is not adequately supported by data. Remove this section, or provide supporting information to justify the proposed ranges.
3. Revise the MDV3132 specification to include a test and acceptance criteria for impurities (Table 8 on page 15, section 3.2.S.2.3).

4. In section 3.2.S.2.6, the Range Examined (Proven Operable Ranges) in Tables 3, 5, 7, 8, 13, 14 are not adequately supported by data. Provide all supporting data in order to evaluate the ranges examined or remove the Proven Operable Ranges from the tables.
5. In accordance to the specification of the drug substance MDV3100, which includes testing for the genotoxic impurities (b) (4) provide the genotoxic impurity levels in the batch analysis for all drug substance batches intended to be used for the manufacturing of commercial drug product.

Drug Product

6. For MDV3100 softgel capsule, (b) (4) determines the physical integrity of the capsule. While no leakage of capsule content (b) (4) the capsules were soft, spongy and stuck together indicating a potential product quality issue. Based on the limited number of drug product batches, (b) (4) drug product specification is not acceptable at this time. Include (b) (4) the quality attributes in the drug product specification for release and stability. In future, (b) (4) the drug product specification based on batch data from release and stability studies.
7. Based on 8 weeks in-use stability study with soft-gel capsules in open bottle environment at 25°C/60%RH, (b) (4) in the first 4 weeks and remained at that level for the next 4 weeks. Considering the use of 120 count capsules for a supply of 30 days, provide additional controls (for example: the use of desiccant) limiting in-use moisture ingress in the container closure system with proper justification to ensure product quality.

If you have any questions, call Deborah Mesmer, Regulatory 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/

JANICE T BROWN

07/03/2012

Janice Brown for Sarah Pope Mikinski, Ph.D.

From: Cottrell, Christy L.
Sent: Friday, June 29, 2012 10:34 AM
To: 'Lynn Seely'
Subject: NDA 203415 for MDV3100: Clinical Pharmacology Request
Dr. Seely,

In your response to the Clinical Pharmacology reviewer dated 6/12/12 you indicated the following:

Sponsor Response:

As discussed at the NDA Orientation Meeting on May 31, 2012, we will submit clinical study reports, supportive datasets, and technical reports for the 3 clinical pharmacology studies listed in Table 1 below by June 29, 2012. All studies were completed in June 2012.

Please verify that you will be sending these study reports and updated labeling today.

Let me know if you have any questions.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
 301.796.4256 (phone) • 301.796.9845 (fax) |  christy.cottrell@fda.hhs.gov



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/s/

CHRISTY L COTTRELL
06/29/2012

From: Cottrell, Christy L.
Sent: Monday, June 25, 2012 2:55 PM
To: 'Lynn Seely'
Subject: RE: MDV3100 NDA 203415
Lynn,

Response from the clinical team:

- Please provide an analysis of all deaths due to an adverse event while on study drug or within 30 of stopping study drug. This should include patients with an adverse event as the primary cause of death, but should also include patients with a grade 5 adverse event in the AE dataset.

Let me know if further clarification is needed.

Christy

From: Lynn Seely [mailto:Lynn.Seely@medivation.com]
Sent: Monday, June 25, 2012 1:43 AM
To: Cottrell, Christy L.; Kacuba, Alice
Subject: MDV3100 NDA 203415

Dear Christy,

I hope you had a nice time away from the office.

As we are preparing our responses to the Clinical information requests dated June 14, 2012, we would like to ask for a clarification. The very first request said, "Please provide an analysis of patients in CRPC2 who died due to an adverse event (adverse event recorded in the dataset) within 30 days of study drug."

In order to make sure we are providing you with the information desired, please let me know if the following information will adequately address the request.

We are planning to provide a table with the patients who died with an adverse event as the primary cause of death within 30 days of starting study drug and 30 days of stopping study drug. The preferred term of the adverse event leading to death will also be presented along with the number of days the death occurred after starting or stopping study drug. We will provide a discussion of the differences observed between treatment groups if any.

Please let us know if this is appropriate or if the reviewers are looking for any additional information.

Best regards, Lynn

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CHRISTY L COTTRELL
06/25/2012

From: Cottrell, Christy L.
Sent: Thursday, June 14, 2012 10:36 AM
To: 'Lynn Seely'
Subject: NDA 203415 for MDV3100: Clinical information requests

Importance: High
Lynn,

Please refer to your NDA 203415 for MDV3100. See below for several information requests from the clinical team.

Please reply within 2 weeks

1. Please provide an analysis of patients in CRPC2 who died due an adverse event (adverse event recorded in the dataset) within 30 days of study drug.
2. In the CRPC2 CSR, Table 10.2-1 provides information on protocol deviations. Tabulation dataset ie.xpt and Listing 16.2.2 provide information on eligibility violations while analysis dataset addv.xpt provides information on protocol violations during the study period. However, addv.xpt appears limited to information on excluded concomitant medications and abnormal laboratory values. It appears that information is not available for patients who had studies performed outside the window, non-compliance with study drug, etc. Please state whether this information is available and its location. Please also provide an analysis of major and minor protocol violations by arm. Please state the events that you have considered major and those you have considered minor violations. Please provide a tabulation dataset to support this analysis.
3. Please provide the IDMC minutes for both the open and closed sessions.
4. In Section 9.7.3 of the CSR for the CRPC2 trial, you note that the statistical analyses used the stratification factors recorded in the electronic CRFs. Did these stratification factors differ from those used by the IVRS at randomization? If so, please provide detailed information on the reasons for this difference and tabulation, by arm and by stratification factor, of the changes in strata.
5. In CRPC2, 1 of the stratification factors was the Brief Pain Inventory-Short Form Question #3 score averaged over the 7 d prior to randomization. In examining the tabulation dataset qs.xpt, a single value is available for IVRS and 1-2 values are available for Worst pain in the last 24 hours from the Brief Pain Inventory. We have been unable to find 7 values or to determine the number of patients in which complete data (7 values) is available. Please explain where this information is located.
6. In Section 12.1.1 of the CRPC2 CSR, you state that there was a difference in the data for study drug dose modification between the adverse event dataset and the dosing CRF. Please outline the extent of these differences and provide a rationale for this discrepancy.
7. Please state the terms you used to characterize prior cardiovascular disease in CRPC2.
8. Please clarify the version of the MedDRA coding used in the datasets associated with each study and in the dataset in Module 5.3.5.3.25.3.1.

Please reply within 4 weeks

9. Please provide an analysis of skeletal related events and fracture, pathologic and otherwise, by bisphosphonate use at study entry and by bisphosphonate use during the study period (prior to the event).

10. In Table 10.1-3 of the CSR for the CRPC2 trial, clinical progression occurred in 231 patients in the MDV3100 and 159 in the placebo arm. Please provide detailed information, by arm, on the first anti-cancer treatment(s) received by these patients after discontinuation of study drug. Please also provide detailed information, by arm, on the timing of these treatments relative to discontinuation of study drug. Please also provide information, by arm, on the percentage rise in PSA compared to nadir in these patients.
11. On the CRPC2 trial, please provide detailed information on the number of patients, in each arm, who underwent radical prostatectomy, definitive primary radiation therapy to the prostate, presented with Stage IV disease and underwent TURP, and had no prostate-directed therapy.
12. On CRPC2, patients received docetaxel up to 2,976 days prior to study entry. Such a long course of metastatic CRPC is surprising. Please provide, for all patients whose last docetaxel dose was at least 3 years prior to study entry, information on their disease course.
13. In CRPC2 trial, among the 490 patients who presented with PSA progression only, please provide an analysis of the percentage of patients, by arm, in which 3 rising PSA values were documented at study entry. Please provide the patient numbers for this group.
14. Please provide the following subgroup analyses of the primary endpoint for CRPC2:
 - a. Patients who used/did not use steroids at study entry;
 - b. Patients who used steroids/did not use steroids during the study period; and
 - c. Disease site (bone only, soft tissue only, bone and soft tissue).
15. Given the long half-life of enzalutamide, we are concerned that adverse events may be slow to resolve. Please provide an analysis of the time to adverse event resolution for adverse events leading to interruption/reduction of study drug in CRPC2.
16. Please provide narratives for patients with visual hallucination. In these narratives, please include information on narcotic use at the time of the visual hallucination.

Feel free to contact me with any questions.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
 301.796.4256 (phone) • 301.796.9845 (fax) |  christy.cottrell@fda.hhs.gov



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/s/

CHRISTY L COTTRELL
06/14/2012

From: Cottrell, Christy L.
Sent: Monday, June 11, 2012 8:35 PM
To: 'Lynn Seely'
Subject: NDA 203415 for MDV3100: Information Requests

Importance: High
Lynn,

Please refer to your pending NDA 203415 for MDV3100. See below for information requests from the review team.

Clinical

1. In addition to the information provided in the clinical overview (2.5.1.4), please provide a concise safety assessment based on all current worldwide clinical trial knowledge regarding enzalutamide. Please include an assessment of the total enzalutamide exposure in all clinical trials.
2. Please provide a description and status for all ongoing trials and a listing of safety reports (listing of the adverse events contained in the safety report along with the MCN number) from ongoing trials. Alternatively, please confirm there are no additional trials ongoing that are not already described in 2.5.1.4 and no additional applicable safety reports not included in 5.3.5.3.28.
3. Please provide the anticipated submission date for the NDA safety update and the dates that will be covered in this update.

We would like to have your agreement to provide the information in #1 and #2, along with the proposed date for the safety update requested in #3 by **this Friday, 6/15 at 10:00am**, but submission of this information prior to the filing date is not required.

QT IRT

1. Please complete the Highlights of Clinical Pharmacology table attached **ASAP** and return to me via email.

Clinical Pharmacology

1. Please clarify which additional Clinical Pharmacology studies you plan to submit for review in the current NDA submission cycle, and when these will be submitted.
2. Please clarify the rationale for selection of your proposed daily dosing regimen (without a loading dose), considering the long elimination half-life of your drug.
3. Please clarify your rationale for administration of your drug twice daily when doses exceeded 360 mg in the phase 1 dose-escalation trial.

Please provide your response to the Clinical Pharmacology information requests **by COB tomorrow, June 12, 2012.**

Feel free to contact me with any questions.

Regards,
Christy Cottrell

Christy Cottrell | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA

10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
☎ 301.796.4256 (phone) • 301.796.9845 (fax) | ✉ christy.cottrell@fda.hhs.gov



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/s/

CHRISTY L COTTRELL
06/11/2012

REQUEST FOR CONSULTATION

TO (Office/Division): QT-IRT

FROM (Name, Office/Division, and Phone Number of Requestor):

Division of Oncology Products 1
Christy Cottrell, RPM

DATE 6/6/12	IND NO.	NDA NO. NDA 203415	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT May 22, 2012
NAME OF DRUG MDV3100 (enzalutamide)		PRIORITY CONSIDERATION High	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE July 30, 2012

NAME OF FIRM: Medivation, 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 checked="" type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input checked="" 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: This is a new NDA that DOP1 will be reviewing under expedited Priority review. PDUFA date is November 22, 2012 - target action date is August 31, 2012. Requesting QT review.

Link to submission: \\CDSESUB1\EVSPROD\NDA203415\203415.enx

MO= Max Ning/Bill Pierce
PM= Christy Cottrell

SIGNATURE OF REQUESTOR Christy Cottrell	METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

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CHRISTY L COTTRELL
06/06/2012

**REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW
CONSULTATION**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

****Please send immediately following the Filing/Planning meeting****

TO: CDER-DDMAC-RPM	FROM: (Name/Title, Office/Division/Phone number of requestor) Division of Oncology Products 1 Christy Cottrell, RPM
------------------------------	---

REQUEST DATE June 6, 2012	IND NO.	NDA/BLA NO. NDA 203415	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW) New NDA
------------------------------	---------	---------------------------	--

NAME OF DRUG MDV3100 (enzalutamide)	PRIORITY CONSIDERATION High	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) July 30, 2012
--	--------------------------------	------------------------	---

NAME OF FIRM: Medivation, Inc.	PDUFA Date: November 22, 2012 (target action date of August 31, 2012)
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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\NDA203415\203415.enx>

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

COMMENTS/SPECIAL INSTRUCTIONS: This is a new NDA that DOP1 will be reviewing under an expedited Priority review. PDUFA date is November 22, 2012, but the targeted action date is August 31, 2012. DDMAC reviewers will be invited to all the review cycle meetings.

Mid-Cycle Meeting: TBD
Labeling Meetings: TBD
Wrap-Up Meeting: TBD

MO= Max Ning/Bill Pierce
PM= Christy Cottrell

SIGNATURE OF REQUESTER
Christy Cottrell

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) <input type="checkbox"/> eMAIL <input type="checkbox"/> HAND
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CHRISTY L COTTRELL
06/06/2012

From: Cottrell, Christy L.
Sent: Wednesday, June 06, 2012 12:47 PM
To: 'Lynn.Seely@medivation.com'
Subject: NDA 203415 for MDV3100: Clinical Pharmacology information request

Importance: High
Dr. Seely,

Please refer to your pending NDA 203415 for MDV3100. See below for a request for information from the clinical pharmacology team.

The clinical pharmacology reviewer notes the following statement by the applicant:

"In total, the PK of MDV3100 has been evaluated in 934 patients with castration-resistant prostate cancer and in 66 healthy male subjects. PK parameters were estimated using non-compartmental methods in WinNonlin® (Pharsight Corp., Palo Alto, CA) and applicable complimentary software, such as SAS® (SAS Institute, Cary, NC) and Microsoft Excel® (Microsoft, Redmond, WA)."

Could you please submit the datasets for the non-compartmental analyses for trial MDV3100-05 and 9785-CL-0001 referred to above as soon as possible or within 5 business days? These datasets are needed to confirm the PK parameters listed for MDV3100 and its metabolites. It is not clear whether these datasets will be submitted as part of the previous Clinical Pharmacology information request dated 5/25/12 (to be submitted to FDA this week).

Feel free to contact me with any questions.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993

 301.796.4256 (phone) • 301.796.9845 (fax) |  christy.cottrell@fda.hhs.gov



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CHRISTY L COTTRELL
06/06/2012

From: Cottrell, Christy L.
Sent: Friday, June 15, 2012 4:42 PM
To: 'Lynn Seely'
Subject: NDA 203415 for MDV3100: Statistical Information Request

Importance: High
Lynn,

Please refer to NDA 203415 for MDV3100. See below for an information request from the statistical team.

- In your dataset ADIPFS there are two variables (DPDUNSLF, RPDUNSFL) with the same label name (“Reported PD Unscheduled Visit Flag”). We found out that the difference is one patient with USUBJID = CRPC2-112-20. Please explain this difference.
- In your rPFS analysis (Section 11.4.1.3.2) there are three rPFS sensitivity analyses. Please explain what the modified censoring assumption and the derived progression are. For each sensitivity analysis please provide details of the censoring rules and computation of event times.

Please provide your response as soon as possible. Feel free to contact me with any questions.

Regards,
Christy

Christy Cottrell | Regulatory Project Manager | Division of Oncology Products 1, CDER, FDA
10903 New Hampshire Avenue, Room 2122 | Silver Spring, MD 20993
 301.796.4256 (phone) • 301.796.9845 (fax) |  christy.cottrell@fda.hhs.gov



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/s/

CHRISTY L COTTRELL
07/24/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 074563

MEETING MINUTES

Medivation, Inc
Attention: Gia DePillis, Ph.D
Senior Director, Regulatory Affairs
201 Spear Street, Third Floor
San Francisco, CA 94105

Dear Dr. DePillis:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MDV3100.

We also refer to the meeting between representatives of your firm and the FDA on December 6, 2011. The purpose of the meeting was discuss the overall Chemistry, Manufacturing and Controls (CMC) plan and data package to support the NDA for MDV3100 in the proposed indication.

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 New Drug Quality Assessment I
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

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: CMC Guidance Meeting

Meeting Date and Time: Tuesday, December 6, 2011
Meeting Location: CDER WO RM 1419 Bldg 22

Application Number: IND 074563
Product Name: MDV3100 Capsules
Indication: Prostate Cancer
Sponsor Name: Medivation, Inc

Meeting Chair: Janice Brown, M.S., CMC Lead Pre-marketing
Meeting Recorder: Deborah Mesmer, M.S., Regulatory Health Project Manager-Quality

FDA ATTENDEES

ONDQA

Janice Brown, M.S., CMC Lead Pre-marketing
Tien-Mien Chen, Ph.D., Biopharmaceutics
Joyce Crich, Ph.D., Review Chemist
Haripada Sarker, Ph.D., CMC Team Lead
Deborah Mesmer, M.S., Regulatory Health Project Manager-Quality

OND/OHOP/DHOT

Wei Chen, P.D., Pharmacologist

MEDIVATION, INC ATTENDEES

Michele D. Bronson, Ph.D. Vice President, Regulatory & Quality
Gia D. DePillis, Ph.D. Senior Director, Regulatory Affairs
Sheila Matz, RPh. Senior Director, Pharmaceutical Development
Rowena Ng Associate Director, CMC
Eric Shen, Ph.D. Director, Analytical Chemistry
Sue Wollowitz, Ph.D. Vice President, Chemistry and Manufacturing
Alison Hayles Associate Director, Regulatory Affairs
Thomas Davey Senior Manager, Regulatory Affairs
Kathleen McLaughlin Assistant Director, CMC Technology, Pharmaceutical Technology Management

1.0 BACKGROUND

MDV3100 is being co-developed by Medivation, Inc. and Astellas Pharma Global Development, Inc. (Astellas) under Investigational New Drug (IND) Application 74,563 for the treatment of prostate cancer. MDV3100 is formulated in the surfactant caprylocaproyl polyoxylglycerides (b) (4). The product is provided as 40 mg liquid-filled soft gelatin capsules for oral administration. An MDV3100 dose of 160 mg (four capsules) given once daily is currently under evaluation in Phase 3 clinical trials. On September 21, 2011, the Applicant submitted a request for a CMC meeting received September 22, 2011 to discuss the overall Chemistry, Manufacturing and Controls (CMC) plan and data package to support the NDA for MDV3100. A Type C meeting was granted on October 6, 2011, and scheduled for December 6, 2011. The meeting briefing package was submitted on November 9, 2011, received November 10, 2011. FDA preliminary comments were archived and shared with Medivation on December 2, 2011. The meeting was held on December 6, 2011, as scheduled. The minutes of the meeting follow.

2.0 SPONSOR QUESTIONS, FDA PRELIMINARY RESPONSES, AND MEETING DISCUSSION

2.1 DRUG SUBSTANCE

Question 1: Does the Agency agree with the proposed designated regulatory starting materials?

- a. Does the Agency agree with the designation of (b) (4) as a regulatory starting material, including its control strategy, specification, and quality oversight?

FDA Response to Question 1a: Based on the information provided in the meeting package, the Agency does not agree with the designation of (b) (4) as a starting material due to its propinquity to the final drug substance. A determination of acceptability for any proposed control strategy, specifications, and quality oversight will be made during the NDA review.

- b. Does the Agency agree with the designation of (b) (4) as a regulatory starting material, including its control strategy, specification, and quality oversight?

FDA Response to Question 1b: See FDA Response to Question 1a.

Meeting Discussion Question 1a and 1b: FDA explained that (b) (4) (b) (4) are not acceptable as starting materials for the manufacture of MDV3100. The starting materials should be separated from the drug substance (b) (4). FDA emphasized that the sponsor implement adequate control of impurities in the starting materials and the carryover of genotoxic impurities (Question 2b.) The Sponsor committed to also describe genotoxic impurities.

FDA recommended that the sponsor address the adequacy of the starting materials at the pre-NDA meeting.

FDA reminded the Sponsor that for dissolution, FDA is targeting $Q = \text{(b) (4)}$. Provide the excipient information in the drug development section.

Question 2: Does the Agency agree with the control strategy for genotoxic impurities?

a. Does the Agency agree with the proposed threshold of toxicological concern (TTC)?

FDA Response to Question 2a: Your proposal for setting the acceptance criterion at (b) (4) for the genotoxic impurity (GTI) is acceptable for the proposed indication of castration-resistant prostate cancer patients who have failed docetaxel-based chemotherapy. Note that the positive genotoxic findings with the GTI(s) may be added to the labeling.

Meeting Discussion Question 2a: The Sponsor acknowledged FDA's response. There was no further discussion at the meeting.

b. Does the Agency agree with the strategy for identification and control of genotoxic impurities in regulatory starting materials and intermediates?

FDA Response to Question 2b: Yes, your proposed strategy for identification of GTI(s) is acceptable. The adequacy of the control of the GTI(s) in the regulatory starting materials and intermediates will be determined after review of the information submitted in the NDA.

Also see FDA response to Question 2a.

Meeting Discussion Question 2b: The Sponsor acknowledged FDA's response. There was no further discussion at the meeting.

c. Does the Agency agree with the control strategy for potential genotoxic impurities below the identification threshold?

FDA Response to Question 2c: No. You need to identify and control any impurity with genotoxic potential. Also see FDA responses to Question 2a and Question 2b.

Meeting Discussion Question 2c: The Sponsor clarified that the wording in their question 2c was not as they intended. They are defining the procedure for *unidentified* impurities (other than genotoxic impurities) below the identification threshold. The Sponsor committed to screen any additional impurities identified in the future for genotoxic potential.

The Sponsor indicated that the NDA will be submitted in the first half of 2012. A pre-NDA meeting will be requested by the end of February 2012.

Question 3: Does the Agency agree that the proposed commercial drug substance specification is acceptable?

- a. Does the Agency agree with not including Powder X-ray Diffraction and Particle Size testing?
- b. Does the Agency agree with not including a Microbial Limits test?

FDA Response to Question 3a and b: While your approach for the specifications seems generally reasonable, we recommend that you retain these tests at this time. The acceptability of omitting the tests for Powder X-ray Diffraction, Particle Size, and Microbial Limits will be assessed during the NDA review.

Testing for genotoxic impurities needs to be included in the specifications for MDV3100 drug substance.

Meeting Discussion Question 3a and b: The Sponsor acknowledged FDA's response. There was no further discussion at the meeting.

Question 4: Does the Agency agree that ongoing stability studies are acceptable as the primary stability studies for the New Drug Application (NDA), including the selection of the batches tested and the differences in their secondary packaging and high performance liquid chromatography (HPLC) test methods?

FDA Response to Question 4: No. Data from formal stability studies should be provided for at least three primary batches of the drug substance manufactured at each proposed manufacturing site. Refer to ICH Q1A.

Meeting Discussion Question 4: The Sponsor clarified that they will follow ICH and will manufacture at greater than pilot scale: one batch at one site, two batches at the other site. The registration batches for stability will be from the two sites. (b) (4) is the proposed commercial site.

FDA stated that 3 batches at the proposed commercial site are required (2 at least pilot scale). The 3 batches used to establish the drug product shelf life should come from the commercial site. Other batches can be used as supporting data. The Sponsor stated that they will have 24 months on all the proposed batches at the time of filing. FDA stated that the Sponsor should include a minimum of 12 months real time and 6 months accelerated stability data. FDA committed to provide a written response regarding site specific stability data with the meeting minutes.

The Sponsor committed to present 3 batches from (b) (4) as the primary lots.

FDA Post-Meeting Comment Question 4: Due to the lack of information in your meeting package for the drug substance critical quality attributes and stability profile, include in your NDA, stability data for three batches of drug substance manufactured at your proposed commercial site (b) (4)

2.2 DRUG PRODUCT

Question 5: Does the Agency agree that the proposed commercial drug product specification is acceptable?

- a. Does the Agency agree that use of a single point dissolution test is acceptable, including Tier 1 and Tier 2 testing?
- b. Does the Agency agree with not including testing for (b) (4) the fill solution?

FDA Response to Question 5a: In general, for immediate release products the final acceptance criterion is set for a single time point. However, during method development and for the setting of the acceptance criterion, complete multi-point dissolution profile data should be collected.

Please include in your NDA, the dissolution method development report for your proposed drug product and include the following information/data:

1. A detailed description of the optimal *in vitro* dissolution methodology and the developmental parameters (i.e., selection of the equipment/apparatus, *in vitro* dissolution media, agitation/rotation speed, pH, assay, sink conditions, etc.) that were used to identify the method as the most appropriate (with your justification) should be included in the report. The report should also include the justification/data supporting the proposed use of pepsin in the dissolution medium, as well as the justification for the proposed Tier 1 or Tier 2 approach.
2. The complete dissolution multipoint profile data collected during the development and validation of the proposed dissolution method. The dissolution profile should cover at least (b) (4) of drug release of the label amount or whenever a plateau (i.e., no increase over 3 consecutive time-points) is reached. We recommend you to use at least twelve test samples per testing variable.

3. The dissolution data (individual, mean, SD, profiles) should be reported as the cumulative percentage of drug dissolved with time (the percentage is based on the product's label claim).
4. The testing conditions used for each test and the manufacturing information on the batch employed should be clearly specified.
5. Also, please include the testing conducted to demonstrate the discriminating capability of the selected test as well as the validation data for the test method (i.e., method robustness, etc.) and analytical method (precision, accuracy, linearity, stability, etc.).

If the above information is available during the IND stage, you are encouraged to submit the dissolution development report to the Agency for review.

For the setting of the drug dissolution acceptance criterion of your product, the following points should be considered:

6. The dissolution profile should encompass the timeframe over which at least (b) (4) of the drug is dissolved or where the plateau of drug dissolved is reached if incomplete dissolution is occurring.
7. The setting of the acceptance criterion should be based on the overall multi-point dissolution profile data from the bio-batches (PK and clinical) and primary stability batches.
8. The specification-time point should be set when $Q =$ (b) (4) of dissolution occurs.

We also remind you that if the Phase 3 clinically tested formulation is different from the to-be-marketed formulation, you should provide in your NDA adequate information/data supporting the bridging between these formulations.

Meeting Discussion Question 5a: See Meeting Discussion for Question 6.

FDA Post-Meeting Comments Question 5a: FDA does not agree with the Sponsor's proposal of using the proposed dissolution test without pepsin only at Tier 1 (n=6) and conducting Tier 2 testing (n=12) with pepsin, if the Tier 1 testing fails (p. 34 out of 49 in the meeting package).

FDA recommends that the proposed dissolution method be evaluated either with or without the use of pepsin. If the dissolution testing without pepsin fails as <USP 711> S1 (n=6), S2 (n=12), and S3 (n=24), then the method with pepsin can be used. FDA requests the submission of the dissolution development report including the use of dissolution media with- and without-pepsin for review.

FDA Response to Question 5b: We recommend that you retain testing for (b) (4) the fill solution at this time. The acceptability of omitting the test will be assessed during the NDA review.

Meeting Discussion Question 5b: The Sponsor acknowledged FDA's response. There was no further discussion at the meeting.

Question 6: Does the Agency agree that ongoing stability studies are acceptable as the primary stability studies for the NDA, including the selection of batches tested, the differences in packaging configurations, and the transition from rupture testing to dissolution testing?

FDA Response to Question 6: Your approach appears reasonable. A full determination of acceptability will be made during the NDA review.

We agree that for the transition from rupture testing to dissolution testing you collect data from the primary stability studies using both tests. Include these data in your NDA submission. For the dissolution testing, please refer to our response for Question 5a.

Meeting Discussion Question 6: The Sponsor clarified that they have only dissolution data. FDA recommended that the Sponsor explain the development background in the NDA.

The Sponsor stated that no dissolution testing was performed at T0 for the primary stability samples but committed to do that for future. FDA advised that the Sponsor needed to decide if they will use Tier 1 or Tier 2. The Sponsor clarified that they will proceed in sequence, as necessary. FDA committed to provide a written response in the meeting minutes. See FDA Post-meeting Comments for Question 5.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no additional issues requiring discussion at this time.

4.0 ACTION ITEMS

FDA committed to provide post-meeting comments regarding stability studies/data (Question 4) and the use of pepsin in dissolution data (Question 5a.) Those comments have been included in these minutes.

5.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for these meeting minutes.

6.0 CONCURRENCE:

{See appended electronic signature page}

Deborah Mesmer
Regulatory Health Project Manager for Quality
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

{See appended electronic signature page}

Janice T. Brown, M.S.
CMC Lead, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation Research

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/s/

DEBORAH M MESMER
04/02/2012

JANICE T BROWN
04/02/2012

MEMORANDUM OF MEETING MINUTES

MEETING DATE: March 30, 2012
TIME: 10:00 am
LOCATION: WO; Building 22; Room 1313
APPLICATION: IND 074563
DRUG NAME: MDV3100
TYPE OF MEETING: Type B, Pre-NDA
MEETING CHAIR: V. Ellen Maher, M.D., Lead Medical Officer, DOP1
MEETING RECORDER: Modupe Fagbami, Regulatory Project Manager, DOP1

FDA ATTENDEES:

Robert Justice, M.D., Director, DOP1
V. Ellen Maher, M.D., Clinical Team Leader, DOP1
Yang-Min Ning, M.D., Medical Officer and Acting Team Leader, DOP1
Jonathan Jarow, M.D., Medical Officer, DOP1
Anne Pilaro, Ph.D., Supervisor, Pharmacology/Toxicology, DHOT?
Haw-Jyh Chiu, Ph.D., Pharmacology/Toxicology Reviewer, DHOT
Qi Liu, Ph.D., Team Leader, Clinical Pharmacology, OTS/OCP/DCPV
Sarah Schrieber, Ph.D., Clinical Pharmacology Reviewer, OTS/OCP/DCPV
Shenghui Tang, Ph.D., Lead Mathematical Statistician, DB5
Qiang (Casey) Xu, Ph.D., Mathematical Statistician, DB 5
Stella Karuri, Ph.D., Mathematical Statistician, DB5
Hui Zhang, Ph.D., Mathematical Statistician, DB5
Robert Young, M.D., Medical Officer, DSI
Haripada Sarker, Ph.D., Lead Quality Assessment, ONDQA
Joyce Crich, Ph.D., CMC Reviewer, ONDQA
Modupe Fagbami, Regulatory Health Project Manager, DOP1

SPONSOR ATTENDEES:

Anne K. Bonneville, Ph.D., Director, Toxicology
Mark Bradin, Associate Director, Regulatory
Michele D. Bronson, Ph.D., Vice President, Regulatory & Quality
Gia DePilllis, Ph.D., Senior Director, Regulatory Affairs
Jackie Gibbons, Ph.D., Director, DMPK
Mohammad Hirmand, M.D., Vice President, Clinical Development

Andy Protter, Ph.D., Vice President, Preclinical
Lynn Seely, M.D., Chief Medical Officer
Sue Wollowitz, Ph.D., Vice President, Chemistry and Manufacturing
Fong Wang, M.D., Ph.D., Senior Director, Clinical Development
Stephen Eck, M.D., Vice President, Global Head of Medical Oncology
Alison Hayles, Director, Regulatory Affairs
Frank Perabo, M.D., Executive Director, Medical Science Urology
Steve van Os, M.D., Senior Director, Global Development Project Lead
Taoufik Ouatas, Ph.D., Scientific Director, Translational & Development, Pharmacology

MEETING OBJECTIVES:

The purpose of the pre-NDA meeting is to confirm critical elements of the proposed NDA submission planned for the 2Q 2012, including reaching consensus on the following:

- The key efficacy and safety data to be used in support of the proposed indications;
- The clinical pharmacology and nonclinical data to be presented in the NDA;
- Outstanding CMC issues; and
- The content and logistics of the proposed NDA update.

BACKGROUND

The purpose of this pre-NDA meeting is to seek advice from the Agency on critical elements for the proposed submission of an NDA for MDV3100, an androgen receptor signaling inhibitor. The proposed indication for MDV3100 is treatment of patients with castration-resistant prostate cancer who have received docetaxel (b) (4)

The planned NDA submission is primarily based on the results of a Phase 3 trial (AFFIRM) of MDV3100 in patients with metastatic castration-resistant prostate cancer who have been previously treated with docetaxel-based chemotherapy. The primary endpoint of the trial was overall survival. The trial randomized 1199 patients in a 2:1 ratio to receive MDV3100 at a dose of 160 mg once daily or placebo treatment. A pre-specified interim analysis, conducted by the Independent Data Monitoring Committee (IDMC) in September of 2011, showed that MDV3100 treatment was associated with an improvement in OS compared to placebo [HR 0.633 (0.531, 0.754) in the unstratified analysis, $p < 0.0001$ (log-rank)]. The estimated median survival for men receiving MDV3100 was 18.4 months compared with a median survival of 13.6 months for men receiving placebo. Along with the safety profile demonstrated, the IDMC recommended that the trial be stopped and men allocated to the placebo arm be offered MDV3100. The data cut-off date for this key study supporting this submission was September 25, 2011.

The submission is planned for 2Q2012. For the safety update of the planned NDA submission, the sponsor proposed January 31, 2012 as the data cut-off date, approximately 4 months after the interim analysis of the above key study.

Clinical and Biostatistics Questions

1. Does the Agency agree that the overall survival result from the Phase 3 study, CRPC2 (AFFIRM), is adequate to support FDA filing and review of MDV3100 in the proposed indication as previously discussed at the End-of-Phase 2 meeting (18 March 2009) and the Type A meeting (15 April 2011)?

FDA RESPONSE:

The results you have presented, if confirmed, appear promising. However, whether the results from the Phase 3 study (AFFIRM) are adequate to support filing and approval of MDV3100 for the proposed indication is a review issue.

Meeting Discussion:

There was no meeting discussion.

2. The proposed overall safety database to be included in the submission includes 1000 MDV3100-treated patients with castration-resistant prostate cancer, as well as data from clinical pharmacology studies. Does the Agency agree that the structure and content of the safety database are acceptable?

FDA RESPONSE:

The structure and content of the proposed safety database appears to be acceptable.

Please comment on the number of patients who have received more than 1 year of study drug. Please comment on whether you will continue to collect adverse event data from patients exposed to study drug after database lock.

Meeting Discussion:

Sponsor specified that there are approximately 250 patients who had more than 1 year of exposure to MDV3100 and that adverse events have been collected continuously after the database lock and will be submitted with the safety update.

3. The integrated safety analyses will include data from the unblinded Phase 3 CRPC2 (AFFIRM) study, as well as the open-label studies in castration-resistant prostate cancer, including the Phase 1 dose-finding study (S-3100-1-01), the Phase 2 CRPC-MDA-1 study, and the Japanese bridging study (9785-CL-0111). The Sponsors propose to include the discussion of the integrated safety analyses within the Summary of Clinical Safety (Module 2.7.4) and the integrated data summaries and the integrated dataset in Module 5.3.5.3. Does the Agency agree with the proposed content and structure of the integrated safety database?

FDA RESPONSE:

The structure and content of the proposed ISS, appears to be acceptable. For the integrated dataset, please include patients' baseline demographic information.

Meeting Discussion:

The Sponsor agreed to include the baseline demographic variables in the ISS dataset.

4. Efficacy data were collected in 1 large randomized placebo-controlled Phase 3 study (CRPC2 [AFFIRM]) and 2 smaller open-label studies in patients with castration-resistant prostate cancer. The Phase 3 CRPC2 (AFFIRM) study is the only study with overall survival data, therefore the Sponsors propose not to include an Integrated Summary of Efficacy in the NDA. Results from the Phase 3 CRPC2 (AFFIRM) study and data from the open-label studies in castration-resistant prostate cancer will be presented and discussed separately in the Summary of Clinical Efficacy (Module 2.7.3). Does the Agency agree with this proposal?

FDA RESPONSE:

An ISE is not indicated for this NDA submission given the differences in the primary objectives and designs of these studies.

Meeting Discussion:

There was no meeting discussion.

5. Individual study datasets in Study Data Tabulation Model (SDTM) format will be submitted for the clinical studies listed in Table 10.3-1. Analysis Data Module (ADaM) datasets will be provided only for the Phase 3 CRPC2 (AFFIRM) trial, the Phase 1 dose-finding study (S-3100-1-01), and for the integrated safety database. Does the Agency agree with this proposal

FDA RESPONSE:

Yes, it is acceptable. The raw and derived datasets should be identified clearly in the submission.

Meeting Discussion:

There was no meeting discussion.

6. A dedicated QT/QTc assessment of MDV3100 was conducted within the Phase 3 CRPC2 (AFFIRM) study as agreed with FDA at the End-of-Phase 2 meeting (18 March 2009). The report of the dedicated QT/QTc assessment will be provided as an appendix to the clinical study report of CRPC2 (AFFIRM). The Sponsors intend to submit electrocardiogram data in XML (aECG) format to the digital data warehouse hosted by (b) (4) prior to the submission of the NDA, but not include these data in the NDA. Does the Agency agree with this plan?

FDA RESPONSE:

Yes, we agree.

Meeting Discussion:

There was no meeting discussion.

Clinical Pharmacology Question

7. Does the Agency agree that the proposed clinical pharmacology and biopharmaceutics studies are adequate to support FDA filing and review of the NDA for MDV3100 in the proposed indication?

FDA RESPONSE:

We refer you to the responses conveyed at the Type C meeting on January 14, 2011. Specifically, we would like to reiterate that the adequacy of the formal population PK analysis to assess the effect of renal and hepatic impairment on the PK of MDV3100 is a review issue. Organ impairment trials do not need to be conducted in your selected patient population, but can be done in patients with a range of solid tumors, or in otherwise healthy volunteers with renal and hepatic impairment (if there are no safety concerns).

If *in vitro* data suggest that MDV3100 solubility is pH dependant, please also address the drug - drug interaction potential with agents that can alter the gastric PH (i.e., proton-pump inhibitors, H2-receptor antagonists, and antacids).

Please refer to the following pharmacometric data and models submission guidelines (<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm180482.htm>):

- a. All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
- b. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
- c. A model development decision tree and/or table which gives an overview of modeling steps.
- d. For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

Meeting Discussion:

The Sponsor agreed to submit the solubility data in the NDA to support their statement that the solubility is pH independent.

Nonclinical Question

8. Does the Agency agree that the proposed nonclinical toxicology and safety pharmacology studies are adequate to support FDA filing and review of the NDA for MDV3100 in the proposed indication?

FDA RESPONSE:

No. Based on the information provided in the pre-NDA Meeting Briefing Package, FDA has identified the following nonclinical issues which should be addressed by the time of NDA submission for MDV3100 in the proposed indication:

- a. **Based on the finding that metabolites M1 (a carboxylic acid derivative) and M2 (N-desmethyl MDV3100) appear to be formed at greater than 10% of MDV3100 systemic exposure at steady state, Medivation should also conduct genetic toxicology studies with M1 and M2 to support marketing of MDV3100, as outlined in the FDA Guidance for Industry, "Safety Testing of Drug Metabolites", posted at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079266.pdf>.**
- b. **Medivation has not provided an adequate scientific justification for the proposed administration of a single dose level of 30 mg/kg MDV3100 in the mammalian *in vivo* mouse micronucleus test outlined in the pre-NDA Meeting Briefing Package. Either conduct this test according to the recommendations outlined in the ICH S2(R1) Guidance, "Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use", posted at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S2_R1/Step4/S2R1_Step4.pdf, or provide an appropriate scientific justification for the proposed study design at the time of NDA submission.**

Meeting Discussion:

The FDA reiterated the need for the Ames assays for the metabolites M1 and M2 but that it will not be a filing issue. The Sponsor committed to provide the results of these assays and their justifications as early as possible during the review period.

Chemistry, Manufacturing, and Controls Questions

9. Does the Agency agree that the proposed regulatory starting materials for the active pharmaceutical ingredient are acceptable?

(b) (4)

(b) (4)

FDA RESPONSE:

Your proposed starting materials (b) (4) appear to be reasonable. However, this is a review issue. In the NDA, include the following to support the use of these compounds as starting materials:

1. A detailed description of the impurity profile.
2. Brief description of synthetic strategies and methods of manufacture.
3. Detailed discussion on carry-forward impurities.
4. Controls and analytical methods to separate and measure appropriate impurities.
5. Supplier information for the starting materials.
6. Information on impurity fate studies. Detailed discussion on (b) (4) studies to demonstrate the ability of the manufacturing process to remove and control the impurities from the starting materials to the desired levels.
7. Change of control strategies for any potential revisions to the manufacture of proposed starting materials including the vendor's reporting of any changes in starting material specification or control.

However, we have concerns on the proposed starting material (b) (4) which not only is (b) (4) steps away from the API, but also carries genotoxic impurities, etc. We recommend you to move the proposed GMP starting point (b) (4) step (b) (4) in the synthesis.

Meeting Discussion:

Sponsor will provide all the justification for the starting materials in the NDA submission. The acceptability of the proposed starting materials will be a review issue.

10. Does the Agency agree with the selected primary stability batches and the proposed stability data package for MDV3100 Drug Substance?

FDA RESPONSE:

No. It is premature to make an assessment without reviewing detailed information (such as defined (b) (4) process, impact of (b) (4) and solubility of drug substance that could affect drug product formulation, refer to one registration batch 09080104 for (b) (4) process; test intervals for batch 09090069, etc).

According to International Conference on Harmonization (ICH) Q1A (R2), "long term testing should cover a minimum of 12 months' duration on at least three primary

batches at the time of submission". While ICH Q1E: Evaluation of Stability Data, allows for the use of extrapolation to extend the shelf life beyond the available real-time long term data, it does not negate the recommended 12 months of long term data cited in ICH Q1A(R2).

Per the Guidance for Review Staff and Industry Good Review Management Principles and Practices for PDUFA Products (GRMPs), all NDAs are to be complete in the original submission. This includes all stability data and corresponding data summaries necessary to establish a shelf life. Any information submitted to an NDA subsequent to the original submission may or may not be reviewed as resources allow.

Meeting Discussion:

Sponsor will provide justification for the inclusion of batch 09080104 as a primary stability batch.

The Sponsor will provide for evaluation a summary of differences between the manufacturing process for batch 09080104 and the proposed commercial manufacturing process prior to NDA submission.

Agency acknowledges the timeline of the stability batches (for drug substance-09090060; and for drug product 1152503) and Agency will follow up with the Sponsor whether the 9-month stability data is acceptable or not.

Comment added after the meeting: Please see minutes from April 11, 2012 teleconference.

11. Does the Agency agree with the proposed stability data package for MDV3100 Drug Product?

FDA RESPONSE:

No. Refer to comments under Question No. 10.

Meeting Discussion:

Reference discussion to question 10

Regulatory Question

12. Are the proposed content, data cutoff date, and timing acceptable for the clinical safety update to the NDA?

FDA RESPONSE:

Yes, the proposed safety update submission is acceptable.

Meeting Discussion:

There was no meeting discussion.

13. MedDRA is the dictionary used to code adverse events in all clinical studies, but because each study was initiated on a different date, various versions of MedDRA have been used to code events. For the Integrated Summary of Safety, all adverse event datasets will be re-coded using MedDRA, version 14.1 (01 September 2011). Does the Agency agree with this proposal?

FDA Response:

The proposal appears acceptable.

Meeting Discussion:

There was no meeting discussion.

14. For the pivotal Phase 3 CRPC2 trial, an analysis data cut-off date of 25 September 2011 will be applied to the SDTM and Analysis Data Model (ADaM) datasets. The analysis cut-off date corresponds to the date of the milestone death used for the pre-planned interim analysis of overall survival. All data for all patients up to and including this cut-off date will be submitted in the NDA. In addition, the following data also will be included in the NDA:
- Patient contact data associated with the event sweep implemented for the interim survival analysis (i.e. patient contacts made after 25 September 2011);
 - Investigator assessment of tumor/lesion scans for visits on or prior to 25 September 2011 (scans tied to a visit scheduled on or prior to the cut-off date may be taken after this date);
 - Deaths and visit dates occurring after 25 September 2011 but prior to database lock (16 December 2011) for the presentation of post-interim overall survival.

Does the Agency agree with this proposal?

FDA Response:

It may be acceptable, however, please explain what is meant by 14.a. and 14.c.

Meeting Discussion:

The sponsor will clearly identify, in the dataset, the deaths which were included in the interim analysis and the additional deaths discovered prior to database lock.

15. Patient Profiles in Electronic Case Report Form format (bookmarked and indexed) will be provided for all patients in the Phase 3 CRPC2 trial. These patient profiles will not include central laboratory data or central ECG data, although the central laboratory data will be available for evaluation in the SDTM and ADaM datasets submitted in the NDA and the central ECG data will be submitted through the ^{(b) (4)} Two representative Patient Profile electronic files (Patient Profile 1, Patient Profile 2) are attached as examples. Although SDTM will be provided for all studies, patient profiles and electronic images of patient case report forms will not be provided for any other studies in the NDA submission. Does the Agency agree with this proposal?

FDA Response:

CRFs from Phase 1 and 2 studies should be available upon request.

Meeting Discussion:

There was no meeting discussion.

16. Narratives for deaths due to adverse events, study drug discontinuations due to adverse events, and other significant adverse events will be presented within the body of each clinical study report (Section 12). All other narratives for serious adverse events will be presented in Appendix 14.3.3. Does the Agency agree with this proposal?

FDA Response:

**Please also include narratives for patients who had any of the following:
Serious adverse events regardless of causality;
Death within 30 days after the last dose of study drug; and
Seizure reported or observed, regardless of severity.**

Further, please include line listings of safety reports from unblinded studies.

Meeting Discussion:

FDA clarified that all patients deaths within 30 days of the last dose of study drug should have a narrative, regardless of causality.

17. Assuming an initial NDA submission on 30 April 2012, would the safety update to the NDA proposed for July 30, 2012 suffice in lieu of the IND annual safety report (due date: 29 August 2012)?

FDA Response:

Please see response to Question 12 of the Type B pre-NDA meeting.

Meeting Discussion:

There was no meeting discussion.

18. The Phase 3 study CRPC2 qualifies as a “covered study” for the provision of Financial Disclosure according to the FDA DRAFT Guidance Financial Disclosure by Clinical Investigators (May 2011). Financial Certification and/or Disclosure information (Form FDA 3454/3455) will be provided for investigators who participated in CRPC2, but not for those in other MDV3100 clinical studies. Does the Agency agree with this proposal?

FDA Response:

This appears to be acceptable. Disclosure of financial interests of investigators in other MDV3100 clinical studies should be available upon request.

Meeting Discussion:

There was no meeting discussion.

19. Because the Phase 3 Study CRPC2 is the single pivotal study supporting the efficacy of MDV3100, it is proposed to submit an Investigator List for the investigators only from this study. This list will contain information for each study site, including the site contact information, the number of patients enrolled, efficacy and SAE information as appropriate, and the number of protocol violations. The following are defined as protocol violations: inclusion/exclusion criteria violations; developed withdrawal criteria during the study but were not withdrawn; received wrong treatment or incorrect dose; and received an excluded concomitant treatment. An example of the format of the Investigator List is attached. Does the Agency agree with the content and format of the proposed Investigator List?

FDA Response:

Yes. Please use Excel to list all the information.

Meeting Discussion:

There was no meeting discussion.

20. The population pharmacokinetics analysis datasets will be provided as NONMEM (version 7.0 or higher) input files, which will be formatted as comma-separated and space-delimited text (CSV) files. The relevant NONMEM run records (“control stream files”) will additionally be provided as text files. Source data will be provided as SAS (version 9.1.3 or higher) datasets in SDTM format. Does the Agency agree with the proposed format of the population pharmacokinetics datasets?

FDA Response:

Refer to response to question #7.

Meeting Discussion:

There was no meeting discussion.

21. Literature references will be provided for citations made in Module 2. It is proposed that all other references will be made available upon request. Does the Agency agree with this approach?

FDA Response:

Please submit literature references for citations in Module 5.

Meeting Discussion:

There was no meeting discussion.

ADDITIONAL COMMENTS

Please comment on whether your study has collected data for validation of circulating tumor cells as a surrogate marker and, if so, the timing for submission of this data.

Please comment on your plans for an expanded access protocol.

At time of your NDA submission, please also submit a completed Clinical Pharmacology Question-Based Review (see Appendix), which includes hyper-linking throughout. This additional document may be submitted to the “Summary of Clinical Pharmacology Studies” subfolder within Module 2.

Appendix.

Clinical Pharmacology Question-Based Review

9 GENERAL ATTRIBUTES

- 9.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Established
name:

Molecular
Weight:

Molecular
Formula:

Chemical Name:

Description:

Polymorphism:

Solubility:

pKa-Values:

Partition
Coefficient:

- 9.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?
- 9.3 What are the proposed dosage(s) and route(s) of administration?

10 GENERAL CLINICAL PHARMACOLOGY

- 10.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?
- 10.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?
- 10.3 What active moieties in the plasma (or other biological fluid) were identified and measured to assess pharmacokinetic parameters and exposure response relationships?

11 EXPOSURE-RESPONSE

- 11.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

- 11.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.
- 11.3 Does this drug prolong the QT or QTc interval?
- 11.4 Is the dose and dosing regimen consistent with the known relationship between dose-concentration-response?

12 PK CHARACTERISTICS OF THE DRUG AND ITS MAJOR METABOLITES.

- 12.1 What are the single dose and multiple dose PK parameters? (summarize individual study report findings and combine data cross-studies as appropriate).
- 12.2 If applicable, how does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?
- 12.3 What are the characteristics of drug absorption?
- 12.4 What are the characteristics of drug distribution?
- 12.5 What are the characteristics of drug metabolism? (This may include data on extraction ratio; metabolic scheme; enzymes responsible for metabolism; fractional clearance of drug.)
- 12.6 What are the characteristics of drug excretion? Does the mass balance study suggest renal or hepatic as the major route of elimination? (This may include table with results of mass balance study).
- 12.7 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?
- 12.8 How do the PK parameters change with time following chronic dosing? (This may include time to steady-state; single dose prediction of multiple dose PK; accumulation ratio.)
- 12.9 What is the inter- and intra-subject variability of PK parameters in volunteers (if applicable) and patients, and what are the major causes of variability?
- 12.10 What are the PD characteristics of the drug and its major metabolites?

13 INTRINSIC FACTORS

- 13.1 What intrinsic factors (e.g., age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ impairment) influence exposure and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?
- 13.2 Based upon what is known about exposure-response relationships and their variability what dosage regimen adjustments, if any, are recommended for the intrinsic factors discussed above? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

14 EXTRINSIC FACTORS

14.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

14.1.1 Drug-drug interactions

14.1.1.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

14.1.1.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced by genetics?

14.1.1.3 Is the drug and/or metabolites an inhibitor and/or an inducer of CYP enzymes?

14.1.1.4 Is the drug and/or metabolites a substrate and/or an inhibitor of P-glycoprotein transport processes?

14.1.1.5 Are there other metabolic/transporter pathways that may be important?

14.1.1.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

14.2 Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for the above extrinsic factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

15 GENERAL BIOPHARMACEUTICS

15.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

15.2 Compare the proposed to-be-marketed formulation to the pivotal trial formulation.

15.2.1 What data support or do not support a waiver of in vivo BE data?

15.2.2 If BE data is required, are the formulations BE? If not, explain.

15.3 What is the effect of food on the bioavailability (BA) of the drug? What dosing recommendation is proposed, if any, regarding administration of the product in relation to meals or meal types?

16 ANALYTICAL SECTION

16.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies? Which metabolites have been selected for analysis and why?

- 16.2 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?
- 16.3 What bioanalytical methods are used to assess concentrations?
- 16.4 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?
- 16.5 What are the lower and upper limits of quantification (LLOQ/ULOQ)? What are the accuracy, precision, and selectivity at these limits?
- 16.6 What is the sample stability under the conditions used in the studies (e.g., long-term, freeze-thaw, sample-handling, sample transport, autosampler)?
- 16.7 What is the QC sample plan?
- 16.8 How are PD Biomarkers identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Meeting Discussion:

There was no meeting discussion.

Action Item:

Agency will follow up with the Sponsor whether the 9-month stability data is acceptable or not.

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/s/

MODUPE O FAGBAMI
04/17/2012

VIRGINIA E MAHER
04/17/2012

IND 074563/MDV3100
Medivation Inc.

1. Does the Agency agree with the proposed plan to reduce the target hazard ratio of the CRPC2 Phase 3 trial from 0.80 to 0.76 and to increase the power to 90%? This change reduces the target number of deaths needed for the final analysis of overall survival from 786 to 650.

FDA Response:

Yes. However, you do so at your own risk.

2. Does the Agency agree with the proposed plan to perform a formal interim analysis of overall survival in the CRPC2 study?
Specifically:

A. The plan to perform the formal interim analysis at approximately 520 events (80% of the 650 targeted number of events for the final analysis)?

FDA Response:

Yes, the timing of the proposed interim analysis is acceptable.

B. The plan to use a two-stage group sequential design with Lan-Demets alpha-spending function determined by means of the O'Brien-Fleming approach to preserve the overall type 1 error rate of 0.05 between the single interim analysis and the final analysis of overall survival?

FDA Response:

Yes, the plan of alpha allocation is acceptable.

C. The plan for the interim analysis to be prepared by an Independent Statistics Unit with the results presented only to the independent Data Monitoring Committee who will make a formal recommendation about the ongoing conduct of the study?

FDA Response:

Yes.

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/s/

JAMILA MWIDAU
04/14/2011



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: EOP2

Meeting Date and Time: January 14, 2011
Meeting Location: WO Building 22 Rm, 1309

Application Number: IND 074563
Product Name: MDV3100
Indication: Prostate Cancer
Sponsor/Applicant Name: Medivation, Inc

Meeting Chair: Edvardas Kaminskas, MD
Meeting Recorder: Jamila Mwidau, RN,BSN,MPH

FDA ATTENDEES

Robert Justice, MD., M.S., Director DDOP
Albert Deisseroth, MD., Clinical Reviewer DHP
Jeanne Fourie Zirchelbach, Ph.D., Acting Team Leader, Clinical Pharmacology
Sophia Abraham, Ph.D., Clinical Pharmacology Reviewer
Jamila Mwidau, RN,BSN,MPH Project Manager

SPONSOR ATTENDEES

Medivation, Inc:

Michele D. Bronson, Ph.D., Vice President Regulatory & Quality
Gia DePilllis, Ph.D., Senior Director, Regulatory Affairs
Jackie Gibbons, Ph.D., Director, DMPK
Mohammad Hirmand, MD., Vice President Clinical Development
Sheila Matz, RPh., Senior Director Pharmaceutical Development
Joyce Mordenti, Vice President, Translational Medicine and DMPK
Lynn Seely, MD., Chief Medical Officer
Bryan Selby, MS., Vice President Biometrics

Astellas:

Meeting Minutes
[Insert Meeting Type]
DATE

[Insert Office/Division]

Alison Hayles, Associate Director Global Development Regulatory Affairs
Walter Krauwinkel, MSc, PharmD Acting Global Head, PK Modeling
Taoufik Ouatas, Ph.D., Scientific Director, Translational & Development

1.0 BACKGROUND

MDV3100 is a 2nd generation androgen receptor (AR) antagonist which has been selected from a (b) (4) for the following features:

MDV 3100 has been found to:

1. Blocks binding of testosterone to the AR
2. Six fold higher affinity for receptor than Casodex
3. Blocks translocation of AR from cytoplasm to nucleus
4. Blocks binding of AR to DNA
5. No agonist activity when bound to AR

MDV 3100 has high cellular membrane permeability and low aqueous solubility. It is formulated in (b) (4) for the current formulation in a liquid filled soft gelatin capsule of 40 mg in (b) (4). It requires 4 large capsules to deliver a 160 mg dose.

(b) (4) The PK characteristics of the liquid filled soft gelatin capsule (b) (4) dosage form were evaluated in a pilot bioequivalence and food effects study (MDV3100-05).

The purpose of the meeting is to discuss the answers to the Sponsor's questions concerning the proposed definitive bioequivalence study of four 40 mg capsules (b) (4) under the fed and fasting conditions (see design of MDV 3100-05 study).

2. DISCUSSION

1. Does the Agency agree with the proposed plan for demonstrating BE (b) (4) (b) (4) liquid-filled soft gelatin capsule?

FDA Response:

Your proposed definitive BE study appears acceptable; except, the bioequivalence between the clinical capsule (b) (4) should be established based on the 90% CIs for the geometric mean ratio for both $AUC_{0-\infty}$ and C_{max} . Please submit protocol for review prior to its initiation. Please refer to the FDA guidance for industry entitled, "Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations" at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070124.pdf> for more information.

Meeting Discussion:

The Agency will consider a proposal submitted by the sponsor for determining BE based on a single dose BE study, modeling and simulation to steady state, and multiple dose PK in patients.

2. Does the Agency agree that the food-effects data from Clinical Study MDV3100-05 (pilot BE study) are adequate to support a label claim that MDV3100 liquid-filled soft gelatin capsules can be taken without regard to meals?

FDA Response:

No. It is preferable to conduct the food effect study with the to-be-marketed formulation. However, if BE (b)(4) capsule formulations was established with respect to both C_{max} and AUC_{0-inf} , the pilot food effect study would be acceptable. Your pilot BE study established the BE between the (b)(4) formulations only with respect to AUC_{0-inf} . We suggest that you include the assessment of food effect using the to-be-marketed (b)(4) formulation in your proposed definitive BE study. Please refer to the FDA Guidance for industry entitled, "Food-Effect Bioavailability and Fed Bioequivalence Studies or and Bioavailability" at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070241.pdf>) for more information.

Meeting Discussion:

FDA clarified that if the to-be-marketed formulation is the capsule , then the current food effect study is acceptable.

3. Does the Agency agree that the proposed plan for assessing clinical drug-drug interactions is adequate to support approval?

FDA Response:

Your drug-drug interactions plan appears acceptable.

Meeting Discussion:

None

4. Does the Agency agree that the proposed plan regarding special population PK studies is adequate to support approval?

FDA Response:

The adequacy of the formal population PK analysis to assess the effect of renal impairment on the PK of your drug is a review issue and labeling will not be discussed prior to NDA review. A population PK approach using phase 2 and 3 data can be useful to assess the impact of renal or hepatic impairment on the PK of your drug. If such analyses are conducted we generally recommend that you enroll a

sufficient number of patients with a wide range of hepatic and renal function in your phase 2/3 studies and get enough PK samples from each patient to characterize their PK. You should pre-plan the analysis and power the study to get precise estimates (relative standard error $\leq 20\%$) of the mean clearance parameter in renal and hepatic impaired patients. For further information, see hepatic and renal impairment guidances at:

Guidance for Industry entitled, "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling" at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf>.

Guidance for Industry entitled, "Pharmacokinetics in Patients with Impaired Renal Function, Study Design, Data Analysis, and Impact on Dosing and Labeling" at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072127.pdf>.

Investigation of the effects of hepatic and renal impairment on the PK of your drug (if these are major pathways of elimination) would be important to establish the optimum dose/dosing regimen in these patient populations. The effect of renal and hepatic impairment can be assessed using population PK approaches as discussed above, or renal and hepatic organ impairment trials. Organ impairment trials do not need to be conducted in your selected patient population, but can be done in patients with a range of solid tumors, or in healthy volunteers with renal and hepatic impairment (if there are no safety concerns) (see guidance links above).

5. Does the Agency agree that an absolute oral bioavailability study will not be required to support approval?

FDA Response:

This will be a review issue.

Meeting Discussion:

None

Additional Comment:



(b) (4)

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None

4.0 ACTION ITEMS

None

5.0 ATTACHMENTS AND HANDOUTS

None

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/s/

EDVARDAS KAMINSKAS
01/18/2011

MEETING MINUTES

MEETING DATE: July 15, 2010 **TIME:** 10 am – 11 am **LOCATION:** FDA, White Oak Building 22, Conference Room 1311

INDA: 074563	Meeting Request Submission Date:	June 9, 2010
	FDA Response Date:	June 23, 2010
	Briefing Document Submission Date:	July 1, 2010

DRUG: MDV3100

SPONSOR/APPLICANT: Medivation, Inc.

TYPE of MEETING: Type A meeting to discuss the February 5, 2010 SPA non-agreement letter.

FDA PARTICIPANTS:

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

Anthony Murgio, M.D., M.S., FACP, Associate Director OODP IO, Acting Deputy Director DDOP

Edvardas Kaminskas, M.D., Acting Deputy Directory, DHP

Albert Deisseroth, M.D., Medical Officer, DHP

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

Yu-ling Chang, Ph.D, Math Statistician, DB 5

Sarah J. Schrieber, Pharm.D, Clinical Pharmacology Reviewer, DCP5

Roman Ivanov, M.D., Visiting Fellow, OODP

Alberta Davis-Warren., Regulatory Health Project Manager

INDUSTRY PARTICIPANTS:

Medivation, Inc.

Craig Berman, M.D., Director, Clinical Development

Michele D. Bronson, Ph.D., Vice President, Regulatory & Quality

Gia DePillis, Ph.D., Senior Director, Regulatory Affairs

Mohammad Hirmand, M.D., Vice President, Clinical Development

Lynn Seely, M.D., Chief Medical Officer

Bryan Selby, M.S., Vice President, Biometrics

Astellas Pharma Global Development:

Alison Hayles, Associate Director, Regulatory Affairs

De Phung, Associate Biostatistics Director

BACKGROUND: Sponsor is using MDV3100 to investigate the treatment of prostate cancer. On June 9, 2010 Medivation Inc. submitted a meeting request to discuss February 5, 2010 non-agreement SPA letter regarding protocol titled “A Multinational Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Oral MDV3100 in Chemotherapy-Naïve Patients with Progressive Metastatic Prostate Cancer Who Have Failed

Androgen Deprivation Therapy/MDV3100-03.” The sponsor submitted a subsequent background package on July 1, 2010. To facilitate the meeting FDA sent preliminary responses by email on July 12, 2010.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. In the original SPA, co-primary endpoints of OS and PFS were requested for the Phase 3 protocol MDV3100-03. The Agency replied:

“No. PFS is not yet an acceptable endpoint in metastatic prostate cancer. This would require an ODAC discussion. The results of bone scans and CT scans of soft tissue deposits in early (asymptomatic or minimally symptomatic) prostate cancer are not reproducible. We strongly urge you to use OS as the primary and only primary efficacy endpoint.”

Cougar Biotechnology issued a press release in February 2009 announcing that the company had reached agreement with FDA on the SPA for a Phase 3 study of abiraterone acetate in chemotherapy-naïve CRPC patients (COU-AA-302; NCT00887198) and that “the agreed upon co-primary endpoints of the trial are progression-free survival and overall survival.”

Based on the precedent for COU-AA-302 and given that Study MDV3100-03 is similarly designed and in the same patient population as the COU-AA-302 study, the Sponsor had considered that OS and PFS would be acceptable co-primary endpoints. The Sponsor has recently received Scientific Advice from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) that agrees with the use of OS and PFS as co-primary endpoints in Study MDV3100-03.

Question: Could the Agency please explain the apparent difference in advice given for the COU-AA-302 study and the Sponsor’s similarly designed Study MDV3100-03? Are there design elements that could be incorporated into the MDV3100-03 study that would lead the Agency to consider OS and PFS as acceptable co-primary endpoints?

FDA response: The use of rPFS to support approval has not been established and has never been used as a primary endpoint for marketing approval in prostate cancer.

In the experience being accumulated by the Agency, it is becoming increasingly clear that PFS may not always be a reliable predictor of benefit as measured by OS. This is especially true of clinical trials in which the treatment effect is projected to be relatively small for the endpoint (which is the case for PFS in your trial), when there are reproducibly issues with the measurements used to define progression in the proposed patient population (which is the case with minimally symptomatic or asymptomatic patients, and when the magnitude of the PFS prolongation is short relative to the projected overall survival for that disease. In addition, the side effects of MDV3100 (vomiting, rash and back pain) would lead to unblinding, increasing the likelihood of informative censoring.

If you choose to use PFS as a primary endpoint for a phase III trial that supports an NDA submission, the acceptability of PFS would be a review issue and there would be an ODAC review of this application. In addition, if you choose to use PFS as a co-primary endpoint, the Agency will not approve your SPA application for protocol MDV3100-03. The approval of Provenge, based on a survival advantage in a similar patient population, has changed the therapeutic landscape.

2. If the Agency reconsiders the use of PFS as a co-primary endpoint, or in the case that PFS is a secondary outcome measure for protocol MDV3100-03, the Sponsor would appreciate answers to the following questions about PFS that were asked in the original SPA. Agreement on these issues would be important even if the Agency agrees to PFS as a secondary efficacy outcome measure, in case the results of bone scans and CT scans in prostate cancer are considered by the Agency to be more reproducible during the time this trial is being conducted. Re-evaluation of PFS as a co-primary endpoint may occur in the future because of more reliable radiographic criteria of progression (PCWG2 criteria) instituted in this and other ongoing prostate cancer Phase 3 programs.

FDA response: The Agency will be happy to review data that you may wish to provide in the future that pertains to the increased reliability of the measurement of progression in prostate cancer patients who are entered into a protocol at a time when they are chemotherapy naïve, androgen deprivation resistant, and are only minimally symptomatic. The Agency refers you to its response to Question #1 in which it states that there are other issues besides reproducibility of measurement of progression using CT and bone scans that reduce the reliability of PFS as an endpoint in your proposed protocol.

- a. The Sponsor asked if the definition of PFS was acceptable. The Agency replied:

“No. The projected increase of 2 months in PFS is not clinically meaningful in this population of prostate cancer patients in whom the survival in untreated patients is projected to be 25 months.”

Based on Agency comments, the Sponsor has revised the projected increase in PFS to 3 months (from 4 months to 7 months). PFS for Study MDV3100-03 will be defined as radiographic progression (soft tissue or bone lesion) or death due to any cause, whichever occurs first. The analysis will occur after a minimum of 410 PFS events are reported or the enrollment is complete, whichever occurs later, and corresponds to a target hazard ratio of 0.57 or a 75% increase in median PFS based on a two-sided log-rank test and a significance level of 0.001. An interim analysis of OS will also be conducted at the time of this PFS analysis. The Sponsors understand that the PFS benefit observed must be both clinically-meaningful and statistically-significant to be considered a positive result.

Question: Is this definition and analysis strategy for PFS acceptable to the Agency?

FDA response: No. See previous comments in the SPA non-agreement letter about the use rPFS in prostate cancer. In addition, the incremental change in the PFS from 2-3 months of a projected PFS for the placebo arm of 4 months may not be clinically meaningful since the projected survival of the control population is 25 months. The question is not what is the p value or the hazard ratio, but how good a surrogate for benefit (survival) is any PFS outcome, irrespective of the p value or the hazard ratio?

The size of the prolongation of PFS in relationship to the projected survival is only one of several factors that lead to unreliability of PFS as a predictor of OS.

Please also see response to question 1.

- b. Are the interval and frequency of measurements of PFS acceptable?

Radiographic disease evaluation will be performed every 8 weeks for the first 6 months and then every 12 weeks until radiographic progression is confirmed. This schedule is designed to detect the differences in progression between the two arms based on the revised estimates for PFS and to minimize radiation exposure.

FDA response: Yes, as long as these measurements are being used to define PFS as a secondary endpoint for the trial.

- c. Is the plan for basing the analysis of PFS upon Independent Central Imaging Radiology Review as described in the revised proposed imaging charter acceptable?

FDA response: This plan is acceptable for the measurement of PFS as a secondary endpoint which will be used as confirmatory of an outcome of significant OS prolongation as a primary endpoint if that occurs.

- d. Is the plan for independent central imaging confirmation of site-determined disease progression acceptable as outlined in the revised proposed imaging charter?

FDA response: Yes, the plan for independent central imaging confirmation of site determined disease progression to define PFS is acceptable as long as it is understood that independent review will pertain to all of the studies in the trial used to define progression, and that PFS will be used as a secondary endpoint only in the event that the trial meets its primary endpoint of OS.

- e. Is the proposed allocation of overall type I error between the PFS and OS co-primary endpoints acceptable as defined in the revised statistical analysis plan?

FDA response: No. As stated in the response to Question #1, the FDA strongly urges the Sponsor not to use PFS as a co-primary endpoint with OS but to use OS as the only primary endpoint and use PFS as a secondary endpoint.

3. If the Agency considers that PFS is not an appropriate co-primary endpoint, in view of the Scientific Advice received from the CHMP and their acceptance of PFS as a co-primary endpoint, the Sponsors would propose to specify a single primary endpoint of OS for the United States and co-primary endpoints for the European Union. A single global protocol would be used describing the co-primary endpoints, but separate statistical analysis plans for the two regions would clearly describe the distinction in primary analyses. Could the Agency please confirm that the use of a separate statistical analysis plan describing OS as the primary endpoint for the US is acceptable?

FDA response: Yes, as long as the protocol documents distributed in the USA clearly stated in the clinical protocol documents as well as in the SAP that the primary endpoint of the trial was OS and the secondary endpoints was PFS. We are concerned that the trial could be stopped early based on the PFS results.

Meeting Discussion: The Agency and the Sponsor agreed with the importance of preserving the ability to analyze overall survival as an endpoint in this trial, and that in the United States regulatory approval would be based as overall survival as the primary endpoint. In order that one protocol can be constructed for this global international trial, the section on primary endpoints in the protocol will state that there are two statistical analysis plans. In the statistical section it will be clear that the study will not be discontinued due to PFS results.

4. The Sponsor plans to submit an initial NDA supported by OS data from Study CRPC2, followed by a sNDA supported by PFS data (and interim OS data) from MDV3100-03. If the Agency reconsiders the use of PFS as a co-primary endpoint, does the Agency agree with this submission strategy if the OS endpoint from Study CRPC2 demonstrates statistical significance according to the statistical analysis plan and the PFS endpoint from the proposed MDV3100-03 study demonstrates a clinically-meaningful and statistically-significant ($p \leq 0.001$) benefit of MDV3100 on PFS?

FDA response: No. The suitability of the OS data from study CRPC2 to support an initial NDA submission will be a review issue. The Agency does not agree with PFS as a co-primary endpoint for MDV3100-03.

5. In the original Special Protocol Assessment, the Sponsor asked if the Agency agreed with the originally proposed sample size calculations for OS. The Agency replied:

“Yes, however, a 6 month improvement in overall survival may not be realistic.”

Based on the Agency's comments, the Sponsor has revised the estimates of overall survival to be 24 months for the placebo group and 29 months for the MDV3100 group.

Question: Are the revised sample size calculations and estimates for OS acceptable to the Agency?

FDA response: The response to this question depends ultimately on the outcome of the trial and therefore will be a review issue. Please see response to Question #1. Because the current statistical analysis plan is based on the use of PFS and OS as co-primary endpoints, it will be necessary for you to revise the SAP to one that uses OS as the only primary endpoint.

6. MDV3100 is an androgen receptor antagonist without agonist activity. To prevent disease flare resulting from increased androgen signaling, continued dosing of MDV3100 is proposed for Study MDV3100-03 despite disease progression until either dosing is limited by death, adverse events, or the patient withdraws consent. MDV3100 treatment would be continued after disease progression, including through chemotherapy, just as treatment with gonadotropin-releasing hormone analogues is continued to prevent increasing testosterone levels from further worsening disease progression. Radiographic imaging will continue until progression is documented; censoring will not occur at the time of initiation of a new systemic anti-neoplastic therapy.

Question: Does the Agency agree that continued MDV3100 dosing following disease progression, including through chemotherapy, is acceptable?

FDA response: No. Although the Agency understands the logic of the proposed continuation of MDV3100 beyond the date at which progression is defined in order to avoid a flare due to testosterone induced stimulation of the androgen receptor, we are requesting that you provide data that continued MDV3100 is beneficial to patients that are progressed. In addition, please provide a plan for tapering the MDV3100 following progression. We would not agree to extend the period of PFS following documented progression just because MDV3100 therapy was continuing to be administered in order to avoid a flare and despite initiation of a new systemic anti-neoplastic therapy. The period of PFS ends as an event with the first documented progression. Censoring should occur at the time of initiation of a new therapy for reasons other than progression.

Meeting Discussion: FDA expressed concern about continuation of MDV3100 beyond progression because it may add toxicity without providing any additional efficacy. The Sponsor believes that there will be little additional toxicity added by continuing the drug beyond progression and will monitor with a data monitoring committee. A second randomization in patients on MDV3100 with disease progression to continuing or discontinuing the drug was discussed. The Sponsor expressed concern that this additional therapy may be needed to contribute to a survival advantage. A separate randomized discontinuation trial was also discussed. The Sponsor will consider this suggestion further. Ultimately it is the Sponsor's risk to proceed with the trial as planned with continued dosing of

MDV3100 through progression and in combination with subsequent therapy. If continuation of the drug does not add significant toxicity it should not be a concern. If it does a post marketing study requirement may be necessary.

Action items: none

Attachment: Handout (table)

Alberta E. Davis-Warren
Project Manager

Concurrence Chair: Edvardas Kaminskas, M.D.
Medical Team Leader

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Application
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Submission
Type/Number

Submitter Name

Product Name

IND-74563

GI-1

MEDIVATION INC

MDV3100

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/s/

EDVARDAS KAMINSKAS
08/13/2010



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 74563

MEETING MINUTES

Medivation, Inc.

Attention: Daven M. Mody, PharmD, MBA
Associate Director, Regulatory Affairs

201 Spear Street -- Third Floor
San Francisco, CA 94105

Dear Dr. Mody:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MDV3100 for treatment of prostate cancer.

We also refer to the meeting between representatives of your firm and the FDA on Monday, September 28, 2009. The purpose of the meeting was meeting to discuss the overall Chemistry, Manufacturing and Controls (CMC) plan; data package to support the marketing application for MDV3100 in the proposed indication; and the proposed plan for the demonstrating bioequivalence with a potential new formulation.

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 me at (301) 796-2055.

Sincerely,

[See appended electronic signature page.]

Scott N. Goldie, Ph.D.
Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF NEW DRUG QUALITY ASSESSMENT**

Sponsor Name:	Medivation
Application Number:	IND 74,563
Product Name:	MDV3100 (Fostamatinib Disodium)
Meeting Requestor:	Daven M Mody, Pharm.D., MBA Associate Director, Regulatory Affairs
Meeting Type:	Type B
Meeting Category:	Chemistry, Manufacturing and Controls, End of Phase 2 Meeting
Meeting Date and Time:	Monday, September 28, 2009 1200 – 1300 ET
Meeting Location:	Food and Drug Administration, White Oak Campus, Silver Spring, MD
Received Briefing Package	August 21, 2009
Meeting Chair:	Sarah Pope Miksinski, Ph.D.
Meeting Recorder:	Scott N. Goldie, Ph.D.

FDA ATTENDEES:

CENTER OF DRUG EVALUATION AND RESEARCH

Office of New Drug Quality Assessment

John Z. Duan, Ph.D., Reviewer, Biopharmaceutics Review Staff (29 Sept 2009)
Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality (28 Sept 2009)
Ravindra K. Kasliwal, Ph.D., Chemistry Reviewer (29 Sept 2009)
Sarah Pope Miksinski, Ph.D., Branch Chief (30 Sept 2009)
Patrick Marroum, Ph.D., Expert, Biopharmaceutics Review Staff (29 Sept 2009)

Division of Drug Oncology Products

Julie Bullock, Pharm.D., Clinical Pharmacology Team Leader (29 Sept 2009)
Anwar Goheer, Ph.D., Pharmacology/Toxicology Acting Team Leader (29 Sept 2009)
Jian Wang, Ph.D., Pharmacology Reviewer

EXTERNAL ATTENDEES:

Michele D. Bronson, Ph.D. Vice President, Regulatory & Quality
Gia DePilllis, Ph.D. Senior Director, Regulatory Affairs
Daven M. Mody, Pharm.D., MBA, Associate Director, Regulatory Affairs
Joyce Mordenti, Ph.D. Vice President, Translational Medicine & DMPK
Sue Wollowitz, Ph.D. Vice President, Chemistry and Manufacturing

1.0 BACKGROUND

MDV3100 is currently being investigated by Medivation, Inc. under Investigational New Drug (IND) Application 74,563 for the treatment of prostate cancer. MDV3100 is indicated for the treatment of castration-resistant prostate cancer previously treated with docetaxel-based chemotherapy. MDV3100 is formulated as a solution in the surfactant caprylocaproyl polyoxylglyceride (b) (4) and provided as liquid-filled capsules for oral administration. The dose in the proposed Phase 3 study is 160 mg orally daily.

On June 8, 2009 (received June 10, 2009), Medivation requested a End-of-Phase 2/Pre-Phase 3 (Type B) meeting with the Division during the week of 24 August 2009 to reach agreement with the Agency on the overall Chemistry, Manufacturing, and Controls (CMC) plan and data package to support the marketing application for MDV3100 in the proposed indication. In addition, Medivation expressed intent to reach agreement with the Agency on the proposed plan for demonstrating bioequivalence (BE) with a potential new formulation.

The meeting was originally scheduled for September 22, 2009. On September 10, 2009, due to unforeseen circumstances, FDA rescheduled the meeting for September 28, 2009.

Medivation's objectives and expected outcomes of the meeting are to reach agreement with FDA on the CMC plan and data package for the approval of MDV3100 in castration-resistant prostate cancer previously treated with docetaxel-based chemotherapy. Specifically:

- Acceptability and control of starting materials;
- Acceptability of the proposed plan to use a rupture test in lieu of dissolution testing for a liquid-filled capsule in which API is fully dissolved;
- Acceptability of the use of in vitro testing to demonstrate comparability of changes to the current caprylocaproyl polyoxylglycerides (b) (4) based capsule formulation;
- Acceptability of the use of (b) (4) in the commercial presentation of MDV3100; and
- Acceptability of the proposed plan for demonstrating BE with a potential new formulation.

The corresponding briefing package that provided additional information on these discussion topics and questions was sent on August 20, 2007, (received August 21, 2007). The preliminary responses to the questions contained in the meeting briefing package were archived and shared with Medivation on September 25, 2009, to promote an efficient

discussion at the face to face meeting scheduled for September 28, 2009. The record of that meeting is below.

2.0 DISCUSSION

2.1 CMC

2.1.1 Briefing Package Question 1: Does the Agency agree with the proposed designated regulatory starting materials for the synthesis of MDV3100 and that their control strategies are appropriate?

FDA Response: No. Sufficient information is not provided to make a definitive assessment.

- Establish reference standards of known purity for each regulatory starting material. Assay the lot of starting materials against the reference standard to determine the content.
- Specifications for (b)(4) will need to be seen. Provide impurity (b)(4) to justify level of impurities in each proposed starting material.
- The need for (b)(4) specification in the drug substance will be evaluated in the NDA and will be based on robustness of the data (b)(4) and process capability.
- The approach to control genotoxic impurities at (b)(4) will be evaluated during NDA submission.
- Provide highlights of the supplier audit program to verify that the supplier meets the agreement obligations on an ongoing basis. Also, describe how manufacturing changes in the starting material that may have an impact on the quality of starting material will be handled in the quality systems

Meeting Discussion: Medivation acknowledged receipt of FDA's preliminary response. No further discussion occurred at the meeting.

2.1.2 Briefing Package Question 2: Does the Agency agree that a rupture test can be used in lieu of dissolution testing for the release of a liquid-filled capsule in which API is fully dissolved?

FDA Response: No. The substitution for dissolution with a rupture test is only possible for highly soluble drugs with rapid dissolution.

Meeting Discussion: Medivation acknowledged receipt of FDA's preliminary response. FDA recommended that Medivation submit sufficient scientific justification to support the proposal for use of rupture testing in lieu of dissolution testing and to support the proposed acceptance criterion. FDA also recommended that Medivation's proposed test be able to differentiate between in and out of specification batches.

- 2.1.3 Briefing Package Question 3: Does the Agency agree that the comparability of the following changes to the current caprylocaproyl polyoxylglycerides (b) (4) based capsule formulation can be demonstrated by in vitro testing as described in the product specification:
- Replacement of a (b) (4)
 - Changes in inactive ingredients that are not expected to have an impact on formulation quality and product performance?

FDA Response: The approach appears to be acceptable, provided that the following items are adequately addressed in your approach:

- Perform dissolution testing as indicated in the response to question 2, and use the resulting data for comparative purposes.
- In the background description provided for question 5, we noticed that the formulation may be further changed from a soft gelatin capsule. Your formulation revision strategy is unclear. Provide details on your proposed product development goals.
- Generate BA/BE information for the formulation used in the pivotal clinical study. If a formulation is going to be used in pivotal clinical studies, you may directly characterize its bioavailability and there will be no need to bridge with other formulations.

Meeting Discussion: Medivation acknowledged receipt of FDA's preliminary response. No further discussion occurred at the meeting.

- 2.1.4 Briefing Package Question 4: Does the Agency agree that (b) (4) is an acceptable solvent for the commercial presentation of MDV3100?

FDA Response: While (b) (4) is acceptable as an excipient, the overall safety of the MDV3100 product will be determined at the time of NDA review.

Meeting Discussion: Medivation acknowledged receipt of FDA's preliminary response. No further discussion occurred at the meeting.

2.2 CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

- 2.2.1 Briefing Package Question 5: Does the Agency agree with the proposed plan for demonstrating BE with a potential new formulation, including the following elements:
- The use of a single-dose, parallel design for assessing bioavailability (BA)/BE?
 - The potential of not having molar dose equivalents between the formulations?
 - Using area under the curve (AUC), and not maximum plasma concentrations (C_{max}), to establish BA/BE?

FDA Response: No. We cannot agree to the use of healthy volunteers in your BA/BE study at this time given that no genotoxicity information about your drug or the doses you propose to use in healthy volunteers are provided in the current submission. Please provide for review, adequate pharmacology and toxicology information to support the use of healthy volunteers. In addition, a final BA/BE protocol with doses along with your PK modeling plan used to select these doses should be submitted for review by OODP. A formal meeting may be the preferred way to facilitate the review of this information prior to final protocol submission.

Lastly, BA/BE should rely on both AUC and C_{max} to assess systemic exposure. Please refer to our guidance documents at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070124.pdf>

Meeting Discussion: Medivation acknowledged receipt of FDA's preliminary response. FDA clarified that because previously submitted genotoxicity studies for MDV-3100 were negative for genotoxicity, Medivation may include healthy volunteers for the assessment of bioavailability (BA) and bioequivalence (BE). The dose to be used is a review issue, to be determined and evaluated by DDOP clinical and clinical pharmacology review teams.

FDA recommended that Medivation submit their proposed BA protocol for evaluation and written feedback. FDA recommended that Medivation label their cover letter as a "Request for Written Feedback RE: Bioavailability (BA) Protocol" and contact the DDOP Regulatory Health Project Manager (RPM) directly to facilitate the review in a timely manner. FDA also committed to a teleconference, if necessary, to discuss the BA protocol.

When the BA evaluation is complete, the FDA recommended that Medivation submit a meeting request to discuss their proposed BE plans. The subsequent meeting package should include results from their BA studies and sufficient scientific justification to support their proposed BE protocol. FDA also recommended that [REDACTED] ^{(b)(4)} be included, where applicable, in future submissions. FDA reiterated that BE should rely on both AUC and C_{max} to assess systemic exposure.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no other issues that were identified during the review of the briefing package or during the meeting 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 Discussion section (2.0) above.

5.0 CONCURRENCE:

/See appended electronic signature page/

Scott N. Goldie, Ph.D.
Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

/See appended electronic signature page/

Sarah Pope Miksinski, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment III & Manufacturing Science
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

IND-74563

GI-1

MEDIVATION INC

MDV3100

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/s/

SCOTT N GOLDIE
10/15/2009

Sarah Pope Miksinski
10/15/2009



**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Oncology Drug Products
Division of Drug Oncology Products**

FACSIMILE TRANSMITTAL SHEET

DATE: March 17, 2009

To: Daven M. Mody, Pharm.D., M.B.A. Associate Director, Regulatory Affairs	From: Alberta E. Davis-Warren Regulatory Health Project Manager Alberta.Davis-Warren@fda.hhs.gov
Company: Medivation, Inc.	Division of Drug Oncology Products
Fax number: daven.mody@medivation.com	Fax number: 301-796-9845
Phone number: 415-829-4154	Phone number: 301-796-3908

Subject: Preliminary responses for March 23, 2009

Total no. of pages including cover: 16

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Dear Dr. Mody,

The attached consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for between you and the Division of Drug Oncology Products. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, important issues, and any action items discussed during the 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. If you choose to cancel the meeting, this document will represent the official record. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or change the format of the meeting (e.g., from face to face to telecon). 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. Note that if there are any major changes to your development plan/the purpose of the meeting/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 to discuss the possibility of including these for discussion at the meeting.

PRELIMINARY RESPONSES for March 23, 2009 End of Phase II meeting with Medivation, Inc. 2 – 3 PM (IND 74, 563 MDV3100)

- 1) Does the Agency agree that the current clinical and nonclinical data package is sufficient to support initiation of the proposed Phase 3 study?**

The clinical and nonclinical data to support the proposed Phase 3 study are presented in Sections 9 and 10.

FDA response: See responses below.

CLINICAL

- 2) Is the design of the proposed Phase 3 study (CRPC2, Appendix A) acceptable to the Agency as an adequate and well-controlled evaluation of the safety and efficacy of MDV3100?**

Specifically, Medivation seeks agreement on the following elements of the protocol:

- a. Does the Agency agree with the proposed dose and regimen?**

Patients enrolled into the proposed Phase 3 trial will receive MDV3100 once daily (QD) at a dose of 240 mg/day or placebo. The dose of 240 mg/day was defined as the maximum tolerated dose in the Phase 1-2 Study (S-3100-1-01). In addition, this dose showed preliminary efficacy, including prostate-specific antigen (PSA) reductions (58% of post-chemotherapy patients demonstrated a 50% decline in PSA levels), radiographic partial responses and stabilization, stabilization of bone disease, as well as effects on circulating tumor cells (CTC; maintenance of favorable counts or conversion from unfavorable to favorable counts).

FDA response: Yes.

- b. Does the Agency agree with the proposed inclusion/exclusion criteria, including the following:**

- 1. Does the Agency agree that the inclusion/exclusion criteria appropriately define CRPC previously treated with docetaxel-based chemotherapy as stated in the proposed indication for labeling?**

FDA response: Yes.

The inclusion/exclusion criteria can be found in the CRPC2 protocol in Appendix A.

2. Does the Agency agree that the Prior Prostate Cancer Treatment—Chemotherapy Case Report Form (CRF) appropriately captures the clinical data needed to define the proposed patient population?

The CRF is located in Appendix D.

FDA response: Yes.

c. Does the Agency agree that placebo is the appropriate control for the proposed patient population?

MDV3100 at a dose of 240 mg/day will be compared to placebo with a 2:1 randomization (MDV3100:placebo). A placebo-controlled study is considered ethical because there is no approved second-line therapy following progression on docetaxel-based chemotherapy for patients with CRPC. All patients in the study must have been treated with at least one docetaxel-based regimen. In addition, all patients may receive prednisone/prednisolone at doses of up to 10 mg/day while on study.

FDA response: Yes.

d. Does the Agency agree with the proposed pharmacokinetic (PK) sampling plan?

MDV3100 has a long half-life ($t_{1/2}$ of approximately one week) relative to the QD dosing interval; therefore, a multiple-trough sampling design will be utilized in accordance with the Food and Drug Administration (FDA) Guidance for Industry “Population Pharmacokinetics” (February 1999). Briefly, a pre-dose PK sample will be taken at the Day 1 (Baseline) visit prior to initiation of study drug treatment and trough PK samples will be taken on Days 8, 29, 57, 85, and every 12 weeks thereafter. Compliance with the two doses prior to PK sampling will be documented, including dosing times. These data will be combined with data from other studies to build a population PK model.

FDA response: Your approach appears acceptable. We recommend that all treated patients participate in the sampling plan.

e. Does the Agency agree that the statistical analysis plan for the proposed Phase 3 study is acceptable, specifically:

1. Does the Agency agree with the proposed randomization stratification variables?

In the proposed Phase 3 study, the stratification variables include Eastern Cooperative Oncology Group (ECOG) performance scores and the pain

burden score from question #3 from the Brief Pain Inventory (Short Form; Protocol appendices in Appendix A). Strata for the ECOG performance scores will include scores of 0 to 1 vs. 2, and the pain scores will be divided into those < 4 and those ≥ 4 . Both stratification variables have been shown to be prognostic factors for overall survival.

FDA response: Yes.

2. Does the Agency agree that demonstrating a statistically significant difference ($\alpha = 0.05$, 2-tail) in overall survival is sufficient to establish efficacy in the proposed Phase 3 study?

The primary endpoint is overall survival. Survival is defined as time from randomization to death due to any cause. Patients who do not reach the endpoint will be right censored at their last assessment. A log rank test stratified by baseline ECOG performance score and pain score will be used to compare the MDV3100-treated and the placebo groups. This comparison will be two-sided test at the 0.05 level of significance. Kaplan-Meier median times to survival and their 95% confidence intervals, as well as survival curves will be used for statistical description. The study is powered to detect a 25% increase in overall survival (assumed 12 months for placebo and 15 months for MDV3100-treated patients) and assumes that 7% of patients will be lost to follow-up.

FDA response:

Yes. There is a discrepancy in the sample size: N=1,170 in the synopsis and 1,158 in the protocol. We recommend that you calculate the sample size and plan the final efficacy analysis using the number of events since the power calculation is based on the number of events.

3. Does the Agency agree with the proposed secondary efficacy outcome measures?

FDA response: If you plan to include some secondary endpoints in the label, your current plan of testing those endpoints at a level of 0.05 separately is not acceptable. A statistical plan controlling overall alpha at 0.05 for those secondary endpoints needs to be pre-specified providing those secondary endpoints are agreed by the Agency.

4. The proposed secondary outcome measures for the Phase 3 study are:

- **To determine the benefit of MDV3100 as compared to placebo as assessed by progression-free survival;**

Progression-free survival is defined as time to the earliest objective evidence of progression (either radiographic or skeletal-related event) or death due to any cause. Patients will be assessed for objective

disease progression at regularly scheduled visits. The consensus guidelines of the Prostate Cancer Clinical Trials Working Group 2 have been taken into consideration for the determination of disease progression. Radiographic disease progression is defined by RECIST 1.1 (see Protocol appendices in Appendix A) for soft tissue disease, or the appearance of two or more new bone lesions on bone scan. Progression at the first scheduled reassessment at Week 13 requires a confirmatory scan 6 or more weeks later. A skeletal-related event is defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain. Patients who do not reach the endpoint will be right censored at their last assessment. A log rank test stratified by baseline ECOG performance score and pain score will be used to compare the MDV3100-treated and the placebo groups. This comparison will be a two-sided test at the 0.05 level of significance. Kaplan-Meier median progression-free survival times and their 95% confidence intervals as well as progression-free survival curves will be used for statistical description.

FDA response: Yes. See statistical comments above. *For any secondary endpoints to be included in the label you must show statistical superiority for the primary endpoint.*

To determine the benefit of MDV3100 as compared to placebo as assessed by CTC conversion rate;

CTC conversion will be assessed for patients with baseline CTC counts of $\geq 5/7.5$ mL of blood. A conversion is defined as a decline in the CTC count to $< 5/7.5$ mL of blood. For analysis, the Week 13 value will be used; if the Week 13 value is missing then the Week 5 value will be used. Conversion rates between the MDV3100-treated and placebo groups will be compared using a two-sided stratified Cochran-Mantel-Haenszel mean score test at the 0.05 level. Baseline ECOG performance score and pain score will be used as stratification factors.

FDA response: FDA will consider reduction in CTC as an exploratory endpoint. What laboratories will determine CTCs and by what methodology?

- **To determine the benefit of MDV3100 as compared to placebo as assessed by radiographic progression;**

Time to radiographic progression is defined as time to the earliest radiographic evidence of progression. Patients will be assessed for radiographic disease progression at regularly scheduled visits. The consensus guidelines of the Prostate Cancer Clinical Trials Working Group 2 have been taken into consideration for the determination of disease progression. Radiographic disease progression is defined by

RECIST 1.1 (see Protocol appendices in Appendix A) for soft tissue disease, or the appearance of two or more new bone lesions on bone scan. Progression at the first scheduled reassessment at Week 13 requires a confirmatory scan 6 or more weeks later. Patients who do not reach the endpoint will be right censored at their last assessment. A log rank test stratified by baseline ECOG performance status and pain score will be used to compare the MDV3100-treated and placebo groups. This comparison will be a two-sided test at the 0.05 level of significance. Kaplan-Meier median time to radiographic progression and their 95% confidence intervals as well as curves will be used for statistical description.

FDA response: Yes. See statistical comments above.

- **To determine the benefit of MDV3100 as compared to placebo as assessed by time to first skeletal related event;**

Patients will be assessed for skeletal-related events at regularly scheduled visits. A skeletal-related event is defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain. Patients who do not reach the endpoint will be right censored at their last assessment.

FDA response: Yes. See statistical comments above.

- **To determine the benefit of MDV3100 as compared to placebo as assessed by pain palliation;**

Pain palliation at Week 13 will be determined for the proportion of men with baseline bone metastasis(es) who have baseline pain attributable to the metastasis(es). Patients will be asked to complete a diary for the seven days preceding their Day 1 and their Week 13 visits. For each of those days, patients will self-report their “worst pain” over the past 24 hours and their analgesic use. To be evaluable for this analysis, a patient must provide answers to above for a minimum of 4 out of 7 days in the baseline run-in period. In addition, a patient must have stable baseline pain (no greater than a 2-point variation in daily pain scores) and analgesic use (no greater than 30% variation in analgesic use), and the average pain score during the baseline run-in period must be ≥ 4 for a patient to be evaluable for the analysis. Palliation is defined as $\geq 30\%$ reduction in average pain score at Week 13 compared to baseline without a $\geq 30\%$ increase in analgesic use.

FDA response: The pain palliation endpoint is problematic. Only a portion of the trial population, not the ITT population, will meet the criteria for this endpoint. Thus it will be a sub-group analysis. In addition, we discourage the use of patient reported outcome

measures unless the assessment instruments are validated and can be reliably used. Please refer to the guidance entitled “Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims” (Feb. 2006) at www.fda.gov/cder/guidance/5460dft.pdf .

- **To determine the benefit of MDV3100 as compared to placebo as assessed by time to PSA progression;**

PSA progression will be assessed for each patient in the study. For patients with PSA declines at Week 13, the PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the nadir is documented, which is confirmed by a second value obtained 3 or more weeks later. For patients with no PSA declines at Week 13, PSA progression date is defined as the date that a $\geq 25\%$ increase and an absolute increase of ≥ 2 ng/mL above the baseline is documented, which is confirmed by a second value 3 or more weeks later. Time to PSA progression is defined as time from randomization to PSA progression. Patients who do not reach the endpoint will be right censored at their last assessment. A log rank test stratified by baseline ECOG performance score and pain score will be used to compare the MDV3100-treated and the placebo groups. This comparison will be a two-sided test at the 0.05 level of significance. Kaplan-Meier median times to PSA progression and their 95% confidence intervals as well as Kaplan-Meier curves will be used for statistical description.

FDA response: Yes. See statistical comments above.

- **To determine the safety of treatment with MDV3100 as compared to placebo;**

Safety will be assessed through summaries of adverse events, the frequency of discontinuation of MDV3100 treatment due to adverse events, laboratory evaluations, and ECGs. Safety analyses will include all randomized patients who receive at least one dose of study drug (safety population). For all safety analyses descriptive statistics will be used rather than inferential statistics.

FDA response: Yes.

- **To determine the effects of MDV3100 on electrocardiographic (ECG) changes as compared to placebo;**

Because it is not ethical to treat healthy volunteers with a potent anti-androgen such as MDV3100 in a thorough QT/QTc study, intensive ECG monitoring will be performed in the proposed Phase 3 study. A formal QT/QTc analysis will be performed by the central ECG laboratory. Change from baseline in the QT interval corrected by the

Fridericia correction formula (QTcF) for both MDV3100-treated and placebo groups will be compared by the ECG laboratory using triplicate ECGs obtained on Days 1 (pre-treatment), 8, 29, and 57. A PK/pharmacodynamic (PD) analysis will explore the relationship between the change from baseline in QTcF and plasma concentrations of MDV3100.

FDA response:

Your ECG evaluation plan incorporated in Study CRPC2 is acceptable. We have the following general comments about the collection and analysis of your ECG data.

- 1. We recommend you incorporate the following elements into your assessment of the ECGs recorded during this study:**
 - a. Use of a central ECG laboratory employing a limited number of skilled readers, to control variability in interpretation,**
 - b. Blinding of ECG readers to treatment, time, and day (i.e., Day -1; Day 1) identifiers.**
 - c. Review of all ECGs from a particular subject by a single reader on one day, and**
 - d. Pre-specify the lead for interval measurements.**
 - e. Baseline and on-treatment ECGs should be based on the same lead.**
- 2. We are also interested in the effects of MDV3100 on other ECG intervals and changes in waveform morphology. Please submit PR and QRS interval data with the study report and descriptive waveform morphology changes.**
- 3. In addition to the analyses you proposed in section 9.6.2.2 of your briefing document, we recommend analyzing the ECG data by treatment as follows:**
 - a. Mean absolute and baseline-adjusted HR, RR, QT, QTcF, PR, and QRS for each assessment timepoint, including two-sided 90% confidence intervals, as well as mean maximum absolute and baseline-adjusted values for each parameter**
 - b. The number and percentage of individuals with absolute QT/QTc values > 450 ms, > 480 ms, > 500 ms, number and percentage of individuals with changes from baseline > 30 ms and > 60 ms**
 - c. Number and percentage of individuals with abnormal ECG findings.**

- **To establish the covariates that may affect variability in PK parameters;**

The impact of patient covariates will be evaluated with a population PK analysis in order to identify underlying factors responsible for the variability of PK parameters and to identify sub-populations.

FDA response: Yes. Your plan to use population PK appears acceptable.

- **To develop a PK model linking MDV3100 exposure with efficacy and safety outcomes.**

Every effort will be made to develop a model that links MDV3100 exposure (e.g., the minimum or trough plasma concentration [C_{min}]) with the outcomes measure, as well as with key adverse events.

FDA response: Yes.

- 3) **Does the Agency agree that if the proposed Phase 3 study meets its primary efficacy endpoint, then the proposed Phase 3 study along with the supporting data provided from Study S-3100-1-01 will be adequate to support the approval of MDV3100 for CRPC previously treated with docetaxel-based chemotherapy?"**

Medivation intends to submit a New Drug Application (NDA) with one adequate and well-controlled study (proposed Phase 3 study CRPC2), the supporting safety and efficacy data from the current Phase 1-2 study (S-3100-1-01), and a clinical pharmacology package. The primary objective of the Phase 3 study is to determine the benefit of MDV3100 as compared to placebo as assessed by overall survival.

FDA response: Approval based on a single randomized trial will depend on the quality of the trial data, the degree of OS superiority, and on safety data. The results of the trial should be sufficiently convincing, so that a confirmatory trial would be difficult to perform.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

- 4) **Does the Agency agree to allow for single-dose PK studies in healthy male volunteers?**

If a bioequivalence study is required for a formulation change, Medivation proposes conducting a single-dose study in healthy volunteers greater than age 55 who have undergone vasectomy or who agree to participation after being fully informed of the potential risk of decreased fertility. Other single-dose studies may also best be performed in healthy male volunteers. The highest dose proposed for such single-dose studies would be the proposed Phase 3 dose of 240 mg. Based upon existing clinical and nonclinical safety data, a single 240 mg dose of MDV3100 would not be expected to

result in any serious adverse events. Dosing would be conducted in a Phase 1 unit to mitigate safety concerns. Subjects would be informed of the anti-androgen effects that are expected to transiently decrease libido, erectile function, spermatogenesis, and which may result in fatigue and muscle weakness. Because a more prolonged effect on spermatogenesis cannot be excluded, men will not be enrolled unless they are > 55 years of age and confirm they are no longer interested in reproduction.

FDA response: No. Safety pharmacology should be evaluated prior to human exposure in healthy volunteers. This includes the assessment of effects on vital functions, such as cardiovascular, central nervous, and respiratory systems (per ICH M3).

5) Does the Agency agree that the assessment of clinical drug-drug interactions within the framework of the Phase 3 study is acceptable?

The potential for MDV3100 to affect the PK of other drugs and potential for other drugs to affect the PK of MDV3100 will be assessed through in vitro studies and population PK modeling of the Phase 3 data (Figure 9.6.3.4-1). The in vitro studies will be conducted in accordance with the FDA Draft Guidance for Industry “Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro” (September 2006) and will include assessments of cytochrome P450 (CYP) inhibition and induction, CYP reaction phenotyping, and P-gp substrate and inhibitor. In addition, population PK modeling will be used to evaluate potential differences in MDV3100 exposure (and metabolites, as appropriate) among population subgroups based on intrinsic and extrinsic factors, including concomitant medications, which will be classified by enzyme and/or transporter inhibition/induction properties.

FDA response: No. It is unlikely that a population PK analysis alone could be used to prove the absence of drug-drug interactions unless you can prove a priori that a significant number of patients enrolled in your study will be co-administered similar CYP450 inhibitors or inducers. This hypothesis is further complicated by the fact that from the information provided, it is not known which CYP450 enzymes metabolize your drug.

The in-vitro screens for your drug to act as a substrate for CYP enzymes need to be completed. If these in vitro studies suggest that your drug is a substrate of a CYP enzyme(s), dedicated in vivo studies with strong inhibitors/inducers will be needed. Please see the Drug-Drug Interaction website and relevant guidances at <http://www.fda.gov/cder/drug/drugInteractions/default.htm>

6) Does the Agency agree with the proposed plan for investigating comparability of a potential new formulation?

The current dosage form is a hard gelatin capsule containing a solution of MDV3100 in (b) (4) Medivation is considering alternate formulations for the marketed product which may be introduced during Phase 3.

If a new formulation is developed that requires a bioequivalence study, then the following strategy will be used to establish bioequivalence. PK studies will be conducted in dogs using the human dosage forms (new vs. current). If the formulation appears to have PK comparability in dogs, then it will be considered for testing in humans. Normal male volunteers > 55 years of age will receive a single dose of MDV3100 in a randomized, parallel-group trial design (new vs. current formulation). If the ratio of adjusted geometric means for area under the curve (AUC_{∞}) falls wholly within the range of 80% to 125%, then no further testing will be conducted, and the new formulation may replace the current formulation in Phase 3 or be introduced as the commercial formulation.

If the ratio of adjusted geometric means for AUC_{∞} does not fall wholly within the range of 80% to 125%, then PK modeling will be used to select a dose for the new formulation that results in a steady-state pre-dose minimum plasma concentration C_{\min} that is equivalent to the current formulation at 240 mg/day. This new formulation and dose will be tested in a separate randomized, open-label crossover PK and tolerability study in CRPC patients. When the bioequivalence testing is complete, patients in the bioequivalence trial will be allowed to continue receiving open-label MDV3100 until marketing approval. The patients will receive the two treatments (current Phase 3 formulation at 240 mg/day or new formulation and dose) in a randomized sequence (8 weeks per sequence). Pre-dose C_{\min} samples will be collected once per week during steady state (Weeks 5–8 of each sequence). Dose adjustments will be considered, as needed, in these patients to achieve a steady-state C_{\min} that is equivalent to the current formulation at 240 mg/day. The new formulation and dose may replace the current formulation during Phase 3 or be introduced as the commercial formulation.

FDA response: No. *Your approach is highly problematic. Please see responses to questions 4 and 5. Your plan will be a review issue as it is not known if C_{\min} is associated with response. If your formulation is significantly different, we suggest you discuss your bridging plans with the agency prior to initiating any studies.*

7) Does the Agency agree with the proposal for assessing metabolism in humans?

MDV3100 has a long $t_{1/2}$ (approximately one week). Therefore, a traditional single-dose ^{14}C -MDV3100 study would require confinement for 6 weeks or longer to ensure adequate recovery (i.e., $\geq 90\%$) of the radioactive dose in excreta.

In lieu of a ^{14}C -MDV3100 study, Medivation proposes to perform single-dose rat and dog ^{14}C -MDV3100 mass balance and biotransformation studies to elucidate the metabolic pathways. The precise identity of prominent metabolites in the nonclinical species would be confirmed through synthesis of reference standards and nuclear magnetic resonance (NMR) analyses. A human mass balance and biotransformation study would then be conducted with unlabeled MDV3100 in CRPC patients. The patients would receive MDV3100 at 240 mg/day to steady state. At steady-state, the

patients would be confined for three days, and plasma, urine, and feces would be collected at pre-specified times and intervals while dosing continues. When the in-patient study is complete, these patients will be allowed to continue receiving open-label MDV3100 until marketing approval.

Using metabolite information and reference standards derived from the ¹⁴C-MDV3100 studies in rats and dogs; the human plasma, urine, and feces samples would be analyzed using full-scan liquid chromatography-mass spectrometry (LC/MS) and Multiple Reaction Monitoring/Information Dependent Acquisition/Enhanced Product Ion (MRM/IDA/EPI) to determine the MDV3100 metabolite composition. Any prominent metabolite that was not detected in the nonclinical species would be confirmed through synthesis of reference standard and NMR analysis. Major metabolites would be defined as per FDA Draft Guidance for Industry "Safety Testing of Drug Metabolites" (June 2005).

FDA response: Your plan to use un-labeled drug is acceptable assuming it provides the relevant information to address the elimination of your drug. Based on elimination pathways, the effect of hepatic and/or renal impairment on the PK of your drug will need to be addressed.

REGULATORY

- 8) Does the Agency agree that the proposed clinical, biopharmaceutics, and nonclinical data package is adequate to support marketing approval of MDV3100?**

The clinical development plan to support marketing approval of MDV3100 is fully described in Section 9.6.

FDA response: No. Please see responses to questions 4, 5, and 6 above.

- 9) Does the Agency agree that the proposed PK data package is sufficient to support the marketing application of MDV3100?**

The PK data package will include data from the Phase 1-2 safety, tolerability and PK study (S-3100-1-01), from the proposed Phase 3 study (CRPC2), and from any additional biopharmaceutics/Phase 1 studies that are performed. The impact of covariates will be evaluated with a population PK analysis in order to identify underlying factors responsible for the variability of MDV3100 plasma concentrations and to identify sub-populations. Every effort will be made to develop a model that links MDV3100 exposure with the efficacy outcome measures, as well as with key adverse events. Also, in the proposed Phase 3 study, a PK/PD analysis will explore the relationship between the change from baseline in the QTcF and plasma concentrations of MDV3100.

FDA response: No. *We continue to be concerned about your plan to change formulation during your clinical development.* Please see responses to questions 4, 5, 6 and 7.

10) Does the Agency agree with the proposed content and structure of the safety database to support the proposed indication? In particular, is the extent of patient exposure at the proposed clinical dose acceptable to support marketing approval of MDV3100?

The safety database in support of the marketing application for MDV3100 will include the Phase 3 study and the supporting Phase 1-2 study with a total of up to 920 patients with CRPC dosed with MDV3100, with at least 800 receiving the proposed commercial dose (240 mg).

FDA response: See response to question 8 above.

11) Does the Agency concur that a pediatric waiver will be granted?

Castration-resistant prostate cancer does not occur in a pediatric population nor is it expected that MDV3100 will be beneficial for any pediatric indication; therefore, Medivation requests a full waiver of the Pediatric Requirement per section 505B(a)(4)(A)(i) of the Pediatric Research Equity Act.

FDA response: It is likely that a pediatric exemption will be granted. Please submit a request for a full waiver for pediatric studies for the prostate cancer indication with the NDA submission. The waiver must be reviewed by PeRC.

FINAL PROTOCOLS:

If you plan on submitting a request for Special Protocol Assessment, please refer to the May 2002 "*Guidance for Industry – Special Protocol Assessment*" (posted on the Internet 5//2002) and submit final protocol(s) to the IND for FDA review as a REQUEST FOR SPECIAL PROTOCOL ASSESSMENT (SPA) in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical) and include a reference to this EOP2 meeting. A sample case report form (CRF), the statistical analysis plan, the independent radiologic review charter (if applicable), and the independent data monitoring committee charter should be included. 10 desk copies of this SPA should be submitted directly to the project manager.

Since we may use our ODAC consultant for this protocol review, and their clearance takes several weeks, we would appreciate any lead-in time you could give us as to when the SPA will be submitted. You should also be aware that our using a consultant extends the due date on these SPAs until 45 days after we receive the consultant's written comments.

SUBMISSION OF CLINICAL TRIALS TO NIH PUBLIC ACCESS DATA BASE:

Section 113 of the Food and Drug Modernization Act (Modernization Act) amends 42 U.S.C. 282 and requires the establishment of a public resource for information on studies of drugs for serious or life-threatening diseases conducted under FDA's Investigational New Drug (IND)

regulations (21 CFR part 312). The National Institutes of Health (NIH) through its National Library of Medicine (NLM), and with input from the FDA and others, developed the Clinical Trials Data Bank, as required by the Modernization Act.

FDA has made available a final guidance to implement Section 113 of the Modernization Act. The guidance describes the type of information to submit and how to submit information to the Clinical Trials Data Bank. The guidance entitled "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions" was made available on March 18, 2002. It is accessible through the Internet at <http://www.fda.gov/cder/guidance/4856fnl.htm>

The clinical trial information for the Clinical Trials Data Bank should include the purpose of the trial, the patient eligibility criteria, the location of the trial sites and, a contact for patients wanting to enroll in the trial. The data fields and their definitions are available in the Protocol Registration System at <http://prsinfo.clinicaltrials.gov/>. Protocols listed in this system by will be made available to the public on the Internet at <http://clinicaltrials.gov>.

If you have any questions, contact Theresa Toigo at (301) 827-4460 or 113trials@oc.fda.gov.

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>.

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.

PEDIATRIC EXCLUSIVITY:

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written

Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

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 Other	Black	Asian

**FOOD AND DRUG ADMINISTRATION
OFFICE OF ONCOLOGY DRUG PRODUCTS**



DIVISION OF DRUG ONCOLOGY PRODUCTS

**HF-D-150, 5901-B Ammendale Road
Beltsville, MD 20705-1266**

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PHONE: (301) 796-1434 FAX: (301) 796-9845

TO: Lynn Seely, M.D.
Fax: 415 543-3411

FROM: Dotti Pease, Project Manager
Phone: (301) 796-1434

Total number of pages, including cover sheet 4

Date: 7-6-06

COMMENTS: Attached are the draft FDA responses to your questions re: MDV3100. You have the option of canceling our telecon of July 10 if these answers are clear to you. 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. If you choose to have the telecon, we will be prepared to clarify any questions you have regarding our responses. Please note that if there are any major changes to your development plan/the purpose of the meeting/to the questions based on our responses herein, we may not be prepared to discuss or reach agreement on such changes at the meeting. Any modifications to the development plan or additional questions, for which you would like FDA feedback, should be submitted as a new meeting request. Please let me know as soon as possible whether you are canceling 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 to discuss the possibility of including these for discussion at the meeting. 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.

Also, note that your pre-IND has been assigned the number 74,563 - please reference this number when submitting your IND as this will be your IND number also. Finally, please include an extra copy of the first volume of your IND including the clinical protocol, when you submit the IND, for our Clinical Pharmacology and Biopharmaceutics reviewers

Thanks

1. Does the Agency agree that the proposed 28-day duration for toxicology studies in rat and dog are sufficient to allow the initiation of the proposed Phase 1 clinical protocol studying MDV3100 in patients with hormone-refractory prostate cancer?

FDA – Yes, the 28-day study in rodents and non-rodents will support initiation of the proposed Phase 1 study in patients with HRPC.

You indicate on p. 29 of your submission that Medivation intends to file draft reports of the dose range-finding and 28-day studies with the IND. Please note that these draft reports should be complete study reports, containing complete data sets, which may be unaudited for quality assurance.

You have proposed conducting additional 3-month studies in rats and dogs to support your 3-month Phase 2 study. While not necessary prior to Phase 2, we would expect the 3-month studies to be complete toxicological evaluations with histopathology following the 3-month dosing period, as well as the 28-day recovery.

2. Does the Agency agree that the proposed 28-day toxicology studies employing the maximum feasible oral dose level will be sufficient to allow the proposed clinical trial to proceed regardless of whether a maximum tolerable dose of frank toxicity is defined?

FDA – Yes, if dosing BID, or change in formulation do not assist in defining the MTD in the 28-day toxicology studies due to saturation of absorption, the maximum feasible oral dose level can provide the basis for the start dose.

3. Does the Agency agree that patients will be eligible to continue treatment in the absence of both disease progression and toxicity at the Day 28 visit?

FDA – Yes, depending on review of the IND submission.

4. In the proposed Phase 1 clinical protocol, dose-escalation will proceed until either: 1) maximum-tolerated dose (MTD) is determined, or 2) peak plasma concentrations reach a plateau despite dose escalation, or 3) the final dose specified in the protocol is completed. The final dose specified in the protocol will be a dose calculated from non-clinical studies to be greater than the anticipated therapeutic range of MDV3100. Does the Agency agree that these criteria will be acceptable to define the doses for the Phase 2 study?

FDA – These criteria will likely be satisfactory, depending on review of the pre-clinical findings, including toxicology and PK.

5. Does the Agency agree that dose-escalation to the next cohort may begin if there is no dose-limiting toxicity in the first three patients by the Day 14 visit?

FDA – No. We believe dose-escalation to the next cohort should not begin until the first three patients have been observed through Day 28.

6. Does the Agency agree that the proposed patient population defined by the inclusion/exclusion criteria constitutes a population of late-stage cancer patients suitable for a Phase 1 study?

FDA – You propose to study a heterogeneous population, in which patients with HRPC may have metastatic disease or only rising PSA, defined as a PSA level of at least 5 ng/ml that has risen on at least 2 successive occasions, at least 2 weeks apart. For patients with demonstrable metastatic disease, docetaxel every 3 weeks, in combination with prednisone, has been shown to have a survival advantage over mitoxantrone with prednisone. These patients do not seem to be appropriate for inclusion in a phase I trial of single agent MDV3100.

For patients with PSA only disease, we request further clarification on the proposed parameters of PSA rise that would define this portion of the proposed study population.

ADDITIONAL FDA COMMENTS:

- 1. 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.
- 2. Certificates of Analysis** should be provided for the drug substance and drug product used for manufacture of the clinical supplies.