

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208692Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 208692

SUPPL #

HFD # 150

Trade Name Cabometyx

Generic Name Cabozantinib

Applicant Name Exelixis, Inc.

Approval Date, If Known April 25, 2016

### 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) SE3

b) 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:

c) Did the applicant request exclusivity?

YES  NO

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

d) 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# 203756 (Cabozantinib) Metastatic medullary thyroid cancer

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:

1. XL 184-308, "A Phase 3, Randomized, Controlled Study of Cabozantinib (XL184) versus Everolimus in Subjects with Metastatic Renal Cell Carcinoma that has Progressed after Prior VEGFR Tyrosine Kinase Inhibitor Therapy."

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 <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>

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 <input type="checkbox"/>	NO <input checked="" type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>

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

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

1. XL 184-308, "A Phase 3, Randomized, Controlled Study of Cabozantinib (XL184) versus Everolimus in Subjects with Metastatic Renal Cell Carcinoma that has Progressed after Prior VEGFR Tyrosine Kinase Inhibitor Therapy."

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !  
!  
IND # 072596 YES  ! NO   
! Explain:

Investigation #2 !  
!  
IND # YES  ! NO   
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !  
!  
YES  ! NO   
Explain: ! Explain:

Investigation #2 !  
!  
YES  ! NO   
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study?

(Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

=====

Name of person completing form: Rajesh Venugopal  
Title: Senior Regulatory Project Manager  
Date: April 19, 2016

Name of Office/Division Director signing form: Geoffrey Kim, MD  
Title: Division Director/OHOP/DOP1

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



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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RAJESH VENUGOPAL  
04/25/2016

GEOFFREY S KIM  
04/25/2016

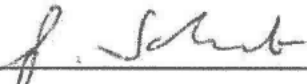


www.exelixis.com

210 E. Grand Avenue  
South San Francisco, CA 94080  
650.837.7000 main

### 3. DEBARMENT CERTIFICATION

Exelixis, 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.

  
\_\_\_\_\_  
Gisela Schwab, MD  
Executive Vice President and Chief Medical  
Officer

12-11-2015  
\_\_\_\_\_  
Date

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 208692	NDA Supplement # N/A	If NDA, Efficacy Supplement Type: N/A <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: Cabometyx Established/Proper Name: Cabozantinib Dosage Form: Tablets, 20 mg, 40 mg, and 60 mg		Applicant: Exelixis, Inc. Agent for Applicant (if applicable): N/A
RPM: Rajesh Venugopal		Division: Division of Oncology Products 1
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)  BLA Application Type: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a) Efficacy Supplement: <input type="checkbox"/> 351(k) <input type="checkbox"/> 351(a)		<p><b><u>For ALL 505(b)(2) applications, two months prior to EVERY action:</u></b></p> <ul style="list-style-type: none"> <li>Review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance.</li> <li>Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul> <p><input type="checkbox"/> No changes  <input type="checkbox"/> New patent/exclusivity (<i>notify CDER OND IO</i>)            Date of check:</p> <p><i>Note: 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.</i></p>
❖ Actions		
<ul style="list-style-type: none"> <li>Proposed action</li> <li>User Fee Goal Date is <u>June 22, 2016</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain <u>N/A</u>		<input type="checkbox"/> Received
❖ Application Characteristics <sup>3</sup>		

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, 505(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).

<sup>3</sup> 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.

Review priority:  Standard  Priority  
 Chemical classification (new NDAs only): SE3  
 (confirm chemical classification at time of approval)

- |  |   |
|--|---|
| <input checked="" type="checkbox"/> Fast Track                       | <input type="checkbox"/> Rx-to-OTC full switch    |
| <input checked="" type="checkbox"/> Rolling Review                   | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation                     | <input type="checkbox"/> Direct-to-OTC            |
| <input checked="" type="checkbox"/> Breakthrough Therapy designation |   |

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;  
 Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: [CST SharePoint](#))

- |   |  |
|---|--|
| NDA: Subpart H  | BLAs: Subpart E  |
| <input type="checkbox"/> Accelerated approval (21 CFR 314.510)    | <input type="checkbox"/> Accelerated approval (21 CFR 601.41)    |
| <input type="checkbox"/> Restricted distribution (21 CFR 314.520) | <input type="checkbox"/> Restricted distribution (21 CFR 601.42) |
| Subpart I   | Subpart H  |
| <input type="checkbox"/> Approval based on animal studies         | <input type="checkbox"/> Approval based on animal studies        |

- |   |   |
|---|---|
| <input type="checkbox"/> Submitted in response to a PMR                       | REMS: <input type="checkbox"/> MedGuide     |
| <input type="checkbox"/> Submitted in response to a PMC                       | <input type="checkbox"/> Communication Plan |
| <input type="checkbox"/> Submitted in response to a Pediatric Written Request | <input type="checkbox"/> ETASU              |
|   | <input type="checkbox"/> MedGuide w/o REMS  |
|   | <input type="checkbox"/> REMS not required  |

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (approvals only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other Burst
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)?	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
• If so, specify the type	
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<b>CONTENTS OF ACTION PACKAGE</b>	
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (approvals only)	<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 and date 4/25/16
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
<ul style="list-style-type: none"> <li>• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ 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"> <li>• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i></li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Labels <b>(full color carton and immediate-container labels)</b> <i>(write submission/communication date on upper right of first page of each submission)</i>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	Acceptable 12/21/15 12/15/15
<ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i></li> <li>• Review(s) <i>(indicate date(s))</i></li> </ul>	
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: <input checked="" type="checkbox"/> 2/5/16 DMEPA: <input checked="" type="checkbox"/> 4/4/16; 3/2/16; 3/29/16 DMPP/PLT (DRISK): <input checked="" type="checkbox"/> None OPDP: <input checked="" type="checkbox"/> 4/11/16 SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input checked="" type="checkbox"/> None Other: <input checked="" type="checkbox"/> Pt. Labeling 4.11.16
Administrative / Regulatory Documents	
❖ RPM Filing Review <sup>4</sup> /Memo of Filing Meeting <i>(indicate date of each review)</i>	2/12/16
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	<input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

<sup>4</sup> Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director’s Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC <u>3/23/16</u> If PeRC review not necessary, explain: _____</li> </ul> </li> </ul>	<p>Full Waiver</p>
<ul style="list-style-type: none"> <li>❖ Breakthrough Therapy Designation</li> </ul>	<input checked="" type="checkbox"/>
<ul style="list-style-type: none"> <li>• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)</li> </ul>	<p>Granted 8/21/15</p>
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul>	<p>8/13/15</p>
<ul style="list-style-type: none"> <li>• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) (<i>include only the completed template(s) and not the meeting minutes</i>)</li> </ul> <p>(<i>completed CDER MPC templates can be found in DARRTS as clinical reviews or on the <a href="#">MPC SharePoint Site</a></i>)</p>	<p>N/A</p>
<ul style="list-style-type: none"> <li>❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) (<i>do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include previous action letters, as these are located elsewhere in package</i>)</li> </ul>	<p>4/12/16(2); 4/11/16; 4/7/16; 4/5/16; 4/4/16; 3/30/16; 3/29/16; 3/24/16; 3/22/16; 3/15/16; 3/10/16(2); 3/8/16 (2); 3/7/16; 3/4/16; 3/3/16; 3/1/16; 2/29/16(2); 2/10/16; 2/9/16(3); 2/8/16; 1/27/16; 1/22/16(2); 1/21/16; 1/20/16; 1/13/16; 12/28/15; 11/10/15</p>
<ul style="list-style-type: none"> <li>❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)</li> </ul>	<p>Medical Policy Council meeting minutes 8/19/15</p>
<ul style="list-style-type: none"> <li>❖ Minutes of Meetings</li> </ul>	
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg 12/12/10
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg 4/19/12, 5/23/11, 5/26/09, 3/6/08,
<ul style="list-style-type: none"> <li>• Mid-cycle Communication (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> N/A 3/21/16
<ul style="list-style-type: none"> <li>• Late-cycle Meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>)</li> </ul>	<p>preNDA CMC (3/4/11)</p>

❖ Advisory Committee Meeting(s) • Date(s) of Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None N/A
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/25/16
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/20/16
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None 1 PMC 4/13/16
<b>Clinical</b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Clinical review(s) ( <i>indicate date for each review</i> )	1/20/16 (Filing); 4/15/16
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	See Medical Officer Review dated: 4/15/16
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	Proprietary Name Review (OSE/DMEPA) 12/21/15
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> N/A
❖ Risk Management	
• REMS Documents and REMS Supporting Document ( <i>indicate date(s) of submission(s)</i> )	N/A
• REMS Memo(s) and letter(s) ( <i>indicate date(s)</i> )	N/A
• 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
❖ OSI Clinical Inspection Review Summary(ies) ( <i>include copies of OSI letters to investigators</i> )	<input type="checkbox"/> None requested 3/28/16
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> No separate review
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 1/21/16 (Filing); 4/14/16
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/14/16
❖ OSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested

<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> 1/21/16 (Filing); 4/15/16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input type="checkbox"/> No carc 3/8/16
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None 3/3/16 Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary ( <i>include copies of OSI letters</i> )	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• Tertiary review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
• Secondary review (e.g., Branch Chief) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/12/2016
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 4/4/2016
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team ( <i>indicate date of each review</i> )	<input type="checkbox"/> None Microbiology 4/4/2016
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion ( <i>indicate review date</i> )( <i>all original applications and all efficacy supplements that could increase the patient population</i> )	See Quality Review 4/5/2016
<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"/> Facilities inspections ( <i>action must be taken prior to the re-evaluation date</i> ) ( <i>only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)</i> )	<input checked="" type="checkbox"/> Acceptable 2/29/2016 Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable



Day of Approval Activities	
❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> <li>• Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)</li> </ul>	<input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity ( <i>Notify CDER OND IO</i> )
<ul style="list-style-type: none"> <li>• Finalize 505(b)(2) assessment</li> </ul>	<input type="checkbox"/> Done <b>N/A</b>
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> <li>• Notify the CDER BT Program Manager</li> </ul>	<input checked="" type="checkbox"/> Done ( <i>Send email to CDER OND IO</i> )
❖ For products that need to be added to the flush list (generally opioids): <a href="#">Flush List</a> <ul style="list-style-type: none"> <li>• Notify the Division of Online Communications, Office of Communications</li> </ul>	<input type="checkbox"/> Done <b>N/A</b>
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	<input checked="" type="checkbox"/> Done
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖ Send approval email within one business day to CDER-APPROVALS	<input checked="" type="checkbox"/> Done

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/s/  
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RAJESH VENUGOPAL  
04/25/2016

## **Addendum to Form FDA 3454**

### **XL184-308 Investigator List for Financial Disclosure**

Financial disclosure information has been collected for the investigators in the XL184-308 Clinical Study Report as follows. In addition, financial disclosure information was collected for other investigative staff not listed. No financial interests have been reported.

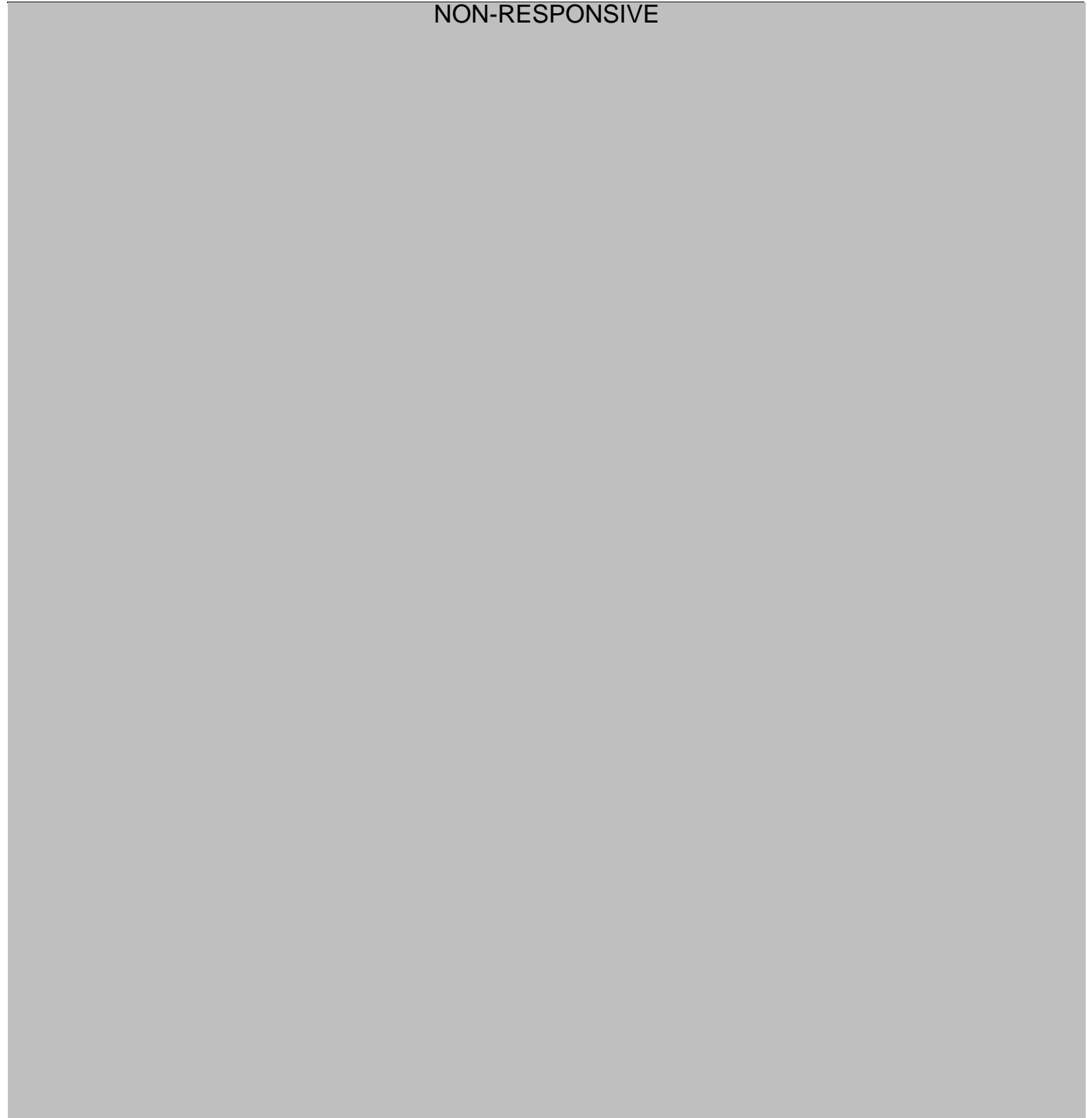
**PeRC Meeting Minutes**  
**March 23, 2016**

**PeRC Members Attending:**

Lynne Yao  
Linda Lewis  
Meshaun Payne  
Dianne Murphy  
Gerri Baer  
Peter Starke  
Gil Burckart  
Raquel Tapia  
Greg Reaman  
Dionna Green  
Robert Skip Nelson  
Gettie Audain  
Kevin Krudys  
Freda Cooner  
Barbara Buch  
Rosemary Addy  
Peter Starke

Agenda

NON-RESPONSIVE



	NDA 208692	Cabometyx (cabozantinib) Full Waiver with Agreed iPSP	DOP1	Rajesh Venugopal	Advanced Renal Cell Carcinoma
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NON-RESPONSIVE



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NON-RESPONSIVE

**Cabometyx (cabozantinib) Full Waiver with Agreed iPSP**

- Proposed Indication: Advanced Renal Cell Carcinoma
- The PeRC recognized that this product has been removed off of the EMA PIP list.
- *PeRC Recommendations:*
  - The PeRC agreed with the division to grant a full waiver in pediatric patients because the disease/condition does not exist in children.

NON-RESPONSIVE

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/s/  
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MESHAUN L PAYNE  
04/12/2016

**From:** [Venugopal, Rajesh](#)  
**To:** "[Lisa Sauer](#)"  
**Subject:** RE: NDA 208692 (Cabozantinib) - PI and PPI  
**Date:** Tuesday, April 12, 2016 3:10:39 PM

---

Hi Lisa,

The Agency proposes combination of the Grade 3-4 Adverse Reactions and laboratory abnormalities which occurred in  $\geq 5\%$  of patients. The Agency agrees to include these in descending order. "Grade 3-4 adverse reactions and laboratory abnormalities which occurred in  $\geq 5\%$  of patients were hypertension, diarrhea, fatigue, palmar-plantar erythrodysesthesia syndrome, hyponatremia, hypophosphatemia, hypomagnesemia, lymphocytes decreased, anemia, and GGT increased". If there are additional G3-4 lab abnormalities not captured in the table please add to this sentence. The statement regarding (b) (4) (b) (4) (b) (4) sentence can then be deleted from the text.

Let me know if you have additional questions.  
rajesh

---

**From:** Lisa Sauer [mailto:lsauer@exelixis.com]  
**Sent:** Tuesday, April 12, 2016 12:59 PM  
**To:** Venugopal, Rajesh  
**Subject:** RE: NDA 208692 (Cabozantinib) - PI and PPI

Dear Rajesh,

As we were double-checking a few things with the new edits, we discovered we had a few questions regarding FDA's earlier changes in Section 6.1:

The following statement was added:

Grade 3-4 adverse reactions which occurred in  $\geq 5\%$  of patients were fatigue, diarrhea, hypertension, palmar-plantar erythrodysesthesia syndrome, and anemia.

Normally, these lists are presented in descending order. If this should be in descending order of the Grade 3-4 events, we would propose this be (b) (4) included only for reference and wouldn't be included in the actual label text):

Grade 3-4 adverse reactions which occurred in  $\geq 5\%$  of patients were hypertension (b) (4), diarrhea (b) (4), fatigue (b) (4), palmar-plantar erythrodysesthesia syndrome (b) (4), and anemia (b) (4).

(b) (4)



I'd be grateful if we can get some direction on how FDA would like to revise these statements so I can include these changes in the version I send back.

Kind regards,  
Lisa

---

**From:** Venugopal, Rajesh [<mailto:Rajesh.Venugopal@fda.hhs.gov>]  
**Sent:** Tuesday, April 12, 2016 5:46 AM  
**To:** Lisa Sauer  
**Subject:** NDA 208692 (Cabozantinib) - PI and PPI

Hi Lisa,

Attached please find our edited package insert as well as for the PPI that require your attention. We made slight additions to section 5.5, 5.6, and 6.1. Let me know if you find our changes acceptable [by COB EST Thursday, April 14, 2016](#) and submit the final label. Please note that in addition to the changes made to the Patient Package Insert, the PPI is also required to be in the boxed framework that you see.

Any questions let me know.

Thanks,  
Rajesh

*Rajesh Venugopal, MPH, MBA  
Senior Regulatory Health Project Manager  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
OND/CDER/FDA  
Bldg. 22, Rm. 2171  
E-mail: [Rajesh.Venugopal@fda.hhs.gov](mailto:Rajesh.Venugopal@fda.hhs.gov)  
Phone: (301) 796-4730  
Fax: (301) 796-9845*

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RAJESH VENUGOPAL  
04/12/2016

**From:** [Venugopal, Rajesh](#)  
**To:** [Lisa Sauer \(lsauer@exelixis.com\)](mailto:Lisa.Sauer@exelixis.com)  
**Subject:** NDA 208692 (Cabozantinib) - PI and PPI  
**Date:** Tuesday, April 12, 2016 8:45:49 AM  
**Attachments:** [1-14-1-3-cabometyx-draft-redline 4.12.16.doc](#)  
[cabozantinib \(CABOMETYX\) NDA 208692 DMPP-OPDP PPI April-2016 Marked.doc](#)

---

Hi Lisa,

Attached please find our edited package insert as well as for the PPI that require your attention. We made slight additions to section 5.5, 5.6, and 6.1. Let me know if you find our changes acceptable [by COB EST Thursday, April 14, 2016](#) and submit the final label. Please note that in addition to the changes made to the Patient Package Insert, the PPI is also required to be in the boxed framework that you see.

Any questions let me know.

Thanks,  
Rajesh

*Rajesh Venugopal, MPH, MBA*  
*Senior Regulatory Health Project Manager*  
*Division of Oncology Products 1*  
*Office of Hematology and Oncology Products*  
*OND/CDER/FDA*  
*Bldg. 22, Rm. 2171*  
*E-mail: [Rajesh.Venugopal@fda.hhs.gov](mailto:Rajesh.Venugopal@fda.hhs.gov)*  
*Phone: (301) 796-4730*  
*Fax: (301) 796-9845*

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/s/  
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RAJESH VENUGOPAL  
04/12/2016

**From:** [Venugopal, Rajesh](#)  
**To:** [Lisa Sauer \(lsauer@exelixis.com\)](mailto:lsauer@exelixis.com)  
**Subject:** NDA 208692 (Cabozantinib) Post Marketing Commitment  
**Date:** Tuesday, April 05, 2016 10:48:45 AM

---

Hello Lisa,

I refer you to our January 27, 2016, filing communication letter in which we notified you of our target date of June 1, 2016, for communicating postmarketing requirements/commitments.

We have the following proposed Postmarketing Commitment for NDA 208692 CABOMETYX (Cabozantinib):

- 3063-1** Combine all available PK data from different patient populations and healthy subjects in an integrated population PK model to evaluate the potential impact of tumor types on the PK of cabozantinib.

**PMC Schedule Milestone:** Final Report  
**Submission:** MM/DD/YYYY

Please respond via email [by 3 PM Friday April 8, 2016](#), and provide me with the Final Report submission date as well as submitting a formal submission indicating the Final Report submission date for the PMC.

Thank you,  
rajesh

*Rajesh Venugopal, MPH, MBA  
Senior Regulatory Health Project Manager  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
OND/CDER/FDA  
Bldg. 22, Rm. 2171  
E-mail: [Rajesh.Venugopal@fda.hhs.gov](mailto:Rajesh.Venugopal@fda.hhs.gov)  
Phone: (301) 796-4730  
Fax: (301) 796-9845*

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/s/  
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RAJESH VENUGOPAL  
04/05/2016



NDA 208692

## INFORMATION REQUEST

Exelixis, Inc.  
Attention: Lisa Sauer  
Vice President, Regulatory Affairs  
210 East Grand Avenue  
South San Francisco, CA 94080

Dear Ms. Sauer:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cabometyx® (cabozantinib) tablets, 20mg, 40mg, 60mg.

We also refer to your December 22, 2015 submission, containing your new drug application.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

### Drug Product:

We refer to section 1.12.14 (ENVIRONMENTAL ANALYSIS) of NDA 208692. The section provides an Environmental Assessment to support a claim for categorical exclusion and cites the exclusion at 21 CFR 25.31(b). However, the claim is incomplete. The following information is required to fully support the claim of categorical exclusion:

The claim for categorical exclusion does not include the required statement that “to the applicant’s knowledge, no extraordinary circumstances exist” (21 CFR 25.15(d)). Please provide the following statement:

Exelixis, Inc. claims that approval of this NDA qualifies for a categorical exclusion in accordance with 21 CFR 25.31(b) and that, to the best of the applicant's knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment.

If you have any questions, please contact me, at (240) 402-5834. Please respond by COB April 8, 2016.

Sincerely,

**Kristine F.**  
**Leahy -S**

Digitally signed by Kristine F. Leahy -  
S  
DN: c=US, o=U.S. Government,  
ou=HHS, ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=200181  
5977, cn=Kristine F. Leahy -S  
Date: 2016.04.04 11:10:38 -04'00'

Kristine Leahy, RPh.  
Regulatory Business Process Manager  
Office of Program and Regulatory Operations  
Office of Pharmaceutical Quality  
Center for Drug Evaluation and Research



**From:** [Venugopal, Rajesh](#)  
**To:** [Lisa Sauer \(lsauer@exeljixis.com\)](mailto:lsauer@exeljixis.com)  
**Subject:** NDA 208692 (Cabozantinib) - Package Insert  
**Date:** Wednesday, March 30, 2016 12:34:42 PM  
**Attachments:** [Cabozantinib Submitted 2.11.16 with PLLR Conversion draft-label-text2.doc](#)

---

Hello Lisa,

Attached please find our edited package insert as well as comments on the PI that require your attention. Please review the document and make changes as required. Let me know if you find our changes acceptable by 1 PM EST Monday, April 4, 2016 and submit the final label. Please note this label does not include changes made to the Patient Package Insert. Those edits will come within two weeks. Please also include the revised by date as 5/2016 to the PI and PPI.

Thank you,  
rajesh

*Rajesh Venugopal, MPH, MBA*  
*Senior Regulatory Health Project Manager*  
*Division of Oncology Products 1*  
*Office of Hematology and Oncology Products*  
*OND/CDER/FDA*  
*Bldg. 22, Rm. 2171*  
*E-mail: [Rajesh.Venugopal@fda.hhs.gov](mailto:Rajesh.Venugopal@fda.hhs.gov)*  
*Phone: (301) 796-4730*  
*Fax: (301) 796-9845*

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RAJESH VENUGOPAL  
03/30/2016

## MEMORANDUM OF TELECONFERENCE

**Teleconference Date:** March 28, 2016

**Application Number:** NDA 208692

**Product Name:** Cabozantinib

**Sponsor/Applicant Name:** Exelixis, Inc.

**Subject:** Discuss the Clinical Pharmacology Information Request with the Applicant

### **FDA Participants :**

Geoffrey Kim, MD, Director, DOP1

Julia Beaver, MD, Medical Team Leader, DOP1

Harpreet Singh, MD, Medical Officer, DOP1

Michael Brave, PhD, Medical Officer, DOP1

Pengfei Song, PhD, Clinical Pharmacology Reviewer, DCP V

Chao Liu, PhD, Pharmacometrics reviewer, OCP, DPM

Jungyu (Jerry) Yu, PhD, Pharmacometrics, OCP, DPM

Rajesh Venugopal, MPH, MBA, Senior Regulatory Health Project Manager, DOP1

### **Sponsor/Applicant Participants:**

Gisela Schwab, President, Product Development and Medical Affairs, and Chief Medical Officer

Steve Lacy, Vice President, Nonclinical Development

Christian Scheffold, Vice President, Clinical Research & Translational Research

Lisa Sauer, Vice President, Regulatory Affairs

### **BACKGROUND:**

The following clinical information request (IR) was sent to the Applicant on March 24, 2016:

1. Provide intensive PK data to clarify whether single dose PK can predict multiple dose PK of cabozantinib including 60 mg tablets and 140 mg capsules.
2. Provide your results of dose-proportionality evaluation using power model for formulations of tablet, capsule, and PIB with data combined and separated.
3. Provide more data to support your statement that “It is possible that saturation of oral absorption could occur following chronic daily dosing of cabozantinib at  $\geq 140$  mg” in your response to FDA IR.
4. Combine all available PK data from different patient populations and healthy subjects in your integrated population PK model to evaluate the potential impact of tumor types on the PK of cabozantinib.

Upon receiving the IR, the Applicant stated that these analyses are quite labor intensive (particularly those requiring data from multiple formulations and studies/tumor types), and in order to adequately address them as requested, it will take much longer than a week to respond.

So as to not delay the ongoing review of their application and to better understand the underlying objectives of this request, the Applicant requested a teleconference with the review team and Senior Managers (as assigned under the Breakthrough Therapy Designation) to discuss this further. They want to understand the importance of these analyses in the review of their application and potential product labeling of cabozantinib tablets and discuss whether there are other ways the Applicant can address the underlying issues.

#### **DISCUSSION:**

The Applicant stated that the reason for this teleconference was primarily to state that IR #4 above would take longer than 1 week as the Agency requested to provide to the Agency. The vendor that is being used by the Applicant to supply this information stated that the IR response would take 3-4 weeks to provide. The first three IR questions can be provided in the allotted timeframe given by the Agency although the response was provided verbally to the Agency during the teleconference while the Applicant questioned the relevancy to the renal cell carcinoma NDA application. The Agency clarified that the requested analyses are important to understand why the systemic exposures at steady-state are similar across different patient populations with different doses and different formulations. The Agency also asked the Applicant to explore whether high doses of cabozantinib are related to more severe local adverse events in GI tract across patient populations.

The Agency stated that the timeframe for getting a response to question #4 is flexible and that it can come later as pre-market commitment (PMC).

#### **ACTION ITEMS:**

- The Applicant will provide responses to the first 3 questions in writing by the appropriate timeframe indicated by the Agency.
- The Applicant will submit a response to question #4 as a PMC.

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/s/  
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RAJESH VENUGOPAL  
03/30/2016

**From:** [Venugopal, Rajesh](#)  
**To:** [Lisa Sauer \(lsauer@exelixis.com\)](mailto:lsauer@exelixis.com)  
**Subject:** NDA 208692 (Cabozantinib) - DMEPA Recommendation  
**Date:** Tuesday, March 29, 2016 2:56:43 PM

---

Hello Lisa,

Our Division of Medication Error Prevention and Analysis (DMEPA) group reviewed the revised container label and has the following recommendation:

We recommend the following be implemented prior to approval of this NDA:

A. Container labels

1. Remove the statement "Store in the original package." Post-marketing surveillance showed confusion during dispensing regarding such statement when the drug product does not need to be dispensed in the original container. We are concerned the statement "Store in the original package" will cause confusion and potential delay in therapy when a partial bottle quantity is prescribed. Since there are no stability or product quality concerns, remove the statement "Store in the original package."

Please respond [by 3 PM April 11, 2016, if not sooner.](#)

Thank you,  
Rajesh

*Rajesh Venugopal, MPH, MBA*  
*Senior Regulatory Health Project Manager*  
*Division of Oncology Products 1*  
*Office of Hematology and Oncology Products*  
*OND/CDER/FDA*  
*Bldg. 22, Rm. 2171*  
*E-mail: [Rajesh.Venugopal@fda.hhs.gov](mailto:Rajesh.Venugopal@fda.hhs.gov)*  
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RAJESH VENUGOPAL  
03/29/2016

**From:** [Venugopal, Rajesh](#)  
**To:** [Lisa Sauer \(lsauer@exelixis.com\)](mailto:Lisa.Sauer@exelixis.com)  
**Subject:** NDA 208692 (Cabozantinib) - Clinical Pharmacology Information Request  
**Date:** Thursday, March 24, 2016 11:48:58 AM

---

Hello Lisa,

Our Clinical pharmacology group has the following information request requiring your response:

Please refer to your NDA208692 submission for Cabozantinib. Please provide a written response and relevant datasets and programs to the following items [by COB of March 31, 2016](#).

- 1) Provide intensive PK data to clarify whether single dose PK can predict multiple dose PK of cabozantinib including 60 mg tablets and 140 mg capsules.
- 2) Provide your results of dose-proportionality evaluation using power model for formulations of tablet, capsule, and PIB with data combined and separated.
- 3) Provide more data to support your statement that "It is possible that saturation of oral absorption could occur following chronic daily dosing of cabozantinib at  $\geq 140$  mg" in your response to FDA IR.
- 4) Combine all available PK data from different patient populations and healthy subjects in your integrated population PK model to evaluate the potential impact of tumor types on the PK of cabozantinib.

Thank you,  
Rajesh

*Rajesh Venugopal, MPH, MBA*  
*Senior Regulatory Health Project Manager*  
*Division of Oncology Products 1*  
*Office of Hematology and Oncology Products*  
*OND/CDER/FDA*  
*Bldg. 22, Rm. 2171*  
*E-mail: [Rajesh.Venugopal@fda.hhs.gov](mailto:Rajesh.Venugopal@fda.hhs.gov)*  
*Phone: (301) 796-4730*  
*Fax: (301) 796-9845*



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RAJESH VENUGOPAL  
03/24/2016

**From:** [Venugopal, Rajesh](#)  
**To:** [Lisa Sauer \(lsauer@exelixis.com\)](mailto:lsauer@exelixis.com)  
**Subject:** NDA 208692 (Cabozantinib) - Clinical Information Request  
**Date:** Tuesday, March 22, 2016 12:21:01 PM

---

Hello Lisa,

The following is a clinical information requesting that requires a response:

In Trial XL184-308, there were 29 venous and mixed/unspecified thrombotic events. Please provide for each patient and/or event (as each patient may have had more than one thrombotic event):

- Baseline platelet count
- Platelet count at time of thrombotic event

Please respond by COB Friday, March 25, if not sooner.

Thank you,  
Rajesh

*Rajesh Venugopal, MPH, MBA*  
*Senior Regulatory Health Project Manager*  
*Division of Oncology Products 1*  
*Office of Hematology and Oncology Products*  
*OND/CDER/FDA*  
*Bldg. 22, Rm. 2171*  
*E-mail: [Rajesh.Venugopal@fda.hhs.gov](mailto:Rajesh.Venugopal@fda.hhs.gov)*  
*Phone: (301) 796-4730*  
*Fax: (301) 796-9845*

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RAJESH VENUGOPAL  
03/22/2016

**From:** [Venugopal, Rajesh](#)  
**To:** [Lisa Sauer \(lsauer@exelixis.com\)](mailto:lsauer@exelixis.com)  
**Subject:** NDA 208692 (Cabozantinib) - Clinical Information Request  
**Date:** Tuesday, March 15, 2016 8:30:10 AM

---

Hi Lisa,

Can you please provide us with the earliest date which you would be able to submit your 120-safety update. Please respond by COB today.

Thanks,  
rajesh

*Rajesh Venugopal, MPH, MBA  
Senior Regulatory Health Project Manager  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
OND/CDER/FDA  
Bldg. 22, Rm. 2171  
E-mail: [Rajesh.Venugopal@fda.hhs.gov](mailto:Rajesh.Venugopal@fda.hhs.gov)  
Phone: (301) 796-4730  
Fax: (301) 796-9845*

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RAJESH VENUGOPAL  
03/15/2016

From: [Venugopal Rajesh](#)  
To: [Lisa Sauer \(lsauer@exelixis.com\)](mailto:Lisa.Sauer@exelixis.com)  
Subject: NDA 208692 (Cabozantinib) - DMEPA and CMC Comments  
Date: Thursday, March 10, 2016 1:44:52 PM

---

Hello Lisa,

Our review teams from CMC and the Division of Medication Error Prevention and Analysis (DMEPA) have the following comments regarding the container label that requires your response:

Container labels

1. Assigning National Drug Codes (NDC) with sequential drug product codes (middle digits) for different strengths of the same drug product do not adequately distinguish the products, and has led to selecting and dispensing of the wrong strength. To better differentiate the NDC numbers, we recommend changing the product codes (middle digits) so that they are not sequential. If these numbers cannot be revised, increase the prominence of the middle digits by increasing their font size in comparison to the remaining digits or putting them in bold type. For example, XXXXX-**XXX**-XX. [\[1\]](#)
2. On the side panel, revise the order of the statements so direction on the action item appears first such that it reads "Take once each day on an empty stomach. Cabometyx should not be taken with food. Do not eat..." Additionally, we recommend bolding the statement "Take once each day on an empty stomach." to improve readability.
3. Remove the statement "store in the original package" on the container labels if there are no stability or product quality concerns that require the tablets be dispensed in the original package to the patients.
4. If possible, ensure there is sufficient white space between the paragraphs on the side panel to improve readability. This may be achieved by removing the statement "store in the original package".
5. Consider adding the statement "Swallow CABOMETYX tablets whole. Do not crush CABOMETYX tablets." on the side panel if space permits.
6. Update the side panel of CABOMETYX Container Label to indicate the amount of salt according to Example 1 in Appendix 2 of the following FDA guidance:  
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM379753.pdf>  
. For example, "Each tablet contains X mg of cabozantinib (equivalent to Y mg of cabozantinib (S)-malate)."

Please respond [by 3 PM EST Monday April 4, 2016](#) with revised container labels.

Thank you,  
rajesh

*Rajesh Venugopal, MPH, MBA  
Senior Regulatory Health Project Manager  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
OND/CDER/FDA  
Bldg. 22, Rm. 2171  
E-mail: [Rajesh.Venugopal@fda.hhs.gov](mailto:Rajesh.Venugopal@fda.hhs.gov)  
Phone: (301) 796-4730  
Fax: (301) 796-9845*

---

[\[1\]](#) Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

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/s/  
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RAJESH VENUGOPAL  
03/10/2016

**From:** [Venugopal, Rajesh](#)  
**To:** [Lisa Sauer \(lsauer@exelixis.com\)](mailto:Lisa.Sauer@exelixis.com)  
**Subject:** NDA 208692 (Cabozantinib) - Clinical Information Request  
**Date:** Tuesday, March 08, 2016 9:13:45 AM

---

Hi Lisa,

Here are a couple of more comments requiring a response:

- 1) The review team has become aware of a reported case of a potential drug-drug interaction (DDI) between warfarin and cabozantinib. In the attached report, the patient was taking both Coumadin and Cabozantinib. His course was complicated by an elevated INR and clinical signs of bleeding in the form of epistaxis. Upon discontinuing the cabozantinib, both the INR and clinical bleeding resolved. Please provide an analysis or potential explanation for the reported case. In addition, conduct an analysis of your database to evaluate further clinical trial results and post-marketing reports of AEs attributed to the combination of cabozantinib and warfarin. Additionally, propose updated labeling if indicated.
- 2) Please provide the liver biopsy report referenced in the Subject Narrative for patient 3910-3100.

Please respond [by 5 PM EST March 11, 2016, if not sooner.](#)

Thank you,  
rajesh

*Rajesh Venugopal, MPH, MBA*  
*Senior Regulatory Health Project Manager*  
*Division of Oncology Products 1*  
*Office of Hematology and Oncology Products*  
*OND/CDER/FDA*  
*Bldg. 22, Rm. 2171*  
*E-mail: [Rajesh.Venugopal@fda.hhs.gov](mailto:Rajesh.Venugopal@fda.hhs.gov)*  
*Phone: (301) 796-4730*  
*Fax: (301) 796-9845*

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/s/  
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RAJESH VENUGOPAL  
03/08/2016

**From:** [Venugopal, Rajesh](#)  
**To:** [Lisa Sauer \(lsauer@exelixis.com\)](mailto:lsauer@exelixis.com)  
**Subject:** NDA 208692 (Cabozantinib) - Clinical Information Request  
**Date:** Tuesday, March 08, 2016 9:13:45 AM

---

Hi Lisa,

Here are a couple of more comments requiring a response:

- 1) The review team has become aware of a reported case of a potential drug-drug interaction (DDI) between warfarin and cabozantinib. In the attached report, the patient was taking both Coumadin and Cabozantinib. His course was complicated by an elevated INR and clinical signs of bleeding in the form of epistaxis. Upon discontinuing the cabozantinib, both the INR and clinical bleeding resolved. Please provide an analysis or potential explanation for the reported case. In addition, conduct an analysis of your database to evaluate further clinical trial results and post-marketing reports of AEs attributed to the combination of cabozantinib and warfarin. Additionally, propose updated labeling if indicated.
- 2) Please provide the liver biopsy report referenced in the Subject Narrative for patient 3910-3100.

Please respond [by 5 PM EST March 11, 2016, if not sooner.](#)

Thank you,  
rajesh

*Rajesh Venugopal, MPH, MBA*  
*Senior Regulatory Health Project Manager*  
*Division of Oncology Products 1*  
*Office of Hematology and Oncology Products*  
*OND/CDER/FDA*  
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*E-mail: [Rajesh.Venugopal@fda.hhs.gov](mailto:Rajesh.Venugopal@fda.hhs.gov)*  
*Phone: (301) 796-4730*  
*Fax: (301) 796-9845*

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/s/  
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RAJESH VENUGOPAL  
03/08/2016

**From:** [Venugopal, Rajesh](#)  
**To:** [Lisa Sauer \(lsauer@exelixis.com\)](mailto:Lisa.Sauer@exelixis.com)  
**Subject:** NDA 208692 (Cabozantinib)  
**Date:** Monday, March 07, 2016 9:00:54 AM

---

Hello Lisa,

Our Clinical team as the following question requiring your response:

Has the Sponsor investigated the use of loperamide or any other antidiarrheal agent as prophylaxis for symptoms of diarrhea while taking cabozantinib? If so, please provide the trial design, disease setting (s), and findings.

Please respond by 5 PM EST Wednesday March 9.

Thank you,  
Rajesh

*Rajesh Venugopal, MPH, MBA*  
*Senior Regulatory Health Project Manager*  
*Division of Oncology Products 1*  
*Office of Hematology and Oncology Products*  
*OND/CDER/FDA*  
*Bldg. 22, Rm. 2171*  
*E-mail: [Rajesh.Venugopal@fda.hhs.gov](mailto:Rajesh.Venugopal@fda.hhs.gov)*  
*Phone: (301) 796-4730*  
*Fax: (301) 796-9845*

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/s/  
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RAJESH VENUGOPAL  
03/07/2016

## MEMORANDUM OF TELECONFERENCE

**Teleconference Date:** March 3, 2016

**Application Number:** NDA 208692

**Product Name:** Cabozantinib

**Sponsor/Applicant Name:** Exelixis, Inc.

**Subject:** Discussion on Pharmacometrics Information Request to Calculate the Response Rate and its 95% confidence interval based on Best Overall Response (BOR).

### **FDA Participants**

Chao Liu, PhD, Pharmacometrics Reviewer, Office of Clinical Pharmacology, Division of Pharmacometrics

Jingyu Yu, PhD, Pharmacometrics Reviewer, Office of Clinical Pharmacology, Division of Pharmacometrics

Yaning, Wang, PhD, Deputy Director, Office of Clinical Pharmacology, Division of Pharmacometrics

Julia Beaver, MD, Medical Officer Team Lead, DOP1

Rajesh Venugopal, MPH, MBA, Senior Regulatory Health Project Manager, DOP1

### **Sponsor/Applicant Participants**

Gisela Schwab, President, Product Development and Medical Affairs, and Chief Medical Officer

Colin Hessel, Vice President, Biostatistics and Clinical Data Management

Steve Lacy, Vice President, Nonclinical Development

Lisa Sauer, Vice President, Regulatory Affairs

### **BACKGROUND:**

On Tuesday, March 1, the Pharmacometrics review team had asked for an information request from the Sponsor to calculate the response rate and its 95% confidence interval based on Best Overall Response (BOR) regarding simulated tumor dynamics under different starting doses for study No. XL184-308.ER.002.

The Sponsor requested a teleconference to discuss further this request from the Agency.

### **DISCUSSION:**

The request (including the 95% confidence intervals) requires new codes to be developed and hundreds of independent simulation runs to generate accurate values, and is expected to take weeks to complete. Therefore, it was not feasible to complete this part of the response by the due date of Friday, March 4, 2016.

**ACTION ITEMS:**

The Agency has stated that the Pharmacometrics review team could generate the response rate and its 95% confidence interval based on BOR themselves instead of the Sponsor using the codes the Sponsor submits to the Agency. The Agency will send the results to the Sponsor.

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/s/  
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RAJESH VENUGOPAL  
03/07/2016



**From:** [Venugopal, Rajesh](#)  
**To:** [Lisa Sauer \(lsauer@exelixis.com\)](mailto:Lisa.Sauer@exelixis.com)  
**Subject:** NDA 208692 (Cabozantinib) - Clinical Pharmacology Information Request  
**Date:** Friday, March 04, 2016 11:01:35 AM

---

Hi Lisa,

Our Clinical Pharmacology team has the following information request that requires your response:

- Provide a scatter plot to visualize  $C_{\min,ss}$  over time among groups of MTC, RCC, prostate cancer, and healthy subjects. Please take dose modifications (dose reduction, dose interruption) into consideration. Please submit relevant datasets and programs.
- Provide potential reasons for the difference in oral clearance of cabozantinib between MTC and RCC patient populations.
- Clarify what percentage of parent drug was recovered in feces and urine in your mass balance trial.

Please provide written responses to the above items by 3 PM, Thursday March 10, 2016.

Thank you,  
rajesh

*Rajesh Venugopal, MPH, MBA*  
*Senior Regulatory Health Project Manager*  
*Division of Oncology Products 1*  
*Office of Hematology and Oncology Products*  
*OND/CDER/FDA*  
*Bldg. 22, Rm. 2171*  
*E-mail: [Rajesh.Venugopal@fda.hhs.gov](mailto:Rajesh.Venugopal@fda.hhs.gov)*  
*Phone: (301) 796-4730*  
*Fax: (301) 796-9845*

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RAJESH VENUGOPAL  
03/04/2016

**From:** [Venugopal, Rajesh](#)  
**To:** [Lisa Sauer \(lsauer@exelixis.com\)](mailto:Lisa.Sauer@exelixis.com)  
**Subject:** NDA 208692 (Cabozantinib) - Clinical Information Request  
**Date:** Thursday, March 03, 2016 12:51:03 PM

---

Hi Lisa,

Another information request from our clinical team:

*Please state the following regarding the results of Trial XL184-308:*

- *How many patients in each treatment arm continued to receive study treatment after Investigator-determined progression?*
- *How many patients in each treatment arm continued to receive study treatment after IRC-determined disease progression?*
- *Did any patients in either treatment arm who continued to receive study treatment beyond disease progression achieve stable disease or a response from post-progression treatment?*

Please provide your response [by 3 PM, Thursday March 17, if not sooner.](#)

Thank you,  
Rajesh

*Rajesh Venugopal, MPH, MBA  
Senior Regulatory Health Project Manager  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
OND/CDER/FDA  
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/s/  
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RAJESH VENUGOPAL  
03/03/2016

## **Executive CAC**

**Date of Meeting: March 1, 2016**

Committee: Abby Jacobs, Ph.D., OND IO, Acting Chair  
Paul Brown, Ph.D., OND IO, Member  
Tim McGovern, Ph.D., OND IO, Member  
Adebayo Laniyonu, Ph.D., DMIP, Alternate Member  
Todd, Palmby, Ph.D., DHOT, Pharm Tox Supervisor  
Eias Zahalka, Ph.D., MBA, DHOT, Presenting Reviewer

Author of Draft: Eias Zahalka, PhD

The following information reflects a brief summary of the Committee discussion and its recommendations.

**NDA # 208692 and 203756**

**Drug Name:** Cabozantinib (S)-malate

**Sponsor:** Exelixis, Inc

### **Background:**

The Applicant submitted a New Drug Application (NDA) on December 22, 2015 for cabozantinib (S)-malate (cabozantinib) for the treatment of advanced renal cell carcinoma (RCC). Cabozantinib is a kinase inhibitor with activity at multiple kinases including RET kinase, mesenchymal epithelial transition factor (MET), and vascular endothelial cell growth factor receptors (VEGFR). Cometriq™ (cabozantinib) is an FDA approved drug since 2012 for the treatment of patients with progressive, metastatic medullary thyroid cancer (NDA# 203756). This patient population is expected to have an extended survival of 5 years or longer. At the time of approval, the Applicant was required to conduct carcinogenicity studies in two species with orally administered cabozantinib as a post marketing requirement (PMR).

A special protocol assessment (SPA) and supporting toxicology data were presented to the ECAC for the 26-week Tg.rasH2 mouse study in December 3, 2013, and concurrence was obtained on study design and dose selection for the study. The final 26-week mouse carcinogenicity report was submitted on 7/6/2015 under NDA 203756/Supp. # 115 (Applicant owned) and the current NDA # 208692 on October 12, 2015.

## **Tg.rasH2 Mouse Carcinogenicity Study**

Male and female mice (CByB6F1-Tg(HRAS)2Jic (hemizygous) mice) were dosed with vehicle (ethanol [EtOH, 200 proof]:polyethylene glycol [PEG] 400:reverse osmosis [RO] water, 5:45:50 [v:v:v {Group 1}]), water, or with cabozantinib S-malate at 2, 5 and 15 mg/kg/day once daily by oral gavage for 26 weeks at a volume of 5 mL/kg. An additional group was dosed with MNU (positive control) via intraperitoneal injection once on Day 1 at a volume of 10 mL/kg.

Statistically significant test article-related increases in mortalities were reported in males at 15 mg/kg/day due to general debilitation of the animals. No test article-related increases in the incidence of neoplastic lesions were reported at any dose tested. At 15 mg/kg/day, non-neoplastic microscopic findings (slight to moderate) were reported in the spleen (lymphocyte depletion), glandular stomach (hyperplasia of the epithelium), duodenum (hyperplasia of the epithelium) and pancreas (zymogen depletion). The positive control, MNU, showed a clear carcinogenic response, and as such the data provided validity to the test assay.

## **Executive CAC Recommendations and Conclusions**

Tg.rasH2 mouse:

- The Committee agreed that the study was acceptable, noting prior approval of the protocol.
- The Committee concurred that there were no drug-related neoplasms in the study.

Abigail Jacobs, Ph.D.

Acting Chair, Executive CAC

cc:\

/Division File, DHOT  
/Todd Palmby, DHOT  
/Eias Zahalka, DHOT  
/Rajesh Venugopal, RPM, DOP1  
/A Seifried, OND IO

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/s/  
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ADELE S SEIFRIED  
03/03/2016

ABIGAIL C JACOBS  
03/03/2016

**From:** [Venugopal, Rajesh](#)  
**To:** [Lisa Sauer \(lsauer@exelixis.com\)](mailto:Lisa.Sauer@exelixis.com)  
**Subject:** NDA 208692 (Cabozantinib) - Pharmacometrics Information Request  
**Date:** Tuesday, March 01, 2016 9:39:58 AM

---

Hi Lisa,

Our Pharmacometrics review team has the following information request requiring your response:

The sponsor's IR response (Study No. XL184-308.ER.002) included simulated tumor dynamics under different starting doses. Please conduct the following analysis:

- Summarize Best Overall Response (BOR) from simulated tumor dynamics. The follow-up time could be tentatively set as one year. The BOR definition, confirmation, minimal duration of SD should be consistent with the ones in pivotal trial (XL184-308).
- Calculate the Response Rate and its 95% confidence interval based on BOR.

All relevant datasets and codes should also be submitted with define files.

Please respond no later than Friday, 3/4/2016, 3PM EST, if not sooner.

Thank you,  
Rajesh

*Rajesh Venugopal, MPH, MBA*  
*Senior Regulatory Health Project Manager*  
*Division of Oncology Products 1*  
*Office of Hematology and Oncology Products*  
*OND/CDER/FDA*  
*Bldg. 22, Rm. 2171*  
*E-mail: [Rajesh.Venugopal@fda.hhs.gov](mailto:Rajesh.Venugopal@fda.hhs.gov)*  
*Phone: (301) 796-4730*  
*Fax: (301) 796-9845*



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RAJESH VENUGOPAL  
03/01/2016

From: [Venugopal, Rajesh](#)  
To: [Lisa Sauer \(lsauer@exelixis.com\)](mailto:Lisa.Sauer@exelixis.com)  
Subject: NDA 208692 (Cabozantinib) Clinical information request  
Date: Monday, February 29, 2016 2:47:06 PM

---

Hello Lisa,

Our clinical review team has the following information request requiring your response:

1) Please provide patient narratives for the following patients:

184308-1563-3097

184308-2002-3762

2) Please provide a table which lists laboratory abnormalities worsening from baseline occurring in  $\geq 10\%$  of Cabozantinib-treated patients and at a higher incidence than in the everolimus arm (Between Arm Difference of  $\geq 5\%$  [All Grades] or  $\geq 2\%$  [Grades 3-4]).

A sample format is provided below:

**Table:** Selected Laboratory Abnormalities Worsening from Baseline Occurring in  $\geq 10\%$  of Cabozantinib-Treated Patients and at a Higher Incidence than in the Everolimus Arm (Between Arm Difference of  $\geq 5\%$  [All Grades] or  $\geq 2\%$  [Grades 3-4])

Test	Cabozantinib N=331		Everolimus N=322	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)

Please provide your response [by COB on Thursday, March 3<sup>rd</sup>](#).

Thank you,  
rajesh

*Rajesh Venugopal, MPH, MBA*  
*Senior Regulatory Health Project Manager*  
*Division of Oncology Products 1*  
*Office of Hematology and Oncology Products*  
*OND/CDER/FDA*  
*Bldg. 22, Rm. 2171*  
*E-mail: [Rajesh.Venugopal@fda.hhs.gov](mailto:Rajesh.Venugopal@fda.hhs.gov)*  
*Phone: (301) 796-4730*  
*Fax: (301) 796-9845*

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RAJESH VENUGOPAL  
02/29/2016

**From:** [Venugopal, Rajesh](#)  
**To:** ["Lisa Sauer \(lsauer@exelixis.com\)"](#)  
**Subject:** RE: NDA 208692 (Cabozantinib) - Pharmacometrics information request  
**Date:** Monday, February 29, 2016 12:36:29 PM

---

Hi Lisa,

With regards to the initial information request #1 below and the response you provided, our Pharmacometrics group requests the following:

Please submit the code, control streams and datasets that you used in the IR response (Study No. XL184-308.ER.002)? The requests are listed as follows:

Please submit all NONMEM control streams, R, SAS codes and related datasets (expect for the ones submitted in along with Study No. XL184-308.ER.002) for model fitting and simulation in the following analysis:

- 1) Tumor Model Development
- 2) AE Model Development
- 3) Simulation analysis in response 1c and 1e

Datasets and codes should be submitted with define files. **Please respond by no later than tomorrow, 3/1/2016, 3PM EST.**

Thank you,  
rajesh

---

**From:** Venugopal, Rajesh  
**Sent:** Thursday, January 21, 2016 9:29 AM  
**To:** Lisa Sauer (lsauer@exelixis.com)  
**Subject:** NDA 208692 (Cabozantinib) - Pharmacometrics information request

Hello Lisa,

Our pharmacometrics review team has the following information request that requires your response. Please have the items of the request back **by COB, Friday February 12, 2016, if not sooner.**

Please address the following questions and submit the dataset regarding the exposure-response (ER) analysis:

1. Please use the exposure-efficacy/safety analyses to assess whether a lower dose of cabozantinib can achieve efficacy similar to the proposed dose, but has less toxicity. In addition to ORR, PFS and OS, the longitudinal continuous tumor size should be analyzed in the following way to evaluate a lower dose:
  - a. Develop an exposure-response model for the time course of tumor size for cabozantinib in RCC patients. Longitudinal drug exposure based on the actual doses should be used.
  - b. Develop a longitudinal exposure – AE model. Sponsor may treat all dose-altering/interrupting AEs as one repeatable event.
  - c. Simulate the dose modification/interruption scenario with a lower starting dose levels (such as 40mg)

using the exposure-AE model developed in step b and the current dose adjustment algorithm.

d. Sponsor could also assess the net benefit of adding an up-titration option to the current titration algorithm.

e. Based on the dose simulated from step c, individual longitudinal exposure can be simulated based on the individual PK parameters from the population PK model. The individual exposure can be used to simulate the time course of tumor size with the lower starting doses.

Related Datasets and code/control streams should be also be submitted along with the above analysis. Define file explaining the dataset and codes should be included.

2. Please submit datasets for FDA reviewer's analysis as SAS transport files (\*.xpt) with define.pdf files. The dataset should include:

- a. Time and reasons (Types of AE) for each dose adjustment and interruption;
- b. Types of co-medications at time point when each dose interruption and adjustment happens;
- c. Dose level after each modification.

Refer to the pharmacometric data submission guidelines

(<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>) for more information.

Please confirm receipt of this and any future information requests regarding your NDA.

Thank you,  
rajesh

*Rajesh Venugopal, MPH, MBA*  
*Senior Regulatory Health Project Manager*  
*Division of Oncology Products 1*  
*Office of Hematology and Oncology Products*  
*OND/CDER/FDA*  
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RAJESH VENUGOPAL  
02/29/2016

**From:** [Venugopal, Rajesh](#)  
**To:** ["Lisa Sauer"](#)  
**Subject:** RE: NDA 208692 (Cabozantinib)  
**Date:** Wednesday, February 10, 2016 7:51:49 AM

---

Please provide the information [by close of business Friday February 12, 2016](#).

---

**From:** Venugopal, Rajesh  
**Sent:** Wednesday, February 10, 2016 7:51 AM  
**To:** 'Lisa Sauer'  
**Subject:** RE: NDA 208692 (Cabozantinib)

Lisa,

We ask that you please provide more details regarding each protocol change or identify the location in the submission where this more detailed information is included. Currently, the CSR appears to only provide line-item bullet points regarding the key changes made to the protocol. We would like a more descriptive report of each key change in the protocol amendment. For example, provide a full description of the "Maintenance Phase" which was added to the Treatment Period in Amendment 1.0, and provide exactly how the assessments were changed and what specific time points were changed.

rajesh

---

**From:** Lisa Sauer [<mailto:lsauer@exelixis.com>]  
**Sent:** Tuesday, February 09, 2016 12:46 PM  
**To:** Venugopal, Rajesh  
**Subject:** RE: NDA 208692 (Cabozantinib)

Rajesh,

This information is summarized in the XL184-308 CSR Section 9.8.1.2.  
Is there something more specific the review team is looking for? We reviewed what is included in this section, and it wasn't so long it needed shortening, but weren't sure if maybe more details about each change were desired.

Lisa

---

**From:** Venugopal, Rajesh [<mailto:Rajesh.Venugopal@fda.hhs.gov>]  
**Sent:** Tuesday, February 09, 2016 3:51 AM  
**To:** Lisa Sauer  
**Subject:** NDA 208692 (Cabozantinib)

Hi Lisa,

Our clinical team has the following information request which requires your response:

**Please briefly summarize all significant changes that Amendment 1.0 introduced to Protocol XL184-308.**

Please respond [by COB Friday February 12, 2016](#).

Thank you,  
Rajesh

*Rajesh Venugopal, MPH, MBA*  
*Senior Regulatory Health Project Manager*  
*Division of Oncology Products 1*  
*Office of Hematology and Oncology Products*  
*OND/CDER/FDA*  
*Bldg. 22, Rm. 2171*  
*E-mail: [Rajesh.Venugopal@fda.hhs.gov](mailto:Rajesh.Venugopal@fda.hhs.gov)*  
*Phone: (301) 796-4730*  
*Fax: (301) 796-9845*

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RAJESH VENUGOPAL  
02/10/2016

**From:** [Venugopal, Rajesh](#)  
**To:** [Lisa Sauer \(lsauer@exelixis.com\)](mailto:Lisa.Sauer@exelixis.com)  
**Subject:** NDA 208692 (Cabozantinib) Regulatory Information Request  
**Date:** Tuesday, February 09, 2016 8:45:22 AM  
**Attachments:** [Exelixis No Filing Review Issues Identified Day 60 NDA 208692 Emailed.pdf](#)

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Hello Lisa,

As we took a cursory review of the PI submitted we are realizing that the PI is not converted into the PLLR requirements for prescribing information. As the letter attached states under "Prescribing Information" on page 2, in addition to the 7 PI items to fix please convert the PI into PLLR. We hope that we can still receive the revised PI by February 16 as the letter states. Please let me know if this is not possible and if you any questions.

Thank you,  
rajesh

*Rajesh Venugopal, MPH, MBA*  
*Senior Regulatory Health Project Manager*  
*Division of Oncology Products 1*  
*Office of Hematology and Oncology Products*  
*OND/CDER/FDA*  
*Bldg. 22, Rm. 2171*  
*E-mail: [Rajesh.Venugopal@fda.hhs.gov](mailto:Rajesh.Venugopal@fda.hhs.gov)*  
*Phone: (301) 796-4730*  
*Fax: (301) 796-9845*



NDA 208692

**FILING COMMUNICATION –  
NO FILING REVIEW ISSUES IDENTIFIED**

Exelixis, Inc.  
Attention: Lisa Sauer  
Vice President, Regulatory Affairs  
210 Grand Avenue  
South San Francisco, CA 94080

Dear Ms. Sauer:

Please refer to your New Drug Application (NDA) dated December 22, 2015, received December 22, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Cabometyx (cabozantinib) Tablets; 20 mg, 40 mg, and 60 mg.

We also refer to your submissions dated October 13 and 20, and November 5, 12, 13, 18, and 24, 2015.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is June 22, 2016. However, we plan to act early on this application under an expedited review, provided that no significant application deficiencies or unexpected shifts in work priorities or team staffing prevent an early action.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by June 1, 2016. This date conforms to the 21<sup>st</sup> Century Review timeline for your application. If our review continues on an expedited timeline, we may communicate revised dates for labeling and postmarketing requirement/commitment requests.

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

## **PRESCRIBING INFORMATION**

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [PLLR Requirements for Prescribing Information](#) websites including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

1. In Highlights, add a numerical reference for INDICATIONS AND USAGE.
2. In Highlights, the product title should be bolded.
3. In Highlights, include the four digit year under Initial U.S. Approval.
4. In Highlights, add the revision date.
5. In the Full Prescribing Information (FPI), the **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1). If a section/subsection required by regulation is omitted, the numbering must not change. In section 8 of your FPI, the subsections are currently titled as 8.1 Pregnancy, 8.2 Nursing Mothers, 8.3 Pediatric Use, 8.4 Geriatric Use, 8.5 Females and Males of Reproductive Potential, 8.6 Hepatic Impairment, and 8.7 Renal Impairment. Please correct the section numbering to omit the sections (and their associated section numbers) that are not included in the FPI.

6. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in italics and enclosed within brackets. For example, “[see *Warnings and Precautions (5.2)*].” The Pharmacokinetics subsection 12.3 is directly referenced in sections 3, 8.6, and 8.7. The cross-reference should be to CLINICAL PHARMACOLOGY (12.3).
7. In the **PATIENT COUNSELING INFORMATION** section in the FPI, you must reference any FDA-approved patient labeling. The reference statement should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Instructions for Use, or Medication Guide). Recommended language for the reference statement should include one of the following five verbatim statements that is most applicable:
  - Advise the patient to read the FDA-approved patient labeling (Patient Information).
  - Advise the patient to read the FDA-approved patient labeling (Instructions for Use).
  - Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
  - Advise the patient to read the FDA-approved patient labeling (Medication Guide).
  - Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

None of the above mentioned verbatim statements are included in your Full Prescription Information. Please add.

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by February 16, 2016. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

### **PROMOTIONAL MATERIAL**

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

#### **REQUIRED PEDIATRIC ASSESSMENTS**

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

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, contact Rajesh Venugopal, Senior Regulatory Project Manager, at (301) 796-4730.

Sincerely,

{ See appended electronic signature page }

Geoffrey Kim, MD  
Director  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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GEOFFREY S KIM  
01/27/2016

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/s/  
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RAJESH VENUGOPAL  
02/09/2016



**From:** [Venugopal, Rajesh](#)  
**To:** [Lisa Sauer \(lsauer@exelixis.com\)](mailto:lsauer@exelixis.com)  
**Cc:** [Karen Hodsdon \(khodsdon@exelixis.com\)](mailto:khodsdon@exelixis.com)  
**Subject:** NDA 208692 (Cabozantinib) - Clinical Pharmacology Information Request  
**Date:** Tuesday, February 09, 2016 8:38:14 AM

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Hi Lisa,

Our clinical pharmacology team asks that you please submit the Exposure-response and POP-PK as soon as possible. We have a tight review timeline for your NDA that we ask for your assistance in getting us the information right away. If you can not submit soon, we may not be able to complete our review on time.

Thank you in advance for your understanding,  
rajesh

*Rajesh Venugopal, MPH, MBA*  
*Senior Regulatory Health Project Manager*  
*Division of Oncology Products 1*  
*Office of Hematology and Oncology Products*  
*OND/CDER/FDA*  
*Bldg. 22, Rm. 2171*  
*E-mail: [Rajesh.Venugopal@fda.hhs.gov](mailto:Rajesh.Venugopal@fda.hhs.gov)*  
*Phone: (301) 796-4730*  
*Fax: (301) 796-9845*

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/s/  
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RAJESH VENUGOPAL  
02/09/2016

**From:** [Venugopal, Rajesh](#)  
**To:** [Lisa Sauer \(lsauer@exelixis.com\)](mailto:lsauer@exelixis.com)  
**Subject:** NDA 208692 (Cabozantinib)  
**Date:** Tuesday, February 09, 2016 6:50:48 AM

---

Hi Lisa,

Our clinical team has the following information request which requires your response:

**Please briefly summarize all significant changes that Amendment 1.0 introduced to Protocol XL184-308.**

Please respond [by COB Friday February 12, 2016](#).

Thank you,  
Rajesh

*Rajesh Venugopal, MPH, MBA  
Senior Regulatory Health Project Manager  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
OND/CDER/FDA  
Bldg. 22, Rm. 2171  
E-mail: [Rajesh.Venugopal@fda.hhs.gov](mailto:Rajesh.Venugopal@fda.hhs.gov)  
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/s/  
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RAJESH VENUGOPAL  
02/09/2016

**From:** [Venugopal, Rajesh](#)  
**To:** [Lisa Sauer \(lsauer@exelixis.com\)](mailto:lsauer@exelixis.com)  
**Subject:** NDA 208692 (Cabozantinib) - Clinical Information Request  
**Date:** Monday, February 08, 2016 9:30:20 AM

---

Hi Lisa,

Below please find our clinical information request requiring your response:

- 1) Please provide death narratives for the following three patients:

184308-2038-3333

184308-9503-3496

184308-1512-3017

- 2) You report that financial disclosure information was collected and reported for all 181 investigators participating in Trial184-308. Clarify if this includes Primary Investigators and Sub-investigators, or if the 181 investigators reported are all Primary Investigators.

Please provide your response [by COB, Wednesday February 10<sup>th</sup>](#).

Thank you,  
Rajesh

*Rajesh Venugopal, MPH, MBA  
Senior Regulatory Health Project Manager  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
OND/CDER/FDA  
Bldg. 22, Rm. 2171  
E-mail: [Rajesh.Venugopal@fda.hhs.gov](mailto:Rajesh.Venugopal@fda.hhs.gov)  
Phone: (301) 796-4730  
Fax: (301) 796-9845*

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RAJESH VENUGOPAL  
02/08/2016



NDA 208692

**FILING COMMUNICATION –  
NO FILING REVIEW ISSUES IDENTIFIED**

Exelixis, Inc.  
Attention: Lisa Sauer  
Vice President, Regulatory Affairs  
210 Grand Avenue  
South San Francisco, CA 94080

Dear Ms. Sauer:

Please refer to your New Drug Application (NDA) dated December 22, 2015, received December 22, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Cabometyx (cabozantinib) Tablets; 20 mg, 40 mg, and 60 mg.

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf> ).

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We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, contact Rajesh Venugopal, Senior Regulatory Project Manager, at (301) 796-4730.

Sincerely,

{ See appended electronic signature page }

Geoffrey Kim, MD  
Director  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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GEOFFREY S KIM  
01/27/2016

**From:** [Venugopal, Rajesh](#)  
**To:** [Lisa Sauer \(lsauer@exelixis.com\)](mailto:Lisa.Sauer@exelixis.com)  
**Subject:** NDA 208692 (Cabozantinib) - Clinical Information Request  
**Date:** Friday, January 22, 2016 8:22:05 AM

---

Hi Lisa,

Our clinical review team has the following information request that requires a response:

We have noticed discrepancies between the datasets and the Study Report.

- Section 12.3 of the Study Report describes Deaths, and Other Serious Events and references Table 14.3.2.5 as a primary source. Table 14.3.2.5 is derived from ADaM datasets ADSL, however the numbers we obtain when working with this dataset are discordant from those reported in Table 14.3.2.5. When using the TRT01A column (Actual Treatment for Period 01), there are 91 deaths in the Cabozantinib arm and 113 deaths in the Everolimus arm. This is discordant from Table 14.3.2.5, which lists 90 deaths and 113 deaths in Cabozantinib and Everolimus, respectively.
- The Study report and Define file note that for SUBJID = 14173624, who was randomized to receive Everolimus but actually was treated with Cabozantinib, TRT01A has been set to Cabozantinib. However, after performing a search in ADSL for this SUBJID, the TRT01A is assigned to Everolimus. This appears to also be the case in other ADAM safety datasets.
- Again in the ADAE dataset, when using the Safety Population Flag and then grouping by Actual Treatment, the numbers are as follows: Cabozantinib = 330, Everolimus = 321. This is discordant from the Safety Population noted in the Study report, which reports 331 patients in the Cabozantinib arm and 322 patients in the Everolimus arm.

Please clarify these discrepancies in every dataset where actual treatment/deaths are defined and/or resubmit corrected datasets/study report.

Please respond by 10 AM on Tuesday, January 26<sup>th</sup>, if not sooner.

rajesh

*Rajesh Venugopal, MPH, MBA*  
*Senior Regulatory Health Project Manager*  
*Division of Oncology Products 1*  
*Office of Hematology and Oncology Products*  
*OND/CDER/FDA*  
*Bldg. 22, Rm. 2171*  
*E-mail: [Rajesh.Venugopal@fda.hhs.gov](mailto:Rajesh.Venugopal@fda.hhs.gov)*  
*Phone: (301) 796-4730*  
*Fax: (301) 796-9845*

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/s/  
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RAJESH VENUGOPAL  
01/22/2016

**From:** [Venugopal, Rajesh](#)  
**To:** ["Lisa Sauer \(lsauer@exelixis.com\)"](#)  
**Subject:** RE: NDA 208692 (Cabozantinib) - Clinical Information Request  
**Date:** Friday, January 22, 2016 12:55:10 PM  
**Importance:** High

---

Hi Lisa,

Our clinical review team would like to retract the previous IR from this morning (the below information request).

We were obtaining the data from an older dataset. So no need to respond to it.

We apologize for any inconvenience.

rajesh

---

**From:** Venugopal, Rajesh  
**Sent:** Friday, January 22, 2016 8:22 AM  
**To:** Lisa Sauer (lsauer@exelixis.com)  
**Subject:** NDA 208692 (Cabozantinib) - Clinical Information Request

Hi Lisa,

Our clinical review team has the following information request that requires a response:

We have noticed discrepancies between the datasets and the Study Report.

- Section 12.3 of the Study Report describes Deaths, and Other Serious Events and references Table 14.3.2.5 as a primary source. Table 14.3.2.5 is derived from ADaM datasets ADSL, however the numbers we obtain when working with this dataset are discordant from those reported in Table 14.3.2.5. When using the TRT01A column (Actual Treatment for Period 01), there are 91 deaths in the Cabozantinib arm and 113 deaths in the Everolimus arm. This is discordant from Table 14.3.2.5, which lists 90 deaths and 113 deaths in Cabozantinib and Everolimus, respectively.
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rajesh

*Rajesh Venugopal, MPH, MBA*  
*Senior Regulatory Health Project Manager*  
*Division of Oncology Products 1*  
*Office of Hematology and Oncology Products*  
*OND/CDER/FDA*  
*Bldg. 22, Rm. 2171*  
*E-mail: [Rajesh.Venugopal@fda.hhs.gov](mailto:Rajesh.Venugopal@fda.hhs.gov)*  
*Phone: (301) 796-4730*  
*Fax: (301) 796-9845*

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/s/  
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RAJESH VENUGOPAL  
01/22/2016



**From:** [Venugopal, Rajesh](#)  
**To:** [Lisa Sauer \(lsauer@exelixis.com\)](mailto:Lisa.Sauer@exelixis.com)  
**Subject:** NDA 208692 (Cabozantinib) - Pharmacometrics information request  
**Date:** Thursday, January 21, 2016 9:28:44 AM

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Hello Lisa,

Our pharmacometrics review team has the following information request that requires your response. Please have the items of the request back [by COB, Friday February 12, 2016, if not sooner.](#)

Please address the following questions and submit the dataset regarding the exposure-response (ER) analysis:

1. Please use the exposure-efficacy/safety analyses to assess whether a lower dose of cabozantinib can achieve efficacy similar to the proposed dose, but has less toxicity. In addition to ORR, PFS and OS, the longitudinal continuous tumor size should be analyzed in the following way to evaluate a lower dose:
  - a. Develop an exposure-response model for the time course of tumor size for cabozantinib in RCC patients. Longitudinal drug exposure based on the actual doses should be used.
  - b. Develop a longitudinal exposure – AE model. Sponsor may treat all dose-altering/interrupting AEs as one repeatable event.
  - c. Simulate the dose modification/interruption scenario with a lower starting dose levels (such as 40mg) using the exposure-AE model developed in step b and the current dose adjustment algorithm.
  - d. Sponsor could also assess the net benefit of adding an up-titration option to the current titration algorithm.
  - e. Based on the dose simulated from step c, individual longitudinal exposure can be simulated based on the individual PK parameters from the population PK model. The individual exposure can be used to simulate the time course of tumor size with the lower starting doses.

Related Datasets and code/control streams should be also be submitted along with the above analysis. Define file explaining the dataset and codes should be included.

2. Please submit datasets for FDA reviewer's analysis as SAS transport files (\*.xpt) with define.pdf files. The dataset should include:
  - a. Time and reasons (Types of AE) for each dose adjustment and interruption;
  - b. Types of co-medications at time point when each dose interruption and adjustment happens;
  - c. Dose level after each modification.

Refer to the pharmacometric data submission guidelines

(<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>) for more information.

Please confirm receipt of this and any future information requests regarding your NDA.

Thank you,  
rajesh

*Rajesh Venugopal, MPH, MBA*  
*Senior Regulatory Health Project Manager*  
*Division of Oncology Products 1*  
*Office of Hematology and Oncology Products*  
*OND/CDER/FDA*  
*Bldg. 22, Rm. 2171*  
*E-mail: [Rajesh.Venugopal@fda.hhs.gov](mailto:Rajesh.Venugopal@fda.hhs.gov)*  
*Phone: (301) 796-4730*  
*Fax: (301) 796-9845*

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/s/  
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RAJESH VENUGOPAL  
01/21/2016

**From:** [Venugopal, Rajesh](#)  
**To:** [Lisa Sauer \(lsauer@exelixis.com\)](mailto:Lisa.Sauer@exelixis.com)  
**Subject:** NDA 208692 (Cabozantinib) - Clinical Information Request  
**Date:** Wednesday, January 20, 2016 7:14:43 AM

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Hi Lisa,

Our clinical team has the following information request that require a response:

Section 10.2 of the Study Report describes Protocol Deviations, including tables which further delineate the nature of protocol deviations. Please indicate which datasets and columns these tables were derived from. In addition, please describe how protocol deviations were determined to be coded as "Important".

Please respond [by 5PM EST Friday, January 22, 2016, if not sooner.](#)

Thank you,  
Rajesh

*Rajesh Venugopal, MPH, MBA*  
*Senior Regulatory Health Project Manager*  
*Division of Oncology Products 1*  
*Office of Hematology and Oncology Products*  
*OND/CDER/FDA*  
*Bldg. 22, Rm. 2171*  
*E-mail: [Rajesh.Venugopal@fda.hhs.gov](mailto:Rajesh.Venugopal@fda.hhs.gov)*  
*Phone: (301) 796-4730*  
*Fax: (301) 796-9845*

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/s/  
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RAJESH VENUGOPAL  
01/20/2016

**Note:** The PeRC review of this product will likely occur *after* the Review Division checks this completed document into DARRTS. The PeRC's recommendation, which may differ from the information in this document, will be described in the PeRC meeting minutes. PeRC meeting minutes are linked in DARRTS to the INDs and applications discussed during each meeting.

Dear Review Division:

The attached template includes the necessary documentation to facilitate the *required* Pediatric Review Committee (PeRC) review of Waivers, Deferrals, Pediatric Plans, and Pediatric Assessments before product approval.

**Complete the section(s) of this template that are relevant to your *current submission*.**

***Definitions:***

***Deferral*** – A deferral is granted when a pediatric assessment is required but has not been completed at the time the New Drug Application (NDA), Biologics License Application (BLA), or supplemental NDA or BLA is ready for approval. On its own initiative or at the request of an applicant, FDA may defer the submission of some or all required pediatric studies until a specified date after approval of the drug or issuance of the license for a biological product if the Agency finds that the drug or biological product is ready for approval in adults before the pediatric studies are completed, the pediatric studies should be delayed until additional safety and effectiveness data have been collected, or there is another appropriate reason for deferral.

***Full Waiver*** – On its own initiative or at the request of an applicant, FDA may waive the requirement for a pediatric assessment for all pediatric age groups if: (1) studies would be impossible or highly impracticable; (2) there is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups; or (3) the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, AND is not likely to be used in a substantial number of pediatric patients. If studies are being waived because there is evidence that the product would be ineffective or unsafe in all pediatric age groups, this information **MUST** be included in the pediatric use section of labeling.

***Partial Waiver*** – FDA may waive the requirement for a pediatric assessment for a specific pediatric age group if any of the criteria for a full waiver are met for that age group or if the applicant can demonstrate that reasonable attempts to produce a pediatric formulation for that age group have failed. If a partial waiver is granted because a pediatric formulation cannot be developed, the partial waiver will only cover the pediatric groups requiring that formulation.

***Pediatric Assessment*** – The pediatric assessment contains data gathered from pediatric studies using appropriate formulations for each age group for which the assessment is required. It also includes data that are adequate to: (1) assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations; and (2) support dosing and administration for each pediatric subpopulation for which the data support a finding that the product is safe and effective.

***Pediatric Plan*** – A pediatric plan is the applicant’s statement of intent describing the planned or ongoing pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that they plan to conduct or are conducting (i.e., the pediatric studies that will comprise the pediatric assessment). If necessary, the plan should address the development of an age-appropriate formulation and must contain a timeline for the completion of studies. FDA recommends that the timeline should include the dates the applicant will: (1) submit the protocol; (2) complete the studies; and 3) submit the study reports.

***Pediatric Population/Patient***- 21 CFR 201.57 defines pediatric population (s) and pediatric patient (s) as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

***PREA Pediatric Record/Pediatric Page*** – The pediatric record is completed for all NDAs, BLAs, or supplemental NDAs or BLAs. This record indicates whether the application triggers the Pediatric Research Equity Act (PREA), and if so, indicates how pediatric studies will be or have been addressed for each pediatric age group. If the Agency is waiving or deferring any or all pediatric studies, the pediatric record also includes the reason(s) for the waiver and/or deferral. (Note that with the implementation of DARRTS, the Pediatric Record is replacing the Pediatric Page for NDAs. The Pediatric Page is still to be used for BLAs.) For NDAs, the information should be entered into DARRTS and then the form should be created and submitted along with other required PeRC materials. Divisions should complete the Pediatric Page for NDAs that do not trigger PREA and submit the Pediatric Page via email to CDER PMHS until further notice.

# Pediatric Research Equity Act (PREA) Waiver Request, Deferral Request/Pediatric Plan and Assessment Template(s)

## BACKGROUND

Please check all that apply:  Full Waiver  Partial Waiver  Pediatric Assessment  Deferral/Pediatric Plan

NDA#: 208692

PRODUCT PROPRIETARY NAME: Cabometyx

ESTABLISHED/GENERIC NAME: Cabozantinib

APPLICANT/SPONSOR: Exelixis, Inc.

### PREVIOUSLY APPROVED INDICATION/S:

(1) Cabozantinib (Cometriq) is approved for the following indication under NDA 203756 that is currently managed by DOP2: Treatment of <sup>(b) (4)</sup>, medullary <sup>(b) (4)</sup> thyroid <sup>(b) (4)</sup> metastatic <sup>(b) (4)</sup> cancer.

- (2) \_\_\_\_\_
- (3) \_\_\_\_\_
- (4) \_\_\_\_\_

### PROPOSED INDICATION/S:

- (1) Treatment of Advanced Renal Cell Carcinoma in patients who received <sup>(b) (4)</sup> prior therapy
- (2) \_\_\_\_\_
- (3) \_\_\_\_\_
- (4) \_\_\_\_\_

NDA STAMP DATE: December 22, 2015

PDUFA GOAL DATE: June 22, 2016/ Target Goal Date: May 13, 2016

SUPPLEMENT TYPE: N/A



**SUPPLEMENT NUMBER:** N/A

*Does this application provide for (If yes, please check all categories that apply and proceed to the next question):*

*NEW  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?*

*Did the sponsor submit an Agreed iPSP? Yes  No*

*Did FDA confirm its agreement to the sponsor's Agreed iPSP? Yes  No*

*Has the sponsor submitted a Proposed Pediatric Study Request (PPSR) or does the Division believe there is an additional public health benefit to issuing a Written Request for this product, even if the plan is to grant a waiver for this indication? (Please note, Written Requests may include approved and unapproved indications and may apply to the entire moiety, not just this product.)*

*Yes  No*

*Is this application in response to a PREA (Postmarketing Requirement) PMR? Yes  No*

*If Yes, PMR # \_\_\_\_\_ NDA # \_\_\_\_\_*

*Does the division agree that this is a complete response to the PMR? Yes  No*

*If Yes, to either question Please complete the Pediatric Assessment Template.*

*If No, complete all appropriate portions of the template, including the assessment template if the division believes this application constitutes an assessment for any particular age group.*

## WAIVER REQUEST

*Please attach:*

- Draft Labeling (If Waiving for Safety and/or Efficacy) from the sponsor unless the Division plans to change. If changing the sponsor's proposed language, include the appropriate language under Question 4 in this form.*
- Pediatric Record*

1. Pediatric age group(s) to be waived. All pediatric age subsets
2. Reason(s) for waiving pediatric assessment requirements (*Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.*)
  - Studies are impossible or highly impractical (e.g. the number of pediatric patients is so small or is geographically dispersed). (Please note that in the DARRTS record, this reason is captured as "Not Feasible.") If applicable, chose from the adult-related conditions on the next page.
  - The product would be ineffective and/or unsafe in one or more of the pediatric group(s) for which a waiver is being requested. Note: If this is the reason the studies are being waived, this information **MUST** be included in the pediatric use section of labeling. Please provide the draft language you intend to include in the label. The language must be included in section 8.4 and describe the safety or efficacy concerns in detail.
  - The product fails to represent a meaningful therapeutic benefit over existing therapies for pediatric patients **and** is unlikely to be used in a substantial number of all pediatric age groups or the pediatric age group(s) for which a waiver is being requested.
  - Reasonable attempts to produce a pediatric formulation for one or more of the pediatric age group(s) for which the waiver is being requested have failed. (Provide documentation from Sponsor) Note: Sponsor must provide data to support this claim for review by the Division, and this data will be publicly posted. (***This reason is for Partial Waivers Only***)

3. Provide justification for Waiver: *Disease/condition (Renal Cell Carcinoma) does not exist in children.*

4. Provide language Review Division is proposing for Section 8.4 of the label if different from sponsor's proposed language:

**Adult-Related Conditions that qualify for a waiver because they rarely or never occur in pediatrics**

These conditions qualify for waiver because studies would be impossible or highly impractical.

actinic keratosis

adjunctive treatment of major depressive disorder

age-related macular degeneration

Alzheimer's disease

amyloidosis

amyotrophic lateral sclerosis

androgenic alopecia

atherosclerotic cardiovascular disease

autosomal dominant polycystic kidney disease (ADPKD)

benign monoclonal gammopathy

benign prostatic hyperplasia

cancer:

    basal cell and squamous cell skin cancer

    bladder

    breast

    cervical

    colorectal

    endometrial

    esophageal

cancer (continued):

    follicular lymphoma

    gastric

    hairy cell leukemia

    hepatocellular

    indolent non-Hodgkin lymphoma

    lung (small & non-small cell)

    multiple myeloma

    oropharynx (squamous cell)

    ovarian (non-germ cell)

    pancreatic

    prostate

    refractory advanced melanoma

    renal cell

    uterine

chronic lymphocytic leukemia

chronic obstructive pulmonary disease

cryoglobulinemia

diabetic peripheral neuropathy / macular edema

digestive disorders (gallstones)  
dry eye syndrome (keratoconjunctivitis sicca)  
erectile dysfunction  
essential thrombocytosis  
Huntington's chorea  
infertility & reproductive technology  
ischemic vascular diseases, such as angina, myocardial infarction, and ischemic stroke  
memory loss  
menopause and perimenopausal disorders  
mesothelioma  
myelodysplasia  
myelofibrosis & myeloproliferative disorders  
osteoarthritis  
overactive bladder  
Parkinson's disease  
paroxysmal nocturnal hemoglobinuria  
plasma cells and antibody production disorders  
polycythemia vera  
postmenopausal osteoporosis  
prevention of stroke and systemic embolic events in atrial fibrillation

psoriatic arthritis  
reduction of thrombotic cardiovascular events in patients with coronary artery disease  
replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone  
retinal vein occlusions  
stress urinary incontinence  
temporary improvement in the appearance of caudal lines  
treatment of incompetent great saphenous veins and varicosities  
type 2 diabetic nephropathy  
vascular dementia/vascular cognitive disorder/impairment

## DEFERRAL REQUEST

Please attach:

*Pediatric Record*

1. Age groups included in the deferral request:
2. Where deferral is only requested for certain age groups, reason(s) for not including entire pediatric population in deferral request:
3. Reason/s for requesting deferral of pediatric studies in pediatric patients with disease: *(Choose one. If there are different reasons for different age groups or indications, please choose the appropriate reason for each age group or indication. This section should reflect the Division's thinking.)*
  - a. Adult studies are completed and ready for approval
  - b. Additional safety or effectiveness data needed (**describe**)
  - c. Other (**specify**)
4. Provide projected date for the submission of the pediatric assessment (deferral date):
5. Did applicant provide certification of grounds for deferring assessments?  Yes  No
6. Did applicant provide evidence that studies will be done with due diligence and at the earliest possible time?  Yes  No

## SPONSOR'S PROPOSED PEDIATRIC PLAN

1. Has a pediatric plan been submitted to the Agency?  Yes  No
2. Does the division agree with the sponsor's plan?  Yes  No
3. Did the sponsor submit a timeline for the completion of studies (must include at least dates for protocol submission, study completion and studies submitted)?  Yes  No

- a. **Protocol Submission:**
- b. **Study Completion:**
- c. **Study Submission:**

4. **Has a Written Request been issued?**  Yes  No (If yes and the WR matches the proposed pediatric plan, please attach a copy. It is not necessary to complete the remainder of this document)
5. **Has a PPSR been submitted?**  Yes  No (If yes, you may submit a draft WR and have PeRC review WR and deferral/plan at the same time.)

*Please note that the remainder of this section should be completed based on what the Division is requiring regardless of what the sponsor is proposing.*

**DIVISION'S PROPOSED PK, SAFETY, AND EFFICACY TRIAL**

*Please complete as much of the information below as possible. Please note that the portions of the document that are shaded are not required for early stage pediatric plans but are useful if available.*

**Types of Studies/Study Design:**

**Nonclinical Studies:**

**Clinical Studies:**

**Age group and population (indication) in which study will be performed:**

This section should list the age group and population exactly as it is in the plan.

*Example:*

*Study 1: patients aged X to Y years.*

*Study 2: sufficient number of subjects to adequately characterize the pharmacokinetics in the above age groups.*

**Number of patients to be studied or power of study to be achieved:**

*Example:*

*Study 1: X subjects in each treatment arm and be powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% must be females and 25% must be less than 3 years.*

*Study 2: This study is powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters.*

**Entry criteria:**

*This section should list pertinent inclusion/exclusion criteria.*

*Example:*

*Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs  
Patients must have a negative pregnancy test if female..*

**Clinical endpoints:**

*Example:*

*Study 1: Clinical outcome and safety will be the primary endpoints.*

*Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG should attempt to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F.*

**Timing of assessments:**



*Example :baseline, week 1, 4, and 6*

**Statistical information (statistical analyses of the data to be performed):**

*Example:*

*Study 1 non-inferiority: two-sided 95% confidence interval (CI) of treatment difference in improvement rates should be within 25% of the control's response rate.*

*Study 2: descriptive statistical methods for AUC, C max, Tmax, CI/F and compared to adults.*

**Division comments on product safety:**

*Are there any safety concerns currently being assessed?*  **Yes**  **No**

*Are there safety concerns that require us to review post-marketing safety data before fully designing the pediatric studies?*  **Yes**  **No**

*Will a DSMB be required?*  **Yes**  **No**

*Other comments:*

**Division comments on product efficacy:**

**Division comments on sponsor proposal to satisfy PREA:**

**PeRC ASSESSMENT TEMPLATE**

*Please attach:*

- Proposed Labeling from the sponsor unless the Division plans to change. If changing the language, include the appropriate language at the end of this form.*
- Pediatric Record*

**Date of PREA PMR:**

**Description of PREA PMR:** *(Description from the PMC database is acceptable)*

Was Plan Reviewed by PeRC?  **Yes**  **No** If yes, did sponsor follow plan?

**If studies were submitted in response to the Written Request (WR), provide the annotated WR in lieu of completing the remainder of the Pediatric Assessment template.**

**Indication(s) that were studied:**

This section should list the indication(s) exactly as written in the *protocols*.

*Example:*

*DRUG for the treatment of the signs and symptoms of disease x.*

**Number of Centers** \_\_\_\_\_

**Number and Names of Countries** \_\_\_\_\_

**Drug information:**

*Examples in italics*

- **Route of administration:** *Oral*
- **\*Formulation:** *disintegrating tablet*
- **Dosage:** *75 and 50 mg*
- **Regimen:** *list frequency of dosage administration*

*\*If the dosage form is powder for oral suspension; provide information on storage statement and concentration after reconstitution (e.g. with water, juice or apple sauce etc.)*

**Types of Studies/ Study Design:**

*Example:*

*Study 1: Multi- center, randomized, active controlled double blind study to evaluate the safety and efficacy of (drug name, concentration, form etc) DRUG administered twice daily for the treatment of patients with disease x.*

*Study 2: PK and safety study of (drug name, concentration, form etc) DRUG in patients with disease x.*

**Age group and population in which study/ies was/were performed:**

*Example:*

*Study 1: patients aged X to Y years.*

*Study 2: sufficient number of patients to adequately characterize the pharmacokinetics in the above age groups.*

**Number of patients studied or power of study achieved:**

*Example:*

*Study 1: X patients in each treatment arm and was powered to show that (drug name, concentration, form etc) DRUG is not inferior to the active comparator. 50% were females and 25% were less than 3 years.*

*Study 2: powered and structured to detect a 30% change in (drug name, concentration, form etc) DRUG clearance and other relevant pharmacokinetic parameters. The study included at least X evaluable patients. .*

**Entry criteria:**

This section should list pertinent inclusion/exclusion criteria.

*Example:*

*Entry criteria: Pediatric patients with disease x diagnosed with laboratory test of LFTs*

*Patients had a negative pregnancy test if female.*

**Clinical endpoints:**

*Example:*

*Study 1: Clinical outcome and safety were the primary endpoints.*

*Study 2: The primary pharmacokinetic analysis of (drug name, concentration, form etc) DRUG attempted to include all the patients in the study with determination of the following parameters: single dose and steady state AUC, Cmax, Tmax, and CL/F*

**Statistical information (statistical analyses of the data performed):**

This section should list the statistical tests conducted.

*Example:*

*Study 1 - two-sided 95% confidence interval (CI) of treatment difference in improvement rates were within 25% of the control's response rate.*

*Study 2: descriptive statistical methods for AUC, C max, Tmax, Cl/F and compared to adults.*

**Timing of assessments:**

*Example:*

*Baseline, week 2, week 6, and end of treatment*

**Division comments and conclusions (Summary of Safety and Efficacy)**

**Provide language Review Division is proposing for the appropriate sections of the label if different from sponsor-proposed language.**

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/s/  
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RAJESH VENUGOPAL  
01/19/2016

**From:** [Venugopal, Rajesh](#)  
**To:** [Lisa Sauer \(lsauer@exelixis.com\)](mailto:lsauer@exelixis.com)  
**Subject:** NDA 208692 (Cabozantinib) - Clinical information request  
**Date:** Wednesday, January 13, 2016 11:22:53 AM

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Hi Lisa,

Our clinical team has the following information request requiring a response:

During the course of our initial review, we have identified 29 AEs that are missing coding in the AE domain. We would request that you provide the appropriate AEDECODs/MedDRA preferred term (using MedDRA version 17.0) associated with the AEs that are not coded. You can provide this in a Table with the following columns: Uncoded AEs, corresponding AEDECOD.

Please provide your response by COB on Tuesday, January 19<sup>th</sup>, 2016, if not sooner.

Thank you,  
Rajesh

*Rajesh Venugopal, MPH, MBA*  
*Senior Regulatory Health Project Manager*  
*Division of Oncology Products 1*  
*Office of Hematology and Oncology Products*  
*OND/CDER/FDA*  
*Bldg. 22, Rm. 2171*  
*E-mail: [Rajesh.Venugopal@fda.hhs.gov](mailto:Rajesh.Venugopal@fda.hhs.gov)*  
*Phone: (301) 796-4730*  
*Fax: (301) 796-9845*

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/s/  
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RAJESH VENUGOPAL  
01/13/2016





NDA 208692

**NDA ACKNOWLEDGMENT**

Exelixis, Inc.  
Attention: Lisa Sauer  
Vice President, Regulatory Affairs  
210 Grand Avenue  
South San Francisco, CA 94080

Dear Ms. Sauer:

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

Name of Drug Product: Cabometyx (Cabozantinib) Tablets, 20 mg, 40 mg, and 60 mg

Date of Application: December 22, 2015

Date of Receipt: December 22, 2015

Our Reference Number: NDA 208692

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 19, 2016, in accordance with 21 CFR 314.101(a).

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

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

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

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Oncology Products 1  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-4730.

Sincerely,

*{See appended electronic signature page}*

Rajesh Venugopal, MPH, MBA  
Senior Regulatory Project Manager  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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RAJESH VENUGOPAL  
12/28/2015



NDA 208692

**PROPRIETARY NAME REQUEST  
CONDITIONALLY ACCEPTABLE**

Exelixis, Inc.  
210 East Grand Avenue  
South San Francisco, CA 94080

ATTENTION: Lisa Sauer  
Vice President, Regulatory Affairs

Dear Ms. Sauer:

Please refer to your presubmission New Drug Application (NDA) for Cabozantinib Tablets, 20 mg, 40 mg, and 60 mg.

We also refer to your correspondence, dated and received November 5, 2015, requesting review of your proposed proprietary name, Cabometyx.

We have completed our review of the proposed proprietary name, Cabometyx and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your November 5, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names  
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,  
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

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 Rajesh Venugopal, Regulatory Project Manager in the Office of New Drugs, at (301) 796-4730.

Sincerely,

*{See appended electronic signature page}*

Todd Bridges, 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/  
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LUBNA A MERCHANT on behalf of TODD D BRIDGES  
12/22/2015

**From:** [Venugopal, Rajesh](#)  
**To:** [Lisa Sauer \(lsauer@exelixis.com\)](mailto:lsauer@exelixis.com)  
**Subject:** Statistics Information Request - NDA 208692 (Cabozantinib)  
**Date:** Tuesday, November 10, 2015 11:25:31 AM  
**Attachments:** [Carci Data Format and Stat Guidance Info Sheets 11-12-13.pdf](#)

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Hello Lisa,

Our statistics reviewers have the following information request that require your response in reference to the October 12, 2015 submission of Module 4 of the rolling submission of NDA 208692:

The study report for study XL184-NC-042 did not provide datasets. Please submit electronic tumor data which includes all the tumor finding for the animals in all six groups (three dose groups, vehicle control, RO water control, and positive control) in SAS transport format (i.e. xpt file) in the format described on page 3 of the attached **Office of Biostatistics Information Sheet for Submission of Data and for Methods of Data Analysis of Carcinogenicity Studies**.

Please respond **by Monday, November 16, 2015 at 3:00 6PM (EST)**, if not sooner. Please also follow-up with an official response submission to your NDA.

Regards,  
rajesh

*Rajesh Venugopal, MPH, MBA*  
*Senior Regulatory Health Project Manager*  
*Division of Oncology Products 1*  
*Office of Hematology and Oncology Products*  
*OND/CDER/FDA*  
*Bldg. 22, Rm. 2171*  
*E-mail: [Rajesh.Venugopal@fda.hhs.gov](mailto:Rajesh.Venugopal@fda.hhs.gov)*  
*Phone: (301) 796-4730*  
*Fax: (301) 796-9845*

## Office of Biostatistics Information Sheet for Submission of Data and for Methods of Data Analysis of Carcinogenicity Studies

**(The electronic data format is for two-year studies as well as transgenic mouse studies using all except the TgAC mouse models)**

Revised 11/12/2013

The statistical reviewer responsible for the review of the carcinogenicity studies of this NDA/IND submission requests that the sponsor recreate the tumor data in conformance to the electronic format specified in the Agency's April 2008 guidance document entitled "*Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications*". The guidance document can be found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>. The cover page of the document is attached to this information sheet (Attachment A).

In Section III.D.3 of the above document the Agency gives a general description of the data formats for the pharmacology and toxicology datasets and refers readers to the associated document "*Study Data Specifications*" for more information about the format specifications of the data submission. This associated document can be found at the FDA website <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163561.pdf>. At this time, we are only requesting the tumor dataset in the format described on pages 9 and 10 (APPENDIX 1) of the associated document. The table containing the format for tumor data in the document is attached to this information sheet (Attachment B).

Please contact the Agency to provide a time line regarding providing the tumor data. The sponsor needs to carefully meet the data format specifications in order to comply with the above guidance. Any data without 100% conformity will have to be returned for resubmission.

Note that the draft guidance for the statistical analysis of chronic rodent carcinogenicity studies is available on the FDA web site at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079272.pdf>

. Sponsors are urged to use the statistical methods recommended in the guidance to analyze the carcinogenicity study data in their IND or NDA submissions. The cover page of the document is also attached to this information sheet (Attachment C).

For questions related to the data format and the methods of statistical analysis, please contact Karl K. Lin, Ph.D., Room 4677, Building 21, Office of Biostatistics, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002, 301-796-0943, [karl.lin@fda.hhs.gov](mailto:karl.lin@fda.hhs.gov).



(Attachment A)

Cover page of "Guidance for Industry: Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions Using the eCTD Specifications"

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# Guidance for Industry

## Providing Regulatory Submissions in Electronic Format — Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)

June 2008  
Electronic Submissions

Revision 2

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(Attachment B)

**Data format table on page 7 (APPENDIX 1) of the associated document "Study Data Specifications"**

<b>Tumor Dataset For Statistical Analysis<sup>1,2</sup> (tumor.xpt)</b>				
<b>Variable</b>	<b>Label</b>	<b>Type</b>	<b>Codes</b>	<b>Comments</b>
STUDYNUM	Study number	char		<sup>3</sup>
ANIMLNUM	Animal number	char		1,3
SPECIES	Animal species	char	M=mouse R=rat	
SEX	Sex	char	M=male F=female	
DOSEGP	Dose group	num	Use 0, 1, 2, 3,4,... in ascending order from control. Provide the dosing for each group.	
DTHSACTM	Time in days to death or sacrifice	num		
DTHSACST	Death or sacrifice status	num	1 = Natural death or moribund sacrifice 2 = Terminal sacrifice 3 = Planned intermittent sacrifice 4= Accidental death	
ANIMLEXM	Animal microscopic examination code	num	0= No tissues were examined 1 = At least one tissue was examined	
TUMORCOD	Tumor type code	char		3,4
TUMORNAM	Tumor name	char		3,4
ORGANCOD	Organ/tissue code	char		3,5
ORGANNAM	Organ/tissue name	char		3,5
DETECTTM	Time in days of detection of tumor	num		
MALIGNST	Malignancy status	num	1 = Malignant 2= Benign 3 = Undetermined	<sup>4</sup>
DEATHCAU	Cause of death	num	1 = Tumor caused death 2= Tumor did not cause death 3 = Undetermined	<sup>4</sup>
ORGANEXM	Organ/Tissue microscopic examination code	num	1 = Organ/Tissue was examined and was usable 2= Organ/Tissue was examined but was not usable (e.g., autolyzed tissue) 3 = Organ/Tissue was not examined	

<sup>1</sup> Each animal in the study should have at least one record even if it does not have a tumor.

<sup>2</sup> Additional variables, as appropriate, can be added to the bottom of this dataset.

<sup>3</sup> ANIMLNUM is limited to no more than 12 characters; ORGANCOD and TUMORCOD are limited to no more than 8 characters; ORGANNAM and TUMORNAM should be as concise as possible.

<sup>4</sup> A missing value should be given for the variable MALIGNST, DEATHCAU, TUMORNAM and TUMORCOD when the organ is unusable or not examined.

<sup>5</sup> Do not include a record for an organ that was useable and no tumor was found on examination. A record should be included for organs with a tumor, organs found unusable, and organs not examined.

(Attachment C)

Cover page of "Guidance for Industry: Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals"

# Guidance for Industry

## Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals

### *DRAFT GUIDANCE*

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. All comments should be identified with the docket number listed in the notice of availability.

For questions regarding this draft document contact (CDER) Karl K. Lin, Ph.D., 301-796-0943, e-mail [link.lin@fda.hhs.gov](mailto:link.lin@fda.hhs.gov) or [link@cder.fda.gov](mailto:link@cder.fda.gov)

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)

May 2001

Pharm/Tox

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11/22/05

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/s/  
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RAJESH VENUGOPAL  
11/10/2015



IND 072596

**GRANT –  
BREAKTHROUGH THERAPY DESIGNATION**

Exelixis, Inc.  
Attention: Lisa Sauer  
Vice President, Regulatory Affairs  
210 East Grand Avenue  
South San Francisco, CA 94080

Dear Ms. Sauer:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for cabozantinib (XL184).

We also refer to your July 27, 2015, request for Breakthrough Therapy designation. We have reviewed your request and have determined that cabozantinib (XL184) for renal cell carcinoma in patients who received one prior therapy meets the criteria for Breakthrough Therapy designation. Therefore, we are granting your request for Breakthrough Therapy designation. Please note that if the clinical development program does not continue to meet the criteria for Breakthrough Therapy designation, we may rescind the designation.

FDA will work closely with you to provide guidance on subsequent development of cabozantinib (XL184) for renal cell carcinoma in patients who received one prior therapy to help you design and conduct a development program as efficiently as possible. For further information regarding Breakthrough Therapy designation and FDA actions to expedite development of a designated product, please refer to section 902 of the Food and Drug Administration Safety and Innovation Act (FDASIA) and the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics*.<sup>1</sup>

In terms of next steps, please submit a Type B meeting request. This meeting will be for a multidisciplinary comprehensive discussion of your drug development program, including planned clinical trials and plans for expediting the manufacturing development strategy. Please refer to MAPP 6025.6 - Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics, Attachment 1, for potential topics for discussion at this initial breakthrough therapy meeting<sup>2</sup>. Please refer to the *Guidance for Industry: Formal Meetings*

<sup>1</sup><http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

<sup>2</sup><http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm>

*between FDA or Sponsors and Applicants*<sup>3</sup> for procedures on requesting a meeting. If you feel that submitting a meeting request for such a meeting at this point is pre-mature or if you have recently held a major milestone meeting, please contact the Regulatory Health Project manager noted below to discuss the timing of this meeting.

If the breakthrough therapy designation for cabozantinib (XL184) for renal cell carcinoma in patients who received one prior therapy is rescinded, submission of portions of the NDA will not be permitted under this program. However, if you have Fast Track designation you will be able to submit portions of your application under the Fast Track program.

If you have any questions, contact Rajesh Venugopal, Senior Regulatory Project Manager, at (301) 796-4730.

Sincerely,

*{See appended electronic signature page}*

Geoffrey Kim, MD  
Director  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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<sup>3</sup><http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>

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/s/  
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GEOFFREY S KIM  
08/21/2015

## Benton, Sandra J

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**From:** Benton, Sandra J  
**Sent:** Wednesday, August 19, 2015 12:18 PM  
**To:** Jarow, Jonathan; Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Moscicki, Richard; Marcus, Kendall; Kehoe, Theresa; Hinton, Denise; Sacks, Leonard V  
**Cc:** Raggio, Miranda; Brounstein, Daniel; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Throckmorton, Douglas C; Venugopal, Rajesh; Kim, Geoffrey; Ibrahim, Amna; Brave, Michael; Maher, Virginia E.  
**Subject:** RE: September 11, 2015 Medical Policy Council – Breakthrough Therapy Designation - IND 072596

As the Council agrees with DOP1's recommendation to grant Exelixis' breakthrough therapy designation request and does not believe a Council discussion is needed, this request will be cancelled from the September 11, 2015 meeting agenda.

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

Sandy Benton  
Senior Policy Analyst  
CDER/Office of Medical Policy  
301-796-1042  
[sandra.benton@fda.hhs.gov](mailto:sandra.benton@fda.hhs.gov)

---

**From:** Benton, Sandra J  
**Sent:** Friday, August 14, 2015 8:29 AM  
**To:** Jarow, Jonathan; Temple, Robert; Jenkins, John K; Woodcock, Janet; Dal Pan, Gerald; Moscicki, Richard; Marcus, Kendall; Kehoe, Theresa; Hinton, Denise; Sacks, Leonard V  
**Cc:** Raggio, Miranda; Brounstein, Daniel; Benton, Sandra J; Cox, Edward M; Unger, Ellis; Beitz, Julie G; Ganley, Charles J; Pazdur, Richard; Rosebraugh, Curtis; Throckmorton, Douglas C; Venugopal, Rajesh; Kim, Geoffrey; Ibrahim, Amna; Brave, Michael; Maher, Virginia E.  
**Subject:** September 11, 2015 Medical Policy Council – Breakthrough Therapy Designation - IND 072596

Hi! OMP has scheduled a Medical Policy Council discussion on September 11, 2015 regarding the breakthrough therapy designation request from Exelixis, Inc. for its IND 072596, Cabozantinib, XL184 in the treatment of Renal cell carcinoma in patients who received one prior therapy.

DOP1 recommends that this breakthrough therapy request be granted. Attached is DOP1's background on the breakthrough therapy designation with its rationale for granting the request.

DOP1 has asked if this request can be reviewed by email.

Would you please review DOP1's recommendation and let me know by COB Friday, August 21 if –

- You agree with DOP1's recommendation regarding this breakthrough therapy request and you do not believe a Council discussion is needed.
- You agree with DOP1's recommendation regarding this breakthrough therapy request. However, you would like a Council discussion regarding any questions you have.
- You disagree with DOP1's recommendation regarding this breakthrough therapy request.



If the Council agrees with bullet 1, I will cancel the discussion for this IND.

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

Sandy Benton  
Senior Policy Analyst  
CDER/Office of Medical Policy  
301-796-1042  
[sandra.benton@fda.hhs.gov](mailto:sandra.benton@fda.hhs.gov)

<< File: CDER-MPC Breakthrough Therapy Designation.cabozantinib.pdf >> << File: IND 72596\_Cabozantinib\_BTDR.PDF  
>>

## CDER Breakthrough Therapy Designation Determination Review Template

<b>IND #</b>	072596
<b>Request Receipt Date</b>	July 29, 2015
<b>Product</b>	Cabozantinib, XL184
<b>Indication</b>	Renal cell carcinoma in patients who received one prior therapy
<b>Drug Class/Mechanism of Action</b>	Kinase inhibitor
<b>Sponsor</b>	Exelixis, Inc.
<b>ODE/Division</b>	OHOP/DOPI
<b>Breakthrough Therapy Request Goal Date (within <u>60</u> days of receipt)</b>	September 27, 2015 (Sunday)

**Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review. \*Section I to be completed within 14 days of receipt for all BTDRs\***

- 1. Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

The proposed indication is for the treatment of renal cell carcinoma in patients who have received one prior therapy.

- 2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?**  YES  NO

*If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:*

- 3. Consideration of Breakthrough Therapy Criteria:**

- a. Is the condition serious/life-threatening<sup>1</sup>?  YES  NO

*If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:*

- b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?
- YES the BTDR is adequate and sufficiently complete to permit a substantive review
  - Undetermined
  - NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):
    - i. Only animal/nonclinical data submitted as evidence
    - ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information)

<sup>1</sup> For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

- about the protocol[s])
- iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression)
- iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease)
- v. No or minimal clinically meaningful improvement as compared to available therapy<sup>2</sup>/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval)

**4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:**

*If 3b is checked “No”, BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If 3b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.*

**5. Clearance and Sign-Off (no MPC review)**

Deny Breakthrough Therapy Designation

Reviewer Signature: {See appended electronic signature page}  
 Team Leader Signature: {See appended electronic signature page}  
 Division Director Signature: {See appended electronic signature page}

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**Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.**

**6. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.**

Renal cell carcinoma (RCC) is diagnosed in about 330,000 individuals worldwide each year and results in 140,000 deaths. Many patients present with advanced or unresectable disease, and up to 30% of patients relapse after surgical management of initially localized RCC.

Cabozantinib is a small molecule that inhibits the activity of multiple tyrosine kinases, including RET, MET, and vascular endothelial growth factor receptor (VEGFR)-2. On November 29, 2012, the U. S. Food and Drug Administration approved cabozantinib for the treatment of patients with progressive metastatic medullary thyroid cancer.

**7. Information related to endpoints used in the available clinical data:**

Data supporting this Breakthrough Therapy Designation request are from Trial XL184-308. This trial randomized 658 patients with metastatic RCC who had disease progression following treatment with a VEGFR tyrosine kinase inhibitor in a 1:1 open-label fashion to receive 60 mg of cabozantinib daily or 10 mg of everolimus daily. Randomization was stratified based on the number of prior VEGFR tyrosine kinase

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<sup>2</sup> For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

inhibitor therapies received, and on Memorial Sloan Kettering RCC risk criteria. No cross-over was allowed between study arms.

The primary endpoint of Trial XL184-308 was progression free survival (PFS), as determined by an independent radiology committee. Median PFS was 7.4 months for cabozantinib versus 3.8 months for everolimus (HR = 0.58 [95% CI 0.45, 0.75], p< 0.0001). All patients in this study had received a prior VEGFR inhibitor. In a planned interim analysis of overall survival (OS), the median had not been reached in either treatment group (HR 0.67 [95% CI 0.51, 0.89], p = 0.005). At the time of this interim analysis, the pre-specified p-value of 0.0019 to achieve statistical significance in the OS analysis was not reached.

- a. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

Several drug products have received full approval for patients with metastatic RCC based on an improvement in PFS.

- b. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

Not applicable for this Breakthrough Therapy Designation Request

8. **A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:**

During the past decade, the FDA granted regular approval to seven targeted drugs for patients with RCC. Six of these drugs were approved based on improvement in PFS, whereas temsirolimus was approved in poor-prognosis patients based on improved OS (Table 1).

**Table 1. RCTs Supporting Drug Approvals for Treatment of Advanced RCC**

Product	Year	Clinical Trial Supporting Approval			
		Population	N	Control	Result
Sorafenib	2005	Prior cytokine therapy	769	Placebo	Median PFS 5.5 v 2.8 mo HR 0.44 (0.35-0.55)
Sunitinib	2006	Newly diagnosed	750	IFN- $\alpha$	Median PFS 10.8 v 5.1 mo HR: 0.42 (0.32-0.54)
Temsirolimus	2007	Newly diagnosed, poor prognosis	417	IFN- $\alpha$	Median OS 10.9 v 7.3 mo HR: 0.73 (0.58-0.92)
Everolimus	2009	Prior sorafenib or sunitinib	416	Placebo	Median PFS 4.9 v 1.9 mo HR: 0.33 (0.25-0.43)
Bevacizumab plus IFN- $\alpha$	2009	Newly diagnosed	649	IFN- $\alpha$	Median PFS 10.2 v 5.4 mo HR: 0.60 (0.49-0.72)
Pazopanib	2009	Newly diagnosed	435	Placebo	Median PFS 9.2 v 4.2 mo HR: 0.46 (0.34-0.62)
Axitinib	2012	Prior anti-angiogenic therapy	723	Sorafenib	Median PFS 6.7 v 4.7 mo HR 0.67 (0.55-0.81)

Both everolimus and axitinib are approved for second-line treatment in patients with renal cell carcinoma. Everolimus was able to demonstrate an improvement in PFS compared to placebo. Axitinib demonstrated an improvement in PFS against an active comparator. However, when when the subgroup of patients who received a VEGFR inhibitor as first-line therapy was examined, median PFS was 4.8 months in the axitinib

arm and 3.4 months in the sorafenib arm. In the US, the most common first-line therapy for patients with RCC is a VEGFR inhibitor.

**9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation<sup>3</sup>.**

On 27 July 2015, Breakthrough Therapy Designation was granted for lenvatinib for patients with advanced RCC.

On 22 July 2015, Bristol-Myers Squibb requested Breakthrough Therapy Designation for nivolumab for patients with advanced RCC. The status of this request is pending.

**10. Information related to the preliminary clinical evidence:**

Study ID	Phase	Design	Endpoints	Treatment Groups	Result
XL184-308	3	Randomized, open-label, active control	PFS, OS, ORR	Cabozantinib 60 mg daily (n = 320) vs. everolimus 10 mg daily (n = 328)	Median PFS 7.4 months vs 3.8 months (HR 0.58 [95% CI 0.45, 0.75], p < 0.0001)  Median OS not reached (HR 0.67 [95% CI 0.51, 0.89], p = 0.005)

b. Include any additional relevant information.

The control group in Trial XL184-308 received everolimus. Everolimus was granted regular approval based on an improvement in median PFS compared to placebo in patients with RCC and disease progression following prior sorafenib or sunitinib and was therefore an appropriate control group for Trial XL184-308.

Trial XL184-308 appears to have been well conducted and adequately controlled. DOP1 will review the primary datasets for Trial XL184-308 when these are submitted with the sNDA.

The safety profile of cabozantinib 60 mg appears very similar to that of everolimus. Deaths due to an adverse event within 30 days of study drug include 7 patients in the cabozantinib and 10 patients in the everolimus arm. Treatment discontinuation occurred in approximately 10% of patients in each arm. Serious adverse events occurred in 39% of patients receiving cabozantinib and 43% of patients receiving everolimus.

**11. Division's recommendation and rationale (pre-MPC review):**

GRANT :

Provide brief summary of rationale for granting:

Based on the preliminary data submitted, XL184-301 appears to demonstrate a marked improvement in median PFS in patients who received a prior VEGFR inhibitor. There also appears to be a trend toward improvement in median OS, and patients will continue to be followed until the final analysis of OS, which is expected in 2016.

DENY:

<sup>3</sup> Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

Provide brief summary of rationale for denial:

**12. Division's next steps and sponsor's plan for future development:**

- a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The Division and the Sponsor had a teleconference on July 22, 2015 to discuss the results of Trial XL184-308. It was agreed that the Sponsor would submit the preliminary datasets and would submit a NDA in the very near future.

- b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

**13. List references, if any:**

Not applicable for this Breakthrough Therapy Designation request

**14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting?** YES  NO

**15. Clearance and Sign-Off (after MPC review):**

Grant Breakthrough Therapy Designation   
Deny Breakthrough Therapy Designation

Reviewer Signature: {See appended electronic signature page}  
Team Leader Signature: {See appended electronic signature page}  
Division Director Signature: {See appended electronic signature page}

**5-7-15/M. Raggio**

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/s/  
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MICHAEL H BRAVE  
08/13/2015

VIRGINIA E MAHER  
08/13/2015

GEOFFREY S KIM  
08/13/2015

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/s/  
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SANDRA J BENTON  
08/19/2015

GEOFFREY S KIM  
08/20/2015



### MEMORANDUM OF MEETING MINUTES

**Meeting Type:** Type B  
**Meeting Category:** End of Phase 2

**Meeting Date and Time:** April 19, 2012  
**Meeting Location:** White Oak Campus

**Application Number:** IND 072596  
**Product Name:** Cabozantinib, XL184  
**Indication:** Advanced Malignancies  
**Sponsor/Applicant Name:** Exelixis  
**Meeting Request Date:** November 3, 2011  
**Meeting BGP date:** March 13, 2012

**Meeting Chair:** V. Ellen Maher, M.D., Clinical Team Leader, DOP 1  
**Meeting Recorder:** Frank H. Cross, Jr., CPMS, DOP1

#### FDA ATTENDEES

Robert Justice, M.D., M.S., Director, DOP 1  
Amna Ibrahim, M.D., Deputy Division Director, DOP 1  
Michael Brave, M.D., Medical Officer, DOP 1  
V. Ellen Maher, M.D., Clinical Team Leader, DOP 1  
Whitney Helms, Ph.D., Pharmacologist/Acting Supervisory Pharmacologist, DHOT  
Capt. Frank Cross Jr., M.A., MT (ASCP), Chief, Project Management Staff, DOP 1  
Qi Liu, Ph.D., Team Leader, Office of Clinical Pharmacology, DCP5  
Elimika Pfuma, Pharm.D., Ph.D., Clinical Pharmacology Reviewer, DCP5  
Shenghui Tang, Ph.D, Team Leader, DB 5  
Somesh Chattopadhyay, Ph.D., Mathematical Statistician, DB 5  
Hui Zhang, Ph.D., Mathematical Statistician, DB 5  
Stella Karati, Ph.D., Mathematical Statistician, DB 5  
Jonathan Jarow, M.D., Medical Officer, DRUP

#### SPONSOR ATTENDEES

Ron Weitzman, MD	Vice President, Clinical Research
Gisela Schwab, MD	Chief Medical Officer and Executive Vice President, Development
Colin Hessel, MS	Vice President, Biostatistics and Clinical Data Management
Lisa Sauer	Senior Director, Regulatory Affairs

## 1.0 BACKGROUND

The Sponsor intends to develop cabozantinib (previously XL184) as monotherapy for patients with metastatic castration-resistant prostate cancer (mCRPC). The sponsor's ongoing double-blind trial (Trial XL184-306) randomizes patients with metastatic CRPC who have received docetaxel to cabozantinib+ prednisone + placebo vs. mitoxantrone + prednisone + placebo. The primary endpoint is the proportion of patients with a pain response at Weeks 9 and 12 and a bone scan response at Week 12. The proposed, double-blind trial (Trial XL184-307) will compare cabozantinib + placebo to placebo + prednisone in patients with CRPC metastatic to bone and who have had prior docetaxel and either abiraterone or MDV3100. Prior cabazitaxel is permitted, but not required. The primary endpoint is OS.

## 2.0 DISCUSSION

1. Eligible subjects will have received prior docetaxel and either abiraterone or MDV3100 treatment and have evidence of disease progression on each agent independently. There will be no limit on the number of prior therapies, which would allow for subjects to also have received agents such as cabazitaxel. Does the Agency agree with the intended patient population?

### **FDA response:**

**Yes; however, the informed consent should provide clear information concerning treatment options and associated improvements in survival. Please see response to Question 2.**

### ***Sponsor Response:***

***The Sponsor acknowledges the Agency's comments. The informed consent will include clear information concerning treatment options (e.g., cabazitaxel) and associated improvements in survival.***

2. The proposed patient population will be required to have received at a minimum prior treatment with docetaxel (minimum cumulative dose of 225 mg/m<sup>2</sup>) and either abiraterone or MDV3100, and therefore will be at least third-line. The Sponsor therefore proposes using prednisone as a comparator to cabozantinib. Prednisolone will be used in countries where prednisone is not available. Does the Agency agree with the choice of comparator in the proposed study?

### **FDA response:**

**Possibly. Please justify the decision not to use cabazitaxel in the control group, given that cabazitaxel has demonstrated a survival advantage in patients with mCRPC after failure of docetaxel. It may be difficult to accrue and to maintain patients on placebo + prednisone. Please clarify in which region(s) of the world you anticipate conducting your trial.**

**Protocol Section 3.3 states, "Subjects who are being maintained on daily doses of prednisone or prednisolone prior to enrollment will be allowed to continue to take these**

**medications. In such cases, prednisone or prednisolone will be regarded as a concomitant medication after randomization in this study.” Please reconcile how prednisone or prednisolone can be regarded as a concomitant medication if started prior to enrollment yet as the primary anticancer treatment when started in the control arm.**

**Please provide an estimate of the proportion of patients you believe will be taking prednisone or prednisolone at enrollment. We recommend that you either exclude those patients from the trial or stratify randomization by use of prednisone or prednisolone at study entry. We note that patients on the control arm could end up receiving higher doses of steroids.**

***Sponsor Response:***

***This study is planned to be conducted in the US, Canada, Europe, and Australia.***

***Patients with CRPC who have failed both docetaxel and a second therapy post-docetaxel have not yet been evaluated in a controlled study and an estimate of the potential treatment benefit of cabazitaxel in this population is unknown. Cabazitaxel is approved in a post-docetaxel setting; patients included in the cabazitaxel registrational trial had not received other prior therapies.***

***The Sponsor proposes that prior treatment with cabazitaxel not be required for study eligibility. At the current approved dose of cabazitaxel, the rate of Grade 5 related adverse events in the registrational Phase 3 study for cabazitaxel was 5%. In consultation with key opinion leaders it has been recommended that treatment with cabazitaxel be allowed but not required as prior therapy given the concern around the rate of treatment-related mortality at the current dose of cabazitaxel.***

***The Sponsor intends to allow patients who have received prior cabazitaxel (in addition to the mandated above mentioned prior docetaxel and abiraterone or MDV3100 therapies) to enter study XL184-307. Subjects in Study XL184-307 will be stratified by prior receipt of cabazitaxel.***

***Prednisone is commonly used as symptomatic/supportive care for patients with CRPC, however there is no known effect of prednisone on survival in this population. Based on the single-agent cabozantinib Phase 2 study, there was no clinical or scientific reason to mandate that any subject receiving cabozantinib also receive prednisone. Similarly there is no good reason to prohibit continuation of this palliative agent if investigators believe patients are benefiting from it.***

***The Sponsor would like to minimize the number of stratification factors to those that are most likely to affect the primary endpoint of overall survival. Hence, the Sponsor chose to stratify randomization by ECOG performance status (0-1 versus 2), prior cabazitaxel (yes/no), and average worst pain at baseline (BPI <4 vs. ≥4).***

*As with any concomitant medication, if a subject in either arm is receiving open-label prednisone as a concomitant medication and the investigator believes the subject is experiencing steroid-related toxicity, the open-label prednisone can be reduced, held or permanently discontinued. The protocol also provides guidance for dose modification of blinded study treatment (including prednisone). In discussion with the Protocol Steering Committee, modestly higher doses of prednisone in the control arm are unlikely to be of clinical significance.*

*It is difficult to accurately predict what fraction of the study population will be receiving prednisone at study entry since subjects may have failed either abiraterone (which requires concomitant prednisone therapy) or MDV3100 (which does not require concomitant prednisone therapy).*

*The Sponsor will consider subgroup analyses based upon use of prednisone as a concomitant medication. Further, the IDMC will be regularly evaluating the safety profiles of each treatment arm.*

**Discussion:**

**The Sponsor plans to include prednisone as a concomitant medication in both arms of the study. They will examine the use of prednisone as a concomitant medication between arms. The Agency stated that the decision to use prednisone as a concomitant medication is at their risk.** (b) (4)

3. The primary endpoint is overall survival. Does the Agency agree with the choice of primary endpoint for the intended patient population?

**FDA response:**

**Yes.**

**Please consider, as an exploratory endpoint, an examination of radiographic PFS as defined in the PCWG2 criteria (JCO 2008 26:1148).**

***Sponsor Response:***

***The Sponsor will consider the proposed exploratory endpoint.***

4. The analysis of OS is event-based and will be conducted after at least 578 deaths have been observed in the study. An interim analysis is proposed after 67% of these deaths are observed with the potential to stop early for overwhelming evidence of efficacy. No formal futility analyses are planned. The total two-sided Type I error rate of 0.05 for the primary endpoint will be controlled over the interim and final analyses by implementing a Lan-DeMets O'Brien-Fleming alpha spending function. The secondary efficacy endpoint will be tested (at the 2-sided 0.05 level) at most once, if the null hypothesis for the primary efficacy endpoint is rejected at either the interim or final analysis. The Sponsor proposes this strategy adequately controls the

familywise error rate, though not in the strong sense. Does the Agency agree with the proposed approach to control for Type 1 error?

**FDA response:**

**Yes; however, the study size is based upon a projected HR of 0.75 with an improvement in median OS from 7 to 9.3 months. In the TROPIC study, median OS was 12.7 months in the mitoxantrone + prednisone arm.**

**Please comment on the assumptions made in determining sample size. It would be helpful if PFS in docetaxel pre-treated patients in Study 203 was examined using the PFS definition in the TROPIC study.**

*Sponsor Response:*

*Overall survival has not yet been evaluated in a population that has received both docetaxel and abiraterone (or MDV3100); therefore, some assumptions were made for OS in this study. In the Phase 3 abiraterone study COU-AA-301 (post-docetaxel), the median OS for the abiraterone arm was 15 months. However, the median time subjects were on abiraterone was 8 months. The target patient population for the proposed Phase 3 cabozantinib study XL184-307 is one that has failed abiraterone or MDV3100 (and have also received docetaxel); a median OS of 7 months was judged to be a reasonable assumption for the control arm in this study.*

*As the primary analysis of OS is event-driven, power is maintained under the assumed hazard ratio even if the assumed median is underestimated.*

*In the setting of CRPC, the definition of PFS has historically varied from study to study. PFS was not factored into the OS assumptions, nor was data from the TROPIC study, as this was conducted in an abiraterone and MDV3100-naïve patient population.*

**Discussion:**

**The Sponsor explained their rationale for the sample size and the assumptions used in deriving the sample size.**

5. Subjects will be randomized 2:1 to cabozantinib or prednisone. Randomization will be stratified according to ECOG performance status (0-1 versus 2), prior cabazitaxel (yes/no), and average worst pain at baseline (BPI <4 vs. ≥4). Does the Agency agree with this proposal regarding stratification of subjects?

**FDA response:**

**Yes. However, see response to Question #2 above.**

*Sponsor Response:*

*The Sponsor acknowledges the Agency's comments.*

*Question regarding the registration pathway:*

6. In this Phase 3 study, the Sponsor is proposing to use OS as the primary endpoint. The secondary endpoint is bone scan response at Week 12. Would the Agency consider data from this single randomized, multi-center, controlled study (N ~ 960) acceptable to support full approval of cabozantinib in metastatic CRPC?

**FDA response:**

**Possibly. The acceptability of a single trial to support approval is a review issue and depends on the magnitude of benefit and the adverse event profile of your product. Here, it would also depend upon the findings from the ongoing trial, XL184-306.**

**For a single randomized trial to support an NDA, the trial must be well designed, well conducted and internally consistent and provide clinically meaningful and statistically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform.**

**We consider your proposed secondary endpoint to be exploratory and unlikely to result in a labeling claim.**

*Sponsor Response:*

*The Sponsor acknowledges the Agency's comments. With regard to the secondary endpoint, the Sponsor hopes that the Agency will reconsider this position at the time of review if the Sponsor provides supportive data from a large well controlled study.*

*To support the assessment of the secondary endpoint, bone scans will be assessed by an independent radiology facility, (b) (4), using their validated CAD-based technology. The CAD system is part of the (b) (4) IBIS Oncology System which has obtained FDA 510K clearance. Bone scans are obtained on equipment at clinical sites that have undergone credentialing from (b) (4) to ensure scans are consistent in acquisition parameters and image quality.*

**Discussion:**

**FDA will provide contact information concerning the FDA's biomarker qualification working group.**

**Comments added after the meeting**

**Please contact Shashi Amur at [shashi.amur@fda.hhs.gov](mailto:shashi.amur@fda.hhs.gov) or at (301) 796-1631.**

7. An interim analysis is proposed after 67% of the planned deaths observed with the potential to stop early for overwhelming evidence of efficacy ( $p < 0.0121$  per the alpha-spending function). Does the Agency agree that meeting the criteria for statistical significance at the interim analysis would support approval?

**FDA response:**

**Possibly. See FDA response to question 6.**

***Sponsor Response:***

***The Sponsor acknowledges the Agency's comments.***

**Additional FDA Comments:**

- Please clarify whether the cabozantinib tablet formulation is bioequivalent to the to-be-marketed capsule formulation that you mentioned in NDA 203756.

***Sponsor's Response:***

***The tablet formulation has been evaluated in a bioavailability study versus the capsule formulation. Study XL184-005 is a Phase 1, open-label, randomized, single-dose, two-treatment, two-way crossover comparative bioavailability study of cabozantinib tablet and capsule formulations in healthy volunteers. Subjects received single oral doses of the assigned treatment of Test (100 mg freebase cabozantinib, dosed as one 100-mg tablet) or Reference (100 mg freebase cabozantinib, dosed as two 50-mg capsules), according to a randomization scheme, each dose was administered under fasting conditions, and blood samples were collected up to 504 hours post-dose for each subject after each treatment to assess plasma cabozantinib PK.***

***Based on the preliminary PK data from 23 subjects who completed both treatments, after a single oral dose of cabozantinib at 100 mg freebase, the terminal  $t_{1/2, z}$  of cabozantinib appeared to be similar for both tablet and capsule formulations, with mean values of approximately 110 hours. The median observed time to maximum plasma concentration ( $t_{max}$ ) was 4 hours for the tablet formulation and 5 hours for the capsule formulation. High inter-subject variability for  $C_{max}$  and AUC values was observed for both formulations [CV%  $C_{max}$ : 51% for the tablet formulation, 61% for the capsule formulation; CV%  $AUC_{0-last}$  or  $AUC_{0-inf}$ : 40-43% for the tablet formulation, 43% for the capsule formulation]. The geometric mean  $C_{max}$  of the tablet formulation was approximately 49% higher than the value observed for the capsule formulation. The geometric mean  $AUC_{0-last}$  and  $AUC_{0-inf}$  values for the tablet formulation were also higher (15% and 19%, respectively) than those observed for the capsule formulation. However, due to the high observed within-formulation variability, no statistical difference in exposure between the two formulations was apparent.***

***The final study report for Study XL184-005 will be submitted to IND 72,596.***

***The Sponsor intends to have a commercial tablet formulation***

(b) (4)

**Discussion:**

**The Sponsor indicated that they plan to use different formulations (which may not be bioequivalent to each other) for different indications. The Agency stated that this is not**

**ideal and encouraged the Sponsor to submit a CMC report or request a meeting with the Agency to further discuss this issue. The Agency also recommended that the DMC examine the safety of this new formulation early in the conduct of their Phase 3 trial. The Agency remains concerned about having two different formulations on the market that may not be bioequivalent.**

- Since the dose of cabozantinib is lower than that used in previous trials, consider an early examination of drug activity by the DMC.

***Sponsor's Response:***

***The Sponsor acknowledges the Agency's suggestion, and will take it under consideration.***

- CTCs will be evaluated as part of the proposed trial. Please comment on any plans to use the results of this trial to validate this endpoint.

***Sponsor's Response:***

***The Sponsor is committed to helping to establish the validity of this endpoint and is using validated methodology from (b) (4). Since validation of CTCs as an endpoint in CRPC would require access to data on other compounds, the Sponsor is open to collaboration and any recommendations the Agency might have.***

**Discussion:**

**FDA will provide contact information concerning the FDA's biomarker qualification working group.**



**3.0 ISSUES REQUIRING FURTHER DISCUSSION**

None.

**4.0 ACTION ITEMS**

None.

Action Item/Description	Owner	Due Date
	FDA	
	Sponsor	

**5.0 ATTACHMENTS AND HANDOUTS**

None.

Minutes Preparer:

Meeting Chair

*{See appended electronic signature page}*

*{See appended electronic signature page}*

Frank H. Cross, Jr.  
CPMS, DOP1

V. Ellen Maher, M.D.  
Clinical Team Leader, DOP 1

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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VIRGINIA E MAHER  
04/24/2012



FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** B  
**Meeting Category:** EOP2

**Meeting Date and Time:** May 23, 2011, 3PM  
**Meeting Location:** White Oak, Building 22, room 1419

**Application Number:** IND 072596  
**Product Name:** XL184  
**Indication:** Treatment of pain related to bone metastasis in patients with castration-resistant prostate cancer (CRPC) who have received prior docetaxel therapy.

**Sponsor/Applicant Name:** Exelixis  
**Meeting Request Date:** March 3, 2011  
**Meeting BGP date:** April 21, 2011

**Meeting Chair:** Ke Liu  
**Meeting Recorder:** Paul Zimmerman

**FDA ATTENDEES**

Richard Pazdur, M.D., Director, OODP  
Anthony Murgo, M.D., Associate Director, OODP  
Amna Ibrahim, M.D., Deputy Division Director  
Ke Liu, M.D., Ph.D., Lead Medical Officer  
Michael Brave, M.D., Medical Officer  
Jane Muret, M.D., Visitor Physician  
Shenghui Tang, Ph.D, Team Leader, DB 5  
Somesh Chattopadhyay, Ph.D., Mathematical Statistician, DB 5  
Elektra Papadopoulos, M.D., MPH, Medical Officer, SEALD  
James Stansbury, Ph.D., MPH, SEALD Reviewer  
Paul Zimmerman, R.Ph., Regulatory Project Manager

**SPONSOR ATTENDEES**

Colin Hessel, M.S., Executive Director, Biostatistics and Clinical Data Management  
Jaymes Holland, Pharm.D., Executive Director, Clinical Research  
Kirk Rosemark, R.A.C., Vice President, Regulatory Affairs  
Lisa Sauer, Director, Regulatory Affairs  
Christian Scheffold, M.D., Ph.D., Senior Director, Clinical Research  
Gisela Schwab, M.D., Chief Medical Officer and Executive Vice President, Development

Ron Weitzman, M.D., Vice President, Clinical Research  
Charlie Zhang, Ph.D., Director, Biostatistics and Clinical Data Management

(b) (4)  
(b) (4) and (b) (4)  
(b) (4)  
(b) (4)  
(b) (4)

## BACKGROUND

Cabozantinib (XL184) is a receptor tyrosine kinase inhibitor which Exelixis is currently developing as treatment for several malignancies including a placebo-controlled phase 3 clinical trial to investigate the safety and efficacy of Cabozantinib in patients with medullary thyroid carcinoma.

The sponsor now proposed a phase 3 placebo-controlled clinical trial to study cabozantinib as monotherapy in patients with androgen-independent prostate cancer who have been previously treated with docetaxel and have painful bone metastases. This proposed clinical trial, XL184-306, would randomize patients to receive cabozantinib plus a mitoxantrone placebo and prednisone placebo vs. mitoxantrone plus prednisone and a cabozantinib placebo. The primary endpoint would be a composite of improvement in pain plus improvement by bone scan.

The sponsor requested this EOP2 meeting to gain the Agency's feedback on this proposed trial.

### 1.0 DISCUSSION

Question 1:

The Phase 3 study will enroll subjects with CRPC previously-treated with docetaxel therapy. There will be no limit on the number of prior therapies, which would allow for subjects to also have received agents such as cabazitaxel and abiraterone (prior mitoxantrone is excluded). Subjects must have bone metastases visualized on technetium bone scan and daily average worst pain (assessed over 7 days)  $\geq 4$  and  $\leq 8$  on an 11-point numerical rating scale (NRS) attributable by the investigator to bone metastases. Randomization will be stratified according to ECOG performance status (0-1 versus 2-3) and baseline average daily worst pain level ( $< 7$  versus  $\geq 7$ ).

Does the Agency agree with the intended patient population and proposed randomization stratification?

**FDA response: No. We do not agree with your trial design, intended patient population, and comparator.**

**Treatment with cabazitaxel plus prednisone and abiraterone acetate with prednisone has been demonstrated to improve overall survival compared to the control in this patient population. Your proposed patient population appears to include patients who may be eligible for the treatment with either cabazitaxel and/or abiraterone.**

**In addition, we are not aware of data suggesting that mitoxantrone/prednisone is efficacious in patients with metastatic CRPC after failure of docetaxel. Your proposal to use mitoxantrone/prednisone as the control group is therefore problematic. We recommend that you redesign your proposed trial so that patients will receive treatment(s) that have shown overall survival benefit.**

*Sponsor's 5-20-11 response:*

*Intended population:*

*The Phase 3 study XL184-306 offers docetaxel pretreated patients with moderate to severe cancer pain the option of first pursuing FDA approved abiraterone and/or cabazitaxel prior to study enrollment. Both agents have demonstrated survival benefit in their respective study populations, including those with moderate to severe pain. Neither drug, however, has been shown to effectively control symptoms of pain.*

*The Sponsor respectfully submits that a reasonable choice is being offered to patients with unrelieved and debilitating symptoms of pain: individual patients may choose between initially receiving an FDA-approved therapy known to prolong survival (median OS benefit measured in months) but with no established efficacy against pain symptoms versus deferral of such therapy following participation in a clinical trial which offers the potential to receive an experimental agent with novel effects on bone scans and associated pain symptoms.*

*Thus, the current protocol design allows patients to select the sequence of therapies thereby affording them the opportunity to weigh the importance of quantity (survival prolongation) versus quality (potential for substantial pain relief) of life.*

*Comparator:*

*After consultation with key CRPC thought leaders, the Sponsor believes that the best available comparator arm for the proposed study population is the combination of mitoxantrone and prednisone, which is the only FDA-approved anti-cancer agent with a pain label. Moreover, precedence exists for the use of this combination as a control arm in a registrational Phase 3 trial in the post-docetaxel patient population (e.g., cabazitaxel versus mitoxantrone and prednisone) despite there being no evidence to date of a survival advantage with mitoxantrone and prednisone. No other available agent has proven effects in the control of cancer-related pain.*

***Discussion:***

***The Agency strongly encouraged the sponsor to redesign the proposed trial so that patients will receive treatment(s) that have shown overall survival benefit. In addition, the trial must describe measures used to optimize opioid use. FDA observed that blinding will be an issue for this trial.***

***The trial must be designed to show superiority over an active control. In a refractory population, mitoxantrone and prednisone can be an appropriate comparator.***

Question 2:

For the assessment of pain response in the Phase 3 study, the Sponsor is proposing to evaluate both patient-reported pain intensity (based on the 11-point NRS, self-reported via an interactive voice response system [IVRS]) and patient-reported narcotic analgesic medication usage. Patient-reported measures will be reported for at least 4 of the 7 days of the last week of each 3-week cycle. Pain response must be confirmed at Week 12 (durable since Week 9) and is described as:

$\geq 30\%$  decrease from baseline in the average daily worst pain intensity score during a 7-day reporting period without a  $\geq 50\%$  increase from baseline in the average daily dose of any narcotic analgesic

*OR:*

$\geq 50\%$  decrease from baseline in the average daily dose of any narcotic analgesic without a  $\geq 50\%$  increase from baseline in any other narcotic analgesic and without a  $\geq 30\%$  increase from baseline in the average daily worst pain intensity score during a 7-day reporting period

Does the Agency agree with the criteria for pain response in the study?

**FDA response: No.**

- a. **We acknowledge that symptom improvement may be an appropriate efficacy endpoint for a phase 3 trial in patients with metastatic CRPC as long as overall survival is not compromised. Your proposed trial design is problematic because it would require that patients not receive treatments that have been demonstrated to improve overall survival.**
- b. **FDA cannot agree to your proposed analgesic use criteria in the pain response definition. Specifically, the response criteria specify a threshold of  $\geq 50\%$  increase in the use of a single narcotic analgesic (“daily average dose of either narcotic analgesic”). We find no evidence that a 50% threshold is a reasonable upper bound for what constitutes stable (normal intra-individual variation in) analgesic use, assuming trial participants maintain the same mix of analgesic medications during the course of the trial.**

**We remain open to reconsidering a threshold value if you can provide empirical data about intra-individual variation in use and demonstrate scientific precedents for such an approach in your dossier. Otherwise the pain responder definition should reflect no increase in analgesic use.**

**FDA does agree with a pain response criterion that is based on a  $\geq 30\%$  decrease in pain intensity for eligible patients with stable or decreasing analgesic use. There are well-known precedents for this threshold and the content validity of paper-and-pencil use of the 11-point NRS is established with patients having metastatic cancer. But for the same reason, we do not agree to a definition of pain response where the averaged change in ‘worst pain’ intensity fails to reach the 30% cut-point. This precludes further consideration of your alternative (second) responder definition.**

**You also propose to use an interactive voice response system to gather patient pain and analgesic use data. There are good precedents for the use of IVRS in clinical research on pain. We recommend that you conduct interviews with members of the proposed population to verify the content validity and feasibility of IVRS responses, as well as a small study that assesses the comparability of measurement properties between the proposed paper diaries, direct telephone interviews, and automated data capture.**

**To refine your definition of pain response for submission of a PRO dossier and assure reliable data collection in proposed study XL 184-306, preliminary work should provide:**

- **CRPC patients' with bone metastasis impressions about reporting pain using the 11-point NRS through an interactive voice response system, with particular attention how patients conceive of scaling response in the event they have to respond without paper-and-pencil versions for reference**
- **patient views on feasibility of responding daily via IVRS and receiving telephone follow-up calls**
- **patient perspectives on what they view as regular, stable pain medication use, particularly shedding light on why, how and by how much patients change dosing regimens; a summary of the analgesic regimens in use; and information on the range of stable baseline pain levels that would be encountered in recruitment to the trial**

**Your Briefing Document further proposes that daily IVRS questions during the run-in will include reminders that promote daily diary recording of analgesic use. We suggest that a small study that assures comparable measurement performance using different modes of administration of the diary and pain scale be conducted in advance of the trial.**

**As you prepare your dossier for use of patient-reported outcomes, please ensure you include your targeted claims, an endpoint model, a conceptual framework and other needed information. In preparing your submission, please consult *Guidance for Industry—Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims***

**(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282>).**

*Sponsor's 5-20-11 response:*

*a) The Sponsor has aimed to design the Phase 3 study in accordance with the Guidance for Industry, "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics," which stipulates that*

*"...cancer drug approval should be based on more direct evidence of clinical benefit, such as improvement in survival, improvement in a patient's quality of life, improved physical functioning, or improved tumor-related symptoms..."*

*As such, there appears to be no explicit requirement for demonstration of improvement in both tumor-related symptoms and survival. The Sponsor, however, proposes maintaining a lack of cross-over and following all patients until death, thus providing additional supportive data that minimize the concern of achieving pain relief at the expense of a detriment in survival.*

*Although the study does not have adequate power to detect small differences in survival, the Sponsor proposes to address the potential for detriment in survival by adding overall survival as a study endpoint and defining a boundary for “harm” based upon the hazard ratio (HR). A detriment in survival will be considered if the observed HR in the study exceeds this boundary. The boundary will be defined as the HR that yields a false positive rate of 20% when the true HR=1.0 (i.e. there is a 20% chance the observed HR will exceed the boundary even if there is no true difference in survival).*

*Assuming the median survival is 9 months in the control arm, that enrollment is completed in 12 months, that survival is evaluated 18 months after the first subject enrolled, and that 155 deaths have been observed at the time of the analysis, the boundary for harm would be HR=1.14. The following table summarizes the probability that the observed HR will exceed 1.14 under different assumptions about the true difference in survival:*

*Probability of Observed HR Exceeding 1.14 at Month 18*

<i>True HR</i>	<i>1.4</i>	<i>1.2</i>	<i>1.0</i>	<i>0.85</i>	<i>0.8</i>
<i>Median OS (month)</i>	<i>Cabo: 6.4</i>	<i>Cabo: 7.5</i>	<i>Cabo: 9</i>	<i>Cabo: 10.6</i>	<i>Cabo: 11.25</i>
<i>(Cabo vs. MP)</i>	<i>MP: 9</i>	<i>MP: 9</i>	<i>MP: 9</i>	<i>MP: 9</i>	<i>MP: 9</i>
<i>Probability</i>	<i>90%</i>	<i>61%</i>	<i>20%</i>	<i>3%</i>	<i>1.2%</i>

*By design, if there is no true difference in survival, there is a 20% chance the boundary for harm will be exceeded. If cabozantinib has a true increase in risk of death, such as a true HR of 1.2 or 1.4, the probability of exceeding the boundary for harm increases to 61% and 90%, respectively. However, if cabozantinib conveys a modest survival benefit, such as a true HR of 0.85, the chance of exceeding the boundary for harm is only 3%.*

*b) Regarding the criteria (% range) to define stable narcotic analgesic use, the Sponsor has employed a rigorous method to quantify narcotic use which is substantially more rigorous than methods used in past oncology applications. Specifically, equianalgesic tables or point scoring systems are not proposed, in favor of an approach which quantifies the dose change of each individual narcotic on a per-patient level. At each time point of interest, the average of multiple days of narcotic use self-reporting will be tabulated. It is known that patients frequently make small changes in the number of narcotic doses they take on a day-to-day basis which do not lead to clinically meaningful differences in their pain.*



*Therefore, in a rigorous narcotic quantification approach such as suggested by the Sponsor, it is necessary to allow some % range within which a dose is considered stable, or else many patients who experience true pain palliation benefits will be considered inevaluable simply because of small non-clinically-meaningful changes in their narcotic dosing. Data are being collected in the ongoing non-randomized CRPC arm in the Phase 2 study XL184-203 (referred to as the “NRE Cohort” in the briefing document) which will be used to establish in the target population what % increase in narcotic use is not associated with clinically meaningful changes in pain intensity. These data will be used as supportive evidence for a % range definition of stable narcotic analgesic use in the proposed Phase 3 trial. Alternatively, the Sponsor is open to other approaches, including: 1) employing a pain palliation responder definition that includes pain intensity measurement but does not consider analgesic use, based on an assumption that in a controlled trial analgesic use patterns will be similar in both study arms; or 2) use of the same analgesic point scoring system that was used in the Novantrone (mitoxantrone) pivotal trial.*

*Regarding the second component of the proposed responder definition in which patients achieve a reduction in analgesic use without reaching a 30% pain intensity response, in light of reviewer comments the Sponsor will remove this criterion from the responder definition.*

*Regarding the content validity and feasibility of the IVRS responses, cognitive interviews are being conducted in the NRE Cohort in Study XL184-203 to establish patient acceptance and comprehension of the IVRS system and questions. Because data for analysis in the proposed trial will only be collected via the IVRS system, and will not be collected by mixed modes/methods (i.e., will not be collected via paper or live interviewer), the Sponsor does not believe that establishment of equivalence between different modes of administration is scientifically necessary in the context of the planned trial. If the study design changes and collection of data from more than one mode/method of questionnaire administration is added, then equivalence of the proposed modes will be established.*

**Question 3:**

Bone scans will be conducted every 12 weeks in accordance with standard clinical practice and will be evaluated by an Independent Radiology Facility (IRF). Bone scan response will be computed using semi-automated computer-aided detection (CAD) software which segments each lesion based on image intensity and then sums the individual areas of lesions to give an overall measure of bone tumor burden.

Response is based on the percent change from baseline in the positive bone scan area. A decrease of at least 30% in positive bone scan area without soft-tissue progression per modified RECIST criteria will be considered a positive response.

Does the Agency agree with the criteria for bone scan response in the study?

**FDA response: No.**

- a. We recommend that you use overall survival as the primary efficacy endpoint for a phase 3 clinical trial of patients with metastatic CRPC.**

- b. Improvement by bone scan may be an acceptable secondary efficacy endpoint. However, it is difficult to interpret the clinical significance of changes in size or intensity of bone metastases on bone scan.**

*Sponsor's 5-20-11 response:*

*a) Please see the Sponsor's response to Questions 1 and 2a. The proposed Phase 3 study, which focuses on the primary endpoint of pain, is the first of at least two planned Phase 3 trials in CRPC patients. The Sponsor proposes a primary endpoint of overall survival in the second planned Phase 3 study. More specific details of the study design, including the proposed comparator, await the completion of the ongoing NRE Cohort in Study XL184-203.*

*The purpose of the current proposed Phase 3 study (XL184-306) is to demonstrate direct evidence of clinical benefit around pain symptom control in an area of unmet medical need, where no other approved agent has shown benefit in the post-docetaxel setting.*

*b) The Sponsor has proposed bone scan response as a component of the primary endpoint to serve as a confirmatory objective finding in support of the more clinically-relevant finding of pain relief. As a result, patients achieving pain response at Week 12 who do not achieve bone scan response will not be considered a responder. Thus, maintaining bone scan response as a component of the primary endpoint provides additional objective confirmation of the primary outcome of this study.*

**Question 4:**

The primary endpoint is the rate of confirmed pain response substantiated by bone scan response at Week 12. A positive response for the primary endpoint at Week 12 will comprise both the confirmed pain response (durable from Week 9) and the bone scan response as defined above in Questions 3 and 4. The rationale for this approach is to substantiate the patient-reported assessment of pain (which may be subject to biased reporting due to inadvertent unblinding of treatment allocation) with an objective measure of tumor response.

Does the Agency agree with the choice of the primary endpoint of the rate of confirmed pain response substantiated by bone scan response at Week 12?

**FDA response: No. See responses above.**

*Sponsor's 5-20-11 response:*

*Please see the Sponsor's response to Questions 1, 2, and 3.*

**Discussion:**

***The acceptability of bone scan as part of a composite efficacy endpoint will be a review issue and may be a risky venture. Sponsor will evaluate pain at 9 weeks and 12 weeks and will propose it with their next protocol.***

Question 5:

Study XL184-306 is designed to provide adequate power to evaluate both the primary and key secondary efficacy endpoints. Assuming 230 randomized subjects (1:1, N = 115 per arm), if the true response rate is 8% in the control arm this study has 90% power to reject the null hypothesis if the true treatment difference is 17 percentage-points (ie, the true cabozantinib response rate is 25%) using a two-sided  $\alpha = 0.05$  chi-squared test.

At the time of the efficacy analysis, if the observed response rates in the control arm are 5% and 8% as expected for the primary and key secondary efficacy endpoints, respectively, the minimum observed response rates in the cabozantinib arm that would result in statistical significance for these endpoints are 15% and 18%, respectively (ie, a 10 percentage-point increase in response rate).

Alternatively, if the observed response rates in control arm at the time of the efficacy analysis are 10% and 15% for the primary and key secondary efficacy endpoints, respectively, the minimum observed response rates in cabozantinib arm that would result in statistical significance for these endpoints are 20% and 25%, respectively (also a 10 percentage-point increase in response rate).

Does the Agency agree that the sample size of this study is appropriate to detect clinically-meaningful differences in the response rates for the primary and secondary efficacy endpoints?

**FDA response: No. See responses above.**

*Sponsor's 5-20-11 response:*

*Please see the Sponsor's response to Questions 1, 2, and 3.*

Question 6:

Mitoxantrone with prednisone was approved by the FDA in 1996 for the treatment of subjects with pain associated with advanced, hormone-refractory prostate cancer and has been used as the comparator treatment in other registrational CRPC studies in the post-docetaxel setting. Neither docetaxel nor cabazitaxel have pain indications. The Sponsor therefore proposes using mitoxantrone (with prednisone) as a comparator in the Phase 3 study. Subjects randomized to mitoxantrone and prednisone will receive placebo cabozantinib; subjects randomized to cabozantinib will receive placebo mitoxantrone (sham infusion including methylene blue) and placebo prednisone. Treatment cross-over will not be allowed. Subjects will receive no more than 10 cycles of mitoxantrone; therefore infusions will be discontinued in both arms after Cycle 10 (prednisone/matched placebo will continue).

Does the Agency agree with the choice of comparator in the Phase 3 study?

**FDA response: No. See response to Question 1 above.**

*Sponsor's 5-20-11 response:*

*Please see the Sponsor's response to Question 1 regarding the choice of comparator.*

Question 7:

The Sponsor proposes the following testing schema to control Type 1 error when evaluating the primary efficacy endpoint, key secondary efficacy endpoint, and other secondary efficacy endpoints:

Efficacy endpoints will be analyzed using a gate-keeping strategy and the Hochberg procedure (Westfall et al, 1999). The hypothesis for the primary efficacy endpoint will be tested first at the 2-sided 0.05 level, and if the p-value is less than 0.05, the hypothesis for the key efficacy secondary endpoint will be tested next at the same level. If this p-value is also less than 0.05, the hypothesis for the rest of the secondary efficacy endpoints will be tested simultaneously using the Hochberg's step-up procedure to control the family-wise error rate (FWE) at the 0.05 level. All secondary efficacy endpoints will be evaluated with 2-sided tests.

Does the Agency agree with the Sponsor's proposal for controlling the Type 1 error for efficacy endpoints?

**FDA response: No. The proposed method for controlling the Type 1 error rate for efficacy endpoint is acceptable in principle. However, the endpoints and the comparator are not acceptable. Please see above.**

*Sponsor's 5-20-11 response:*

*Please see the Sponsor's response to Questions 1, 2, and 3 regarding the endpoints and the comparator.*

Question 8:

The Sponsor is considering designing Study XL184-306 as a 3-arm study to include two starting dose levels of cabozantinib, both evaluated against the comparator (mitoxantrone plus prednisone). Direct inference would not be performed between the two cabozantinib arms. Using the Bonferroni method to account for the two sets of comparisons, a significance level of 0.025 would be employed for each set of comparisons (all p-values are two-sided). Within each comparison, the same testing strategy as proposed for the 2-arm study (Question 6) would be employed.

If the Sponsor opts to conduct Study XL184-306 as a 3-arm study, does the Agency agree with the proposed method for controlling the Type 1 error inflation associated with multiple comparisons to the control group?

**FDA response: The control arm is not appropriate. Please see responses above.**

**The proposed method for controlling the Type 1 error rate for multiple comparisons in a 3-arm trial is acceptable if the endpoints are tested hierarchically.**

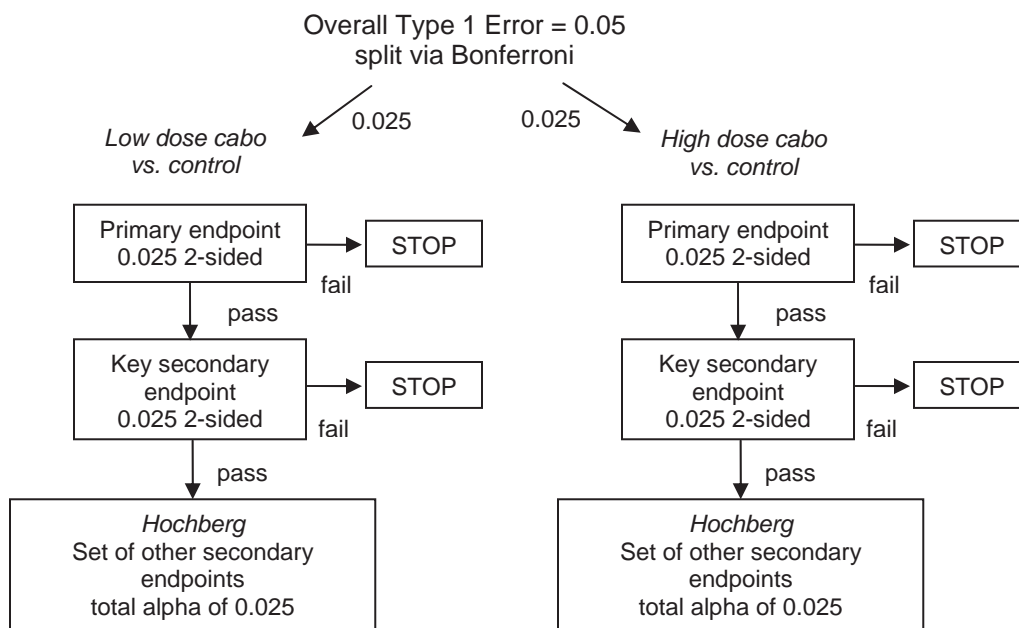
**Please explain how this Bonferroni adjustment along with Hochberg's step-up procedure will control for overall type I error rate for the secondary endpoints other than the key secondary endpoint.**

*Sponsor 5-20-11 response:*

*Please see the Sponsor's response to Question 1 regarding the control arm.*

*The Bonferroni adjustment divides the 2-sided 0.05 experiment-wise error in two, allotting 0.025 (2-sided) to each of the two experimental comparisons to the control group. Key and other secondary endpoints within a given arm are only tested if the preceding endpoints are statistically significant within the same arm (e.g. secondary endpoints in the low dose experimental arm cannot be tested if the primary endpoint in the low dose arm fails to reach statistical significance, even if the primary endpoint in the high dose arm is significant).*

*As noted, the validity of the testing strategy depends upon hierarchical testing. The Hochberg procedure is a hierarchical method, with the hierarchy determined by the observed p-values rather than defining the order of evaluation a priori. The following schema illustrates the testing strategy:*



Question 9:

Study XL184-306 will evaluate pain response and bone scan response in subjects with pain attributable to bone metastases. Bone pain data will be captured in the Case Report Form. The Sponsor proposes that bone pain not be reported as a Serious Adverse Event (SAE). The study will be monitored by an Independent Data Monitoring Committee.

Does the Agency agree with this proposal regarding safety reporting for the Phase 3 study XL184-306?

**FDA response: Yes.**

- a. We agree with capturing all patient reported outcomes in the Case Report Form.**

- b. **21CFR314.30 defines a *serious adverse drug experience* as any adverse drug experience occurring at any dose that results in death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Therefore, not all instances of bone pain need necessarily be reported as SAEs.**

*Sponsor's 5-20-11 response:*

*The Sponsor acknowledges the Agency's comments.*

Question 10:

The Sponsor intends to pursue a marketing application for cabozantinib (b)(4) in the treatment of (b)(4). This indication would be based upon one multi-center, randomized, controlled, double-blind, Phase 3 study (N = 230) of cabozantinib compared to an active control, mitoxantrone plus prednisone, and one Phase 2 open-label study (Study XL184-203) of cabozantinib that includes two cohorts (N = 171, 150) of subjects with CRPC.

Would the Agency consider data from this single randomized, multi-center, controlled study supported by data from the Phase 2 study XL184-203 acceptable to support full approval of cabozantinib for the treatment of patients (b)(4)?

**FDA response: No.**

**The trial as proposed has significant design flaws as noted above.**

**In general, we suggest that you conduct two adequate and well-controlled trials to demonstrate the effectiveness of your agent because a conclusion based on two persuasive studies will always be more secure. For a single randomized trial to support an NDA, the trial must be well designed, well conducted, internally consistent and provide statistically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform. Please refer to *Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* which describes both the characteristics of a single trial and the results that may suffice for approval (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071590.pdf>).**

### **3.0 ISSUES REQUIRING FURTHER DISCUSSION**

There were no issues requiring further discussion.

#### 4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
None		

#### 5.0 ATTACHMENTS AND HANDOUTS

Sponsor's slides for the May 23, 2011 meeting are attached.

Minutes Preparer:

Meeting Chair

*{See appended electronic signature page}*

*{See appended electronic signature page}*

Paul Zimmerman, R.Ph.  
Regulatory Project Manager

Ke Liu, M.D., Ph.D.  
Lead Medical Officer

Attachment(s)  
Sponsor's slides

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KE LIU  
06/03/2011



# MEETING MINUTES

**MEETING DATE:** March 4, 2011 **TIME:** 11AM **LOCATION:** room 1415

**Drug Name:** XL184 **IND:** 072596 **Type of meeting:** preNDA CMC

**Sponsor:** Exelixis **Meeting Request Submission Date:** 11-23-10  
**Briefing Document Submission Date:** 2-3-11

## **FDA Invitees, titles and offices:**

Amna Ibrahim, M.D., Deputy Division Director  
Anthony Murgo, M.D., M.S., FACP, Associate Director  
OODP IO, Acting Deputy Director  
John K. Leighton, Associate Director for  
Pharmacology/Toxicology  
Qi Liu, Ph.D., Team Leader, Office of Clinical  
Pharmacology, DCP5  
Haripada Sarker, Ph.D., CMC Lead, DNDQA1/ONDQA  
Sarah Pope Miksinski, Ph.D., Branch Chief,  
ONDQA/DNDQA1/Branch 2  
Patrick J. Marroum, Ph.D., Biopharmaceutics  
Supervisor, ONDQA  
Robert Dorsam, Ph.D., Acting Supervisory  
Pharmacologist  
Whitney Helms, Ph.D., Pharmacologist  
Paul Zimmerman, R.Ph., Regulatory Project Manager

## **Sponsor, titles and offices**

JoAnn Wilson, Ph.D., Vice President, Chemistry,  
Manufacturing and Controls  
Khalid Shah, Ph.D., Director, Formulation Development  
Otute Akiti, Ph.D., Director, Process Engineering  
Amanda Zhang, MS, Director, Analytical Development  
Kirk Rosemark, RAC, Vice President, Regulatory Affairs  
Steve Lacy, Ph.D., Vice President, Nonclinical  
Development  
Lisa Sauer, Director, Regulatory Affairs  
Gisela Schwab, M.D., Executive Vice President and  
Chief Medical Officer

## **Meeting Objective:**

To obtain Agency feedback regarding the CMC program for XL184 in preparation of an NDA submission.

## **QUESTIONS for DISCUSSION with FDA RESPONSE:**

### 1. Drug Product Data in NDA

The two XL184 capsule strengths of 25 mg and 100 mg have been manufactured, are undergoing International Conference on Harmonisation (ICH) stability studies, and are being used in the Phase 3 registrational study in MTC (in which the starting dose is 175 mg daily). Quality data for the capsule formulations will be presented in Modules 2.3 and 3 of the NDA, as these are also the intended formulations for commercialization.

Exelixis is planning to include clinical safety data in Module 5 of the NDA from an ongoing non-pivotal study which does not utilize the Phase 3 and proposed commercial (b) (4) formulation. Information on this formulation will be presented as part of the formulation development history, but Quality data for this formulation will not be included in the NDA.

Does the Agency agree with Exelixis' proposal to only include Quality data on the (b) (4) formulations in the proposed NDA?

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SARAH P MIKSINSKI  
05/06/2011

# MEETING MINUTES

**MEETING DATE:** December 12, 2010 **TIME:** 12:30PM **LOCATION:** room 1419

**Drug Name:** XL184 **IND:** 072596 **Type of meeting:** preNDA

**Sponsor:** Exelixis **Meeting Request Submission Date:** 9-9-10  
**Briefing Document Submission Date:** 11-15-10

## **FDA Invitees, titles and offices:**

Amna Ibrahim, M.D., Deputy Division Director  
Ke Liu, M.D., Ph.D., Lead Medical Officer  
Michael Brave, M.D., Medical Officer  
Shenghui Tang, Ph.D, Team Leader, DB 5  
Somesh Chattopadhyay, Ph.D., Mathematical Statistician, DB 5  
Sophia Abraham, Ph.D., Clinical Pharmacology Reviewer, DCP5  
Jeanne Fourie Zirkelbach, Ph.D., Clinical Pharmacology Reviewer, DCP5  
Paul Zimmerman, R.Ph., Regulatory Project Manager

## **Sponsor, titles and offices**

Natalie Sacks, M.D., Vice President, Clinical Development  
Colin Hessel, M.S., Executive Director, Biostatistics and Clinical Data Management  
Margaret Tonda, PharmD., Executive Director, Clinical Science  
Jennifer Huber, M.S., Associate Director, Medical Writing and Regulatory Operations  
Lisa Sauer, Director, Regulatory Affairs  
Yifah Yaron, M.D., Ph.D., Director, Clinical Research  
Steven Lacy, Nonclinical Development

## **Meeting Objective(s):**

To discuss the scope and presentation of data in the planned NDA for XL184 in medullary thyroid cancer.

## **QUESTIONS for DISCUSSION with FDA RESPONSE:**

The NDA submission for XL184 for the treatment of MTC will be based upon one randomized, controlled Phase 3 study (Study XL184-301), and will be supported by the Phase 1 first-in-human study XL184-001, which includes a subset of 37 subjects with MTC. Supportive safety data will come from the ongoing Phase 2 studies XL184-201 (glioblastoma multiforme [GBM]) and XL184-203 (a randomized discontinuation trial in multiple tumor types). The submission will also include a mass balance study of the absorption, distribution, metabolism, and excretion (ADME) of XL184 in normal healthy volunteers (XL184-012).

1. Exelixis plans on submitting full clinical study reports for clinical studies XL184-301 and XL184-001 and the mass balance study XL184-012, and abbreviated (safety data only) interim study reports for ongoing clinical studies XL184-201 (175 mg cohort) and XL184-203 (to include safety data from the first 12 weeks prior to blinding and randomization). These studies have been chosen for inclusion as they evaluate single-agent XL184 and are considered relevant to this application. In total, it is expected that safety data from approximately 600 subjects will be included in the planned NDA. Does the Agency agree with the proposed studies to be included in the NDA, as well as the proposed clinical study report formats (full versus abbreviated) for each?

**FDA response: No.**

**In addition to the mass balance study (XL184-012), we recommend that you include the following clinical pharmacology studies (full study reports & datasets) in your anticipated NDA submission at the time of filing:**

- **PK data from studies XL184-001 and XL184-301**
- **QTc evaluation study**
- **Food effect study**
- **Hepatic impairment study**
- **DDI study with ketoconazole**
- **DDI study with phenytoin**
- **DDI study with rosiglitazone**
- **P-gp in vitro study (as a substrate and an inhibitor)**
- **Population PK analysis from Studies XL184-201, (b) (4) and XL184-301 for assessment of exposure-response relationships.**
- **Pharmacogenomics study report**

*Sponsor Response:*

*PK data and study reports from studies XL184-001 and XL184-301, a QTc evaluation study (conducted within the pivotal study XL184-301, and as agreed upon within the Special Protocol Assessment for this study), and P-gp in vitro study data (report) will be included in the NDA. A Population PK analysis from Studies XL184-001, XL184-201, XL184-203, and XL184-301 will also be included in the NDA. (The Sponsor would like to clarify that (b) (4) is not planned to be included in the NDA. Please also see the below comment regarding XL184-203.) A DDI study with rosiglitazone (Study XL184-008) is ongoing, and the PK data (SAS XPT) and a report supporting this analysis is planned to be included in the NDA.*

*A food effect study has not yet been performed; study subjects are instructed to fast before and after dosing. This guidance will similarly be included in the product label.*

*Metabolite profiling of plasma PK samples from the Mass Balance study (XL184-012) is planned. When available, these data will provide information on the extent of XL184 metabolism clinically and the number and structures of metabolites. These results will help drive the decision on the DDI studies with ketoconazole and phenytoin (or rifampin). Additionally, the Mass Balance study will evaluate the extent of hepatic (versus renal) elimination, which will determine the necessity of a hepatic impairment study. Hepatic impairment is also a covariate that will be used in the Population PK analysis, and these data will be informative as to the degree that hepatic impairment may relate to XL184 exposure. We anticipate discussing the **timing** of these remaining studies with the FDA at the pre-NDA meeting.*

*The Sponsor would like to ask for clarification on the pharmacogenomics study report, and what is expected to be included.*

*The Sponsor also seeks FDA's comment on whether the proposed clinical data package (to support safety and efficacy) is acceptable. The proposal was to include:*

Study	Type of Study Report	Proposed Role of Study in NDA		Anticipated Number of Subjects	
		Efficacy	Safety	175 mg XL184	Other Doses
XL184-301	Full	X	X	210 <sup>a</sup>	0
XL184-001	Full	X	X	35	50
XL184-201	Abbreviated		X	46	0
XL184-203	Abbreviated		X	0	170

<sup>a</sup> Randomized to XL184 arm.

The Sponsor notes that subjects in Study XL184-203 are administered a different dose than that in the pivotal study XL184-301.

The daily 100 mg (expressed as the freebase equivalent) dose of XL184 in Study XL184-203 is not equivalent to the daily 175 mg dose (expressed as the salt weight, used in the pivotal study XL184-301). The daily 100 mg dose is equivalent to a daily 125 mg dose (salt weight).

If the FDA maintains that data from Study XL184-203 will not be able to support the safety of XL184 in the intended patient population (MTC), the Sponsor will not include it in the planned NDA. Therefore, there will not be a clinical study report (Question 1), data from this study in the ISS (Question 3), datasets (Question 5), or case report forms (Question 8b) provided in the NDA.

**Discussion:**

**FDA continues to recommend that you include the food effect study, organ impairment studies and drug-drug interaction studies with the initial NDA submission.**

2. The integrated summary of efficacy (ISE) will include efficacy data from the controlled Phase 3 study XL184-301 (175 mg qd or matched placebo) and from the subjects with MTC in the uncontrolled Phase 1 dose-escalation study XL184-001. These studies evaluate distinct efficacy endpoints. These data will be presented in separate columns (rather than pooled), with columns for active and placebo subjects in XL184-301 and MTC subjects treated with 175 mg qd capsules in XL184-001. Does the Agency agree with this proposal to not pool data across studies, but rather present data side-by-side?

**FDA response: Yes. This appears acceptable.**

3. The integrated summary of safety (ISS) will include safety data from approximately 600 subjects with multiple tumor types treated at 175 mg and 125 mg starting doses. Exelixis intends to present safety data in separate columns from study XL184-301 (active and placebo arms), study XL184-001 at the 175 mg dose, study XL184-201 at the 175 mg dose, and study XL184-203 (open-label) at the 125 mg dose. Does the Agency agree with this proposal?

**FDA response: Yes. Please clarify how many patients you expect to include from Studies 201 and 203.**

*Sponsor Response:*

*Forty-six subjects from Study XL184-201 and approximately 170 from Study XL184-203 (see the table in Response to #1) are planned to be included in the NDA. (See also the Response to #1.)*

**Discussion: see discussion for Question 8b.**

4. Because the indication of MTC is based on one Phase 3 study and supported by one Phase 1 study, Exelixis proposes to include the ISS and ISE in Module 2.7 rather than Module 5.3.5.3 of the planned submission in the electronic common technical document (eCTD) format. Additional tables, appendices, and datasets supporting the ISS and ISE will be provided in Module 5.3.5.3. Does the Agency agree with this proposal to include the integrated summaries in Module 2.7?

**FDA response: Yes.**

5. Exelixis proposes the following scope and format for SAS data sets to support the NDA review:
- SAS XPT analysis data sets used as the basis of the ISE summaries (with associated “define” files). These will include primary efficacy data from studies XL184-301 and XL184-001 as described above.
  - SAS XPT analysis data sets used as the basis of the ISS summaries (with associated “define” files). These will include primary safety data from studies XL184-301, XL184-001, XL184-201, and XL184-203 as described above.
  - CDISC SDTM-compliant SAS XPT data sets with all clinical data for pivotal study XL184-301 (with associated “define” files hyperlinked to annotated Case Report Forms).
  - SAS XPT data sets with all clinical data from Phase 1 study XL184-001. These data sets will not be CDISC SDTM-compliant, but will be in the “native” format as extracted from the clinical database. Associated “define” files hyperlinked to annotated Case Report Forms will be provided.
  - SAS XPT data sets will not be provided separately for studies XL184-201 and XL184-203, as the relevant data for these trials will be provided in the SAS XPT files to support the ISS as described above.
  - SAS XPT data sets will not be provided for study XL184-012.
  - Does the Agency agree with Exelixis’ proposal for electronic data sets?

**FDA response: Your proposal appears reasonable. All raw data should also be submitted. In addition, we recommend that you also submit the following:**

**a. Datasets from all clinical pharmacology studies above (see FDA response to Question #1), in addition to the mass balance study (XL184-012) in SAS XPT format.**

**b. Population PK analysis datasets:**

- **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.**
- **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).**
- **A model development decision tree and/or table which gives an overview of modeling steps.**

**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.**

*Sponsor response:*

*To clarify, regarding clinical datasets, Exelixis proposes that “raw” data be provided for pivotal study XL184-301 as CDISC SDTM-compliant case report tabulation datasets in SAS XPT format, and raw data for study XL184-001 be provided as case report tabulation datasets that are not necessarily CDISC SDTM-compliant.*

*Raw data for uncontrolled safety-supportive studies XL184-201 and XL184-203 would not be submitted because the relevant safety and associated data for these trials would be included in the analysis data sets submitted to support the ISS. The ISS analysis data sets are expected to be sufficiently granular that inclusion of raw data for these studies would be duplicative.*

***Discussion:***

***The sponsor states that the raw data within the analysis datasets will be clearly identified. This proposal is acceptable to the FDA***

6. Data for each study will be summarized in Tables (Section 14) and detailed by subject in Listings (Section 16.2) within the clinical study report. Exelixis does not plan to provide Integrated Individual Patient Data Listings (Section 16.4) unless requested by the Agency during review. Does the Agency agree with this proposal?

**FDA response: Possibly. Please clarify what you mean by Integrated Individual Patient Data Listings.**

*Sponsor response:*

*To clarify, in the clinical study reports Exelixis plans to provide listings organized by domain (e.g. separate listings for demographics, medical history, adverse events, etc.) with data sorted by subject within each domain listing. Exelixis does not plan to provide “patient profile” style listings that contain all data grouped together for each individual subject.*

**Discussion:**

***This proposal is acceptable to the FDA.***

7. In the clinical study reports, individual subject narratives will be written for subjects who experienced one of the following: death occurring within the 30 days of last dose and beyond 30 days of last dose if assessed as related to XL184; serious adverse events assessed as possibly, probably, and definitely related to XL184; adverse events of interest irrespective of causal relationship with XL184; and adverse events leading to dose discontinuation with the exception of adverse events attributed to disease progression. Does the Agency agree with the proposal for subject narratives in the clinical study reports?

**FDA response: Yes. However, you should be prepared to submit additional narratives upon request in a timely fashion.**

8. In the clinical study reports for studies XL184-301, XL184-001, and XL184-201, Exelixis proposes to provide copies of completed CRFs for subjects who:
  - o Died within 30 days of last dose of study drug
  - o Experienced a related serious adverse event
  - a. Does the Agency agree with this proposal regarding CRFs for studies XL184-301, XL184-001, and XL184-201?

**FDA response: Yes. In addition, for Study XL184-301, please provide CRFs for all XL-184 patients who had not progressed by the data cutoff and for all placebo patients who did progress. You should be prepared to submit CRFs requested during the review period within 48 hours.**

*Sponsor Response:*

*For Study XL184-301, the Sponsor agrees to provide CRFs for all XL184 subjects who had not progressed and for all placebo subjects who did progress by the date of the data cut-off for the primary efficacy analysis.*



8. Continued

It is planned to only include data from the first 12 weeks of open label treatment from subjects in the randomized discontinuation study XL184-203. XL184-012 is a single-dose mass balance study in normal healthy volunteers. In the clinical study reports for these studies, Exelixis proposes to not include CRFs. SAS data sets for XL184-203 (as described above) will be provided, including safety data for all XL184-203 subjects included in the submission.

- b. Does the Agency agree with the proposal regarding CRFs for Studies XL184-203 and XL184-012?

**FDA response: No. For Study 203, please submit CRFs for all patients who died within 30 days of the last dose of study drug or experienced SAEs. In addition, please clarify 1) how many patients you plan to include from Study XL184-203 and 2) whether the daily 100 mg dose of XL184 as free base used in XL184-203 is equivalent to 175 mg daily. If not equivalent the data from study XL184-203 will not be able to support the safety in the intended patient population. If they are equivalent, provide supporting data.**

*Sponsor Response:*

*The daily 100 mg (expressed as the freebase equivalent) dose of XL184 in Study XL184-203 is not equivalent to the daily 175 mg dose (expressed as the salt weight, used in the pivotal study XL184-301). The daily 100 mg dose is equivalent to a daily 125 mg dose (salt weight).*

*Please refer to the Response #1.*

***Discussion:***

***It is acceptable that safety data from study XL184-203 not be included in the NDA.***

9. The primary endpoint of Study XL184-301 is progression-free survival (PFS). This will be determined by an independent radiology facility review performed by (b) (4), (b) (4). The primary efficacy analysis requires 138 events (progressive disease or death). For the Agency's review of the radiological scans, Exelixis proposes that scans for all subjects (enrolled at that time) performed up to the time the 138<sup>th</sup> event has occurred will be provided. (b) (4) will provide the database of scans on a workstation loaded with the appropriate viewing software. (b) (4) will also provide trained personnel to guide a reviewer through the software. Does the Agency agree with this proposal?

**FDA response: Scans should not be submitted unless they are submitted as images in PDF format. If this is not feasible, please schedule a meeting with FDA to discuss the approach you could take to make those images available to FDA by a link to your system and through a VPN secure connection. In addition, please include links to all images within the CRFs or on the evaluation forms of the independent image review committee (IRC).**

*Sponsor's Response:*

*The Sponsor acknowledges the FDA's comments. Please advise the appropriate contact for scheduling a separate meeting.*

***Discussion:***

***Please contact Bioinformatics at [ESUB@fda.hhs.gov](mailto:ESUB@fda.hhs.gov)***

10. The Phase 3 study XL184-301 has an enrollment target of 315. The primary efficacy endpoint analysis of PFS requires 138 events, and the secondary efficacy endpoint analysis of OS (to be conducted at a later date than the PFS analysis) requires 217 events.

- The sample size of 315 is largely driven by the number of OS events required, and was in part calculated based upon an estimated enrollment rate which projected enrollment would be complete prior to achieving the required number of PFS events.
- The enrollment rate has not been consistent with the estimates used for calculating the sample size, and it is now anticipated that the 138 PFS events will occur before enrollment is complete.
- Originally, the primary efficacy analysis of PFS was to be conducted when all 315 subjects had been enrolled. However, if a sufficient number of subjects have been enrolled (eg, 275) to enable maintaining similar power for the secondary efficacy endpoint OS by prolonging study duration, Exelixis may consider stopping enrollment before 315 subjects have been accrued.
- Does the Agency agree to the possible modifications to enrollment, with the assurance that the final sample size will be adequate to yield at least 138 PFS events and 217 OS events?

**FDA response: Your current statistical analysis plan (page 32 of 117) states, "The primary analysis of PFS will be conducted after at least 315 subjects have been randomized (or the study has other wise been closed to accrual) and at least 138 PFS events have been observed." We strongly recommend that you not change your plan during the trial. Decreasing the number of patients enrolled may mean that the overall survival analysis will take longer.**

***Discussion:***

*The sponsor stated that they do not plan to change the trial design.*

**Additional FDA comment:**

**Please clarify the contents of Case Report Tabulations.**

*Sponsor response:*

*The scope, format and file-type of planned case report tabulations (CRTs) are described in Question #5 and the associated sponsor response.*

*The CRTs will contain data for the standard domains for study findings and events: Demographics, Concomitant medications, Exposure (dosing), AEs, Disposition, Medical History, Eligibility, Laboratory tests, ECG, Subject Characteristics, Vital Signs, and Tumor Assessments (for trials supporting efficacy).*

***Discussion:***

***The Agency finds this proposal acceptable.***

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12/22/2010

# MEETING MINUTES

**MEETING DATE:** May 26, 2009      **TIME:** 10am      **LOCATION:** room 1309

**Drug Name:** XL184      **IND:** 72,596      **Type of meeting:** EOP2

**Sponsor:** Exelixis      **Meeting Request Submission Date:** 3-20-09  
**Briefing Document Submission Date:** 4-23-09

## **FDA Invitees, titles and offices:**

Robert Justice, M.D., Division Director  
Ke Liu, M.D., PhD, Medical Team Leader  
Kun He, Ph.D., Statistical Team Leader  
Huanyu Chen, Ph.D., Statistical Reviewer  
Qi Liu, Ph.D., Acting Clinical Pharmacology Team Leader  
Doo Lee Ham, Ph.D., Pharmacology Reviewer  
Leigh Verbois, Ph.D., Pharmacology Team Leader  
Elektra Papadopoulou, M.D., SEALD  
Paul Zimmerman, R.Ph., Regulatory Project Manager

## **Sponsor, titles and offices**

Gisela Schwab, MD, Chief Medical Officer and Executive Vice President, Development  
Ron Weitzman, MD, Vice President, Clinical Research  
Paul Woodard, MD, Director, Clinical Research  
Jaymes Holland, MD, Senior Director, Clinical Development  
Colin Hessel, MS, Senior Director, Biostatistics and Clinical Data Management  
Steven Lacy, PhD, Vice President, Nonclinical Development  
Lisa Sauer, Associate Director, Regulatory Affairs  
**BMS representatives**  
Rachel Humphrey, MD, Vice President, Clinical Development  
Renzo Canetta, MD, Vice President, Global Clinical Research  
Eric Masson, PharmD, Director, Clinical Pharmacology  
Meenal Pai, Associate Director, Regulatory

## **Meeting Objective(s):**

The objective of this meeting is to discuss the development program for XL184 in recurrent glioblastoma multiforme and to obtain Agency feedback regarding the planned pivotal study.

## **QUESTIONS for DISCUSSION with FDA RESPONSE**

Questions:

1. In this phase 3 study, the Sponsor is proposing to use overall survival and progression-free survival as co-primary endpoints. Objective response rate will be a secondary efficacy endpoint. Would the Agency consider data from this single randomized, multi-center, controlled study (n = 375) supported by data from a single-arm phase 2 study in the same patient population (n = 146) acceptable to support full approval of XL184 in patients with progressive or recurrent GBM?

## **FDA:**

**This will be a review issue. In general, we suggest that you conduct two adequate and well-controlled trials to demonstrate the effectiveness of your agent because a conclusion based on two persuasive studies will always be more secure. For a single**

**randomized trial to support an NDA or sNDA, the trial must be well designed, flawlessly executed, internally consistent and provide statistically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform. Please refer to Guidance for Industry Cancer Drug and Biological Products – Clinical Data in Marketing Applications (<http://www.fda.gov/cder/guidance/4332fnl.pdf>) and Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (<http://www.fda.gov/cder/guidance/1397fnl.pdf>).**

**We recommend that Overall Survival (OS) be the sole primary endpoint since Progression-Free Survival (PFS) is very difficult to measure accurately in this disease setting, the treatment arms may become unblinded due to different toxicities, and the expected overall survival is short.**

**See additional comments below.**

*Sponsor Response:*

*The Sponsor acknowledges the Agency’s position that approval based on a single randomized trial would be a review issue. In addition, the Sponsor acknowledges the Agency’s recommendations regarding the conduct of two adequate and well-controlled trials.*

*Overall survival, unlike PFS, may be affected by crossover and sequential therapy. The reliance on overall survival as the sole primary endpoint in the setting of widely-available and active salvage therapy, may result in an observed survival effect that underestimates the true clinical benefit afforded to these patients.*

*The most notable impact on patients is rapid neurologic deterioration, affecting the ability to perform everyday functions. As tumor invades brain tissue, it can also distort aspects of personality and identity, such as mood, memory, emotion and intelligence. Therefore tumor stabilization is expected to translate to clinical benefit (Lamborn 2008).*

*Based upon Kaplan-Meier and Cox proportional hazard analyses of data from 596 subjects NABTC Phase II protocols from Feb 1998 and December 2002, Lamborn et al (2008) concluded that PFS “is a strong predictor of survival, and ... is a valid end point for trials of therapy for recurrent malignant glioma.”*

*Taken together, the co-primary endpoints of PFS and overall survival in a study powered for overall survival provide the best opportunity to demonstrate evidence of clinical benefit in this population.*

*The Sponsor acknowledges the treatment blind may become compromised due to different toxicity profiles of XL184 and lomustine. Such unblinding however, is unlikely to affect the outcome of this clinical trial for the following reasons:*

- *Every effort will be made to document progression using radiographic methods, and progression will be based upon assessment by a blinded and independent*

*radiology facility. The independent radiologists will not have access to the outside radiology reports or the investigator classification of response.*

- *Lomustine is administered once every 6 weeks. The first scheduled post-baseline tumor assessment will occur at 6 weeks and coincides with the estimated median PFS for subjects receiving this treatment. Unblinding to treatment assignment before the first scheduled tumor assessment cannot influence the exposure to lomustine during this period. Thus, for the purpose of determining radiographic progression, lomustine patients who receive their tumor assessment at the first scheduled visit will be unaffected by unblinding.*
- *Unblinding may result in tumor assessments (both radiographic and/or neurological) being performed earlier than scheduled, a source of ascertainment bias. The Statistical Analysis Plan defines a prospective sensitivity analysis that applies the principle of uniform dates, analyzing tumor assessments performed off schedule at the date of the next scheduled assessment.*

*For these reasons the Sponsor believes that PFS, collected with the appropriate level of rigor, is a meaningful endpoint in patients with recurrent GBM and should be a co-primary endpoint for the study.*

***Discussion:***

***FDA reiterated its recommendation that OS be the sole primary endpoint and stated that whether PFS as a co-primary endpoint could support either accelerated or full approval would be a review issue and would likely require an ODAC discussion.***

2. In order to minimize the potential influence of salvage bevacizumab therapy on survival outcome in this study population, the Sponsor plans to enroll the study primarily outside of the United States in regions with low bevacizumab penetration that administer temozolomide and radiation therapy as the standard of care in the first-line setting. Would the Agency accept a study conducted mostly ex-US to support registration?

**FDA:**

**a. Please clarify what percentage of patients you expect to enroll outside of the United States and which geographic regions you expect will provide the majority of patients.**

**b. You appear to be concerned that, based on the recent approval of bevacizumab, a substantial number of investigators now consider bevacizumab to be the preferred chemotherapeutic agent for patients with previously treated, recurrent GBM, and therefore, in countries where bevacizumab is available, may be reluctant to enroll such patients on a trial where the comparator arm is single-agent lomustine. We share this concern and therefore suggest that you design your study with bevacizumab as the comparator arm in those countries where bevacizumab is available. This might entail either stratifying enrollment by availability of bevacizumab (leaving the choice of control treatment up to individual investigators, according to availability of**

**bevacizumab) or conducting two separate trials (i.e., one in countries where bevacizumab is available and another in countries where it is not).**

*Sponsor Response:*

*With the current protocol design, approximately 99% of the subjects would be enrolled outside of the US. Based on preliminary feasibility, the Sponsor plans to enroll the majority of subjects in Western and Eastern Europe. Final feasibility is to be conducted to further define specific countries which will participate in this study.*

*The Sponsor plans to utilize a single comparator drug in this study due to the complexities introduced when a second comparator drug is permitted. Lomustine is consistently available as a fully approved agent in the countries identified to participate in this study. Bevacizumab has been granted a conditional approval via Subpart H through the use of a surrogate end-point which has not been proven to result in a clinical benefit. As such, the Sponsor has chosen lomustine as the comparator for this study.*

*Based upon the level of enrollment in prior and current studies which employ lomustine as a comparator arm, as well as initial study feasibility responses, the Sponsor expects that physicians and patients would be willing to enroll in a study with single-agent lomustine as the comparator arm.*

*No other anti-angiogenic agent, including bevacizumab, has shown an effect as a single agent when directly compared to nitrosoureas. Further, no direct evidence of clinical benefit, as reflected by improvements in time to event analyses, have been demonstrated to date. As such, the outcome of a randomized study comparing an anti-angiogenic agent such as XL184 against an extensively studied and approved agent such as lomustine is an important prerequisite prior to the consideration of including bevacizumab as a comparator.*

***Discussion:***

***The sponsor stated that the proposed study will be conducted almost entirely outside of the US in regions where the standard of care for first-line treatment includes standard use of radiation therapy and temozolomide. The sponsor noted that lomustine is a standard of care in the countries in which the study will be conducted. FDA concurred that lomustine is an appropriate control treatment. FDA stated that the informed consent document should describe other available therapies including bevacizumab.***

3. Nitrosoureas are DNA alkylating agents capable of crossing the blood-brain barrier are approved in the refractory setting, and include orally administered lomustine and intravenous carmustine. The Sponsor is proposing to use lomustine (administered 100 mg/m<sup>2</sup> every 6 weeks) as a comparator to oral XL184 in the setting of refractory GBM. Does the Agency agree with the choice of comparator and dose in the proposed study?

**FDA:**



**See response to #2 above.**

Sponsor Response:

*The Sponsor would like to direct the Agency to the information provided in response to the questions listed above pertaining to the choice of comparator drug.*

4. Randomization will be stratified according to age at randomization (< 50 vs.  $\geq$  50 years), ECOG PS (0 and 1 vs. 2), and number of prior regimens (1 vs. 2). Due to a potentially low number of subjects enrolled at each site and country, neither study center nor country will be included as a stratification factor. Does the Agency agree with this protocol?

**FDA:**

**We understand the need to limit the number of stratification factors and do not object to your proposed selection. Nonetheless, it will be important that the results of any study not be driven by subsets of patients from a limited geographic region or regions. In addition, you may consider an unadjusted log-rank test as the primary analysis in case the number of subjects in a stratum is small.**

**Also see response to 2b above.**

Sponsor Response:

*The Sponsor acknowledges the requirement to determine whether study results are driven by geographic region or other subsets. The Statistical Analysis Plan includes exploratory analyses to investigate efficacy endpoints for a variety of subsets, including sets defined by geographic region. Stratification by region and the use of the unadjusted log-rank test as the primary analysis will be considered.*

5. Eligible subjects will have evidence of investigator-determined progressive disease prior to study entry based on the following criteria, which will be retrospectively confirmed by Independent Radiology Committee (IRC):

Subjects who have received prior standard radiation for GBM < 12 weeks from completion of radiation must demonstrate:

- a) New enhancing lesion(s) on T1 post-contrast imaging outside of the radiation field or
- b) Unequivocal histological evidence of viable tumor at the time of recurrence (e.g. sheets of solid tumor or increased Ki67/MIB-1 labeling)

Subjects who have received prior standard radiation for GBM  $\geq$  12 weeks from completion of radiation must demonstrate:

- a) Unequivocal radiographic demonstration of progression on MRI:
  - 1) Increase in enhancing disease or the appearance of a new lesion on T1 post-contrast images and/or
  - 2) Increase in volume on T2 weighted attributed to GBM
- b) Unequivocal histologic disease (response may only be SD or PD for these patients)

Does the Agency agree with this proposal?

**FDA:**

**The proposal appears to be reasonable as an exploratory analysis. However, the primary analysis should be based on all patients randomized.**

*Sponsor Response:*

*The Sponsor acknowledges the Agency's response.*

6. The Sponsor proposes that the primary efficacy analyses be performed in a modified ITT (mITT) population that is composed of all randomized subjects who are determined to have GBM by retrospective pathology review. Randomized subjects for whom progressive disease cannot be retrospectively confirmed by IRC will be included in the mITT population.

Does the Agency agree with this proposal?

**FDA:**

**No. The primary efficacy analyses should be performed on the entire ITT population.**

*Sponsor Response:*

*The Sponsor acknowledges the Agency's response.*

7. For the assessment of PFS or ORR in the study, the Sponsor is proposing to utilize modified MacDonald criteria (see Section 5.3.2.1 of this document, and Appendix C of draft Protocol XL184-302). The modifications primarily address VEGF imaging concerns and provide operational conventions to ensure consistent application. Specifically:
  - Inclusion of non-enhancing lesions on T2/FLAIR imaging and morphological changes as non-target lesions to be evaluated in the criteria for response and progression.
  - Guidance for how to evaluate and record changes in neurological status
  - Allowance of a physiologic replacement dose of glucocorticoids in the definition of complete response.
  - Removal of the glucocorticoid component of the criterion for progressive disease, resulting in a more conservative definition.

Does the Agency agree with this proposal?

**FDA:**

**The first three bullets above are acceptable. However, please clarify what you mean by the glucocorticoid component and clarify that patients whose average doses of glucocorticoids over five days increase will be considered to have progressive disease.**

Sponsor Response:

*To clarify, the original MacDonald criteria defined progression as radiographic progression or neurological deterioration in the setting of a stable or increasing dose of glucocorticoid. The proposed modified criteria defined progression on the basis of radiographic progression or neurological deterioration irrespective of the status of glucocorticoid dose. In neither the original nor modified MacDonald criteria is an increase in glucocorticoid alone defined as progressive disease. Per MacDonald (1990), “patients requiring escalating steroid doses to maintain neurologic function, in the absence of significant CT worsening (ie, < 25% increase or no change)...are included in the stable category.”*

*However, this component of the proposed modified criteria is pending finalization as the Sponsor awaits the recommendations from the (b) (4) education session (b) (4) (b) (4) being held on (b) (4).*

8. For the analysis of PFS and ORR, disease progression and response will be based upon modified MacDonald criteria (see Section 5.3.2.1 and the proposed clinical protocol in Appendix A) that incorporate the components of radiographic assessment, changes in neurologic status, and changes in glucocorticoid use. For the primary analysis, the radiographic component will be based upon evaluations by the IRC. The IRC will not perform independent clinical evaluations. Changes in neurologic status and steroid use, as required by the MacDonald criteria, will be derived from study case report forms and integrated with the IRC radiographic assessments during statistical analysis. Does the Agency agree with this approach?

**FDA:**

**Yes, assuming overall survival is the sole primary endpoint. An independent blinded neurologic exam would strengthen the PFS endpoint.**

Sponsor Response:

*Please clarify:*

- *With PFS as a co-primary endpoint, does the Agency agree with the proposed approach to programmatically apply the clinical components of the MacDonald criteria?*
- *Which scale or tool does the Agency think would be most appropriate for the independent blinded neurological exam?*

**Discussion:**

***FDA clarified that PFS should be based on radiologic assessments only. Sponsor agreed. However, the sponsor could consider a secondary endpoint of time to neurologic progression. An independent blinded neurologic assessment could strengthen the later endpoint but may not be necessary. Additional secondary analysis such as steroid sparing would be of interest.***

9. The Sponsor is proposing to power the study to detect a 50% improvement in OS (HR 0.667) with a 2-sided Type 1 error rate of 5% and an expected median OS of 7 and 10.5 months in the lomustine and XL184-treated arms, respectively. With this design, under the assumption of proportional hazards a minimum observed improvement of 28% (NR = 0.78, or an increase in median OS of 2 months if the observed lomustine median OS is 7 months and with the assumption of exponential survival) would be statistically significant. As the primary analysis of PFS is performed at the time of the primary OS analysis (rather than at the interim analysis), more than the minimum required number of at least 127 PFS events will have been observed at the time of the analysis. Does the Agency agree with this proposal?

**FDA:**

**We recommend using OS as the sole primary efficacy endpoint. The choice of PFS as a primary endpoint in clinical oncology trials is usually based on the premise that PFS is reasonably likely to correlate with OS. However, in your proposed trial design, OS data will already be available at the time of the first PFS analysis. Your rationale for designating PFS as a co-primary endpoint, once OS data will already be available, is therefore unclear. In addition, whether a difference of 1.5 months in median PFS is clinically meaningful is uncertain.**

**As noted in our response to #2 above, if you are concerned that the use of bevacizumab as cross-over therapy could confound an OS analysis in geographic regions where it is available, you should include bevacizumab in the comparator arm in those regions.**

Sponsor Response:

*See the Sponsor's responses to the Agency's comments to questions #1 and #2. The Sponsor acknowledges that an increase in PFS must be considered as part of the totality of evidence which includes safety and other efficacy endpoints, as well as a stabilization of neurologic function and ability to perform everyday tasks.*

10. For the Phase 3 study, the Sponsor plans a single interim analysis for efficacy to be conducted by an Independent Data Monitoring Committee (IDMC). The recommendation by the IDMC to terminate the trial early for overwhelming evidence of efficacy will be based upon a stopping boundary for OS defined by an alpha-spending function, as well as an evaluation by the committee of the strength of safety parameters. The Sponsor plans to pursue registration if efficacy is demonstrated in this study at either the interim or final analysis. Does the Agency agree with this proposal in the context of the proposed registration strategy?

**FDA: Yes.**

Sponsor Response:

*The Sponsor acknowledges the Agency's response.*

11. The Sponsor plans to evaluate the impact of XL184 treatment compared with lomustine on patient reported health-related quality of life, symptom burden, and health outcomes as measured by the EORTC QLQ-C30, BN-20, and EQ-5D instruments, respectively. Does the Agency agree that these are appropriate instruments to measure subject quality of life and symptoms burden, and could results from these assessments be suitable for inclusion in the package insert?

**FDA:**

**No. We do not have documentation of content validity for these patient reported outcome instruments: EORTC QLQ C-30/BN 20 and EQ-5D. We do not know that all of the most important aspects of illness and treatment in the recurrent glioblastoma multiforme patient population are covered and weighted appropriately in order to support an HRQoL claim or a symptom burden claim.**

**We also do not have documentation that patients in the target patient population understand the instructions, items and response options.**

**The EQ-5D is a measure of quality-adjusted-life-years intended to provide a single index value for use in economic analysis. Results based on the EQ-5D should not be used to support the Agency's regulatory decision making or labeling claims of treatment benefit.**

- **Critical elements were omitted from the submission precluding full FDA evaluation of the adequacy of the proposed PRO tools. These included:**
  - **The EORTC QLQ BN20 form submitted does not include response options. We cannot fully evaluate the adequacy of a tool without having a copy of the form that will be administered in the study.**
  - **Information on the conceptual framework and scoring of the PRO instruments were omitted.**

**The Agency's concerns regarding the EORTC QLQ-30 and the EORTC QLQ BN20 questionnaires are exemplified by the following.**

- **The EORTC QLQ C-30 includes items on symptoms (e.g., pain) that are unclear with regard to what aspect of patients are being asked to rate (e.g., intensity, frequency, duration). Similarly, the item on shortness of breath may be difficult to interpret because it is not asked in the context of activity.**
- **Some items include aspects of life that can be affected by many other factors besides the underlying condition and treatment (e.g., economic status) and therefore are not appropriate to support labeling claims (e.g. "How would you**

rate your overall quality of life during the past week?” and “Did you feel uncertain about the future?”).

- Certain items do not describe a treatment effect (e.g., “Has your physical condition or medical treatment caused you financial difficulties?”).
- The respondent burden of the EORTC-QLQ 30 and the EORTC QLQ BN 20, a total of 50-items, is a concern because of the potential for missing data.
- Patients are asked to rely on memory and to average their responses over a period of 1 week. We do not have evidence that this recall period is appropriate for each of the measurement concepts, especially symptoms that may fluctuate (e.g., pain).

**Other comments:**

Anticipated toxicities of the study agents may be queried in the form of a PRO instrument. However, comparative safety labeling claims may not be supported on the basis of the proposed instruments and study design, because we do not have documentation that all of the relevant toxicities are adequately measured.

Quality of life data are difficult to interpret in a trial that may unintentionally become unblinded because patient knowledge of assigned treatment could influence their responses to questions and lead to reporting bias. In addition, large amounts of missing data increase the risk of informative censoring.

To reduce the risk of false positive conclusions due to multiple hypotheses and analyses, your prospective statistical plan should outline each primary and secondary efficacy endpoint, order of testing for all endpoints, and allocation of type I error rate to each hypothesis being tested.

We refer you to our draft **Guidance for Industry on Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims**  
[www://fda.gov/cder/guidance5460dft.htm](http://www.fda.gov/cder/guidance5460dft.htm).

**Sponsor Response:**

*The BN 20 module of the EORTC quality of life instruments was developed through several stages including the listing of patient, family and healthcare professional concerns; the writing of items; field testing with patients with brain cancer - specifically those with newly diagnosed or recurrent glioblastoma; subsequent item reduction and scale construction after multi-trait scaling analysis and assessment of internal consistency. The questionnaire has the desired psychometric properties of scalability and test-retest reliability, as well as capturing responses to frequently encountered problems in this population. It is responsive to differences in patient groups at different disease stages and when compared to the known external measures of physical activity, there is high correlation between items associated*

*with physical functioning. The intention is to combine this instrument with a general quality of life instrument (QLQ-C30) in order to capture items specific to brain cancer subjects as well as more general questions pertaining to overall quality of life. The full module is shown below (Osoba et al. Quality of Life Research 1996; 5: 139-150).*

*A manual is available from the EORTC regarding the scoring, administration, scaling and recommended interpretation of the instruments. There are also suggestions of how to deal with missing-ness of question data as well a missing questionnaire data.*

*The Sponsor agrees that the EQ-5D results would not be appropriate for labeling claims.*

*The Sponsor also agrees that these data would not support a comparative safety labeling claim.*

**Appendix: Final brain cancer module (BCM 20) for use in combination with QLQ-C30**

Please indicate how much you experienced the following during the past week.

<b>During the past week:</b>	<b>Not at all</b>	<b>A little</b>	<b>Quite a bit</b>	<b>Very much</b>
1. Did you feel uncertain about the future?	1	2	3	4
2. Did you feel you had setbacks in your condition?	1	2	3	4
3. Were you concerned about disruption of family life?	1	2	3	4
4. Did you have headaches?	1	2	3	4
5. Did your outlook on the future worsen?	1	2	3	4
6. Did you have double vision?	1	2	3	4
7. Was your vision blurred?	1	2	3	4
8. Did you have difficulty reading because of your vision?	1	2	3	4
9. Did you have seizures?	1	2	3	4
10. Did you have weakness on one side of your body?	1	2	3	4
11. Did you have trouble finding the right words to express yourself?	1	2	3	4
12. Did you have difficulty speaking?	1	2	3	4
13. Did you have trouble communicating your thoughts?	1	2	3	4
14. Did you feel drowsy during the daytime?	1	2	3	4
15. Did you have trouble with your coordination?	1	2	3	4
16. Did hair loss bother you?	1	2	3	4
17. Did itching of your skin bother you?	1	2	3	4
18. Did you have weakness of both legs?	1	2	3	4
19. Did you feel unsteady on your feet?	1	2	3	4
20. Did you have trouble controlling your bladder?	1	2	3	4

12. Does the Agency agree with the key elements of the study design, including the patient selection criteria, endpoints, proposed independent radiology review and planned statistical analyses to support registration?

**FDA:**

**No. We have significant concerns regarding some of the key elements of your proposed study design, as discussed above.**

Sponsor Response:

*The Sponsor would like to direct the Agency to the information provided in response to the questions listed above pertaining to study design issues.*

**Discussion:**

***FDA stated that the only remaining issue is the question of PFS as the co-primary endpoint. See discussion in question 1.***

13. A dose of 125 mg qd XL184 will be used in the proposed Phase 3 pivotal study. Approximately 187 subjects with GBM will be dosed at this level (per 1:1 randomization) in the proposed pivotal study. Approximately 100 subjects in the Phase 2 GBM study XL184-201 will also receive XL184 at this dose. An additional 46 GBM subjects have been dosed at 175 mg XL184 (the MTD from Phase 1). Additionally, approximately 600 subjects with solid tumors being treated in other XL184 studies will have received XL184 at 125 mg and this data will be available at the time of NDA filing.

Does the Agency agree that the population exposed to XL184 at the recommended Phase 3 dose for this pivotal study is adequate to characterize the safety profile of XL184 and to support registration?

**FDA:**

**Yes, the size of the safety database appears adequate for purposes of NDA filing.**

Sponsor Response:

The Sponsor acknowledges the Agency's response.

14. XL184 did not inhibit HERG channel activity when tested at 1, 10, and 30  $\mu\text{M}$  as determined by patch-clamp electrophysiology. In a cardiovascular safety pharmacology study in dogs, XL184 administration at either 150 or 1000 mg/kg had no effect on electrocardiographic parameters. No events of QTc interval prolongation from baseline have been reported in the Phase 1 study XL184-001 or the current GBM Phase 2 study XL184-201. Regular monthly pre-dose ECG monitoring will be incorporated into the proposed pivotal study in GBM, which will not be time-matched to pharmacokinetic sampling.

The Sponsor proposes that the thorough monitoring in the Phase 3 MTC study (XL184-301), as agreed by the Agency under the Special Protocol Assessment for the study (06 June 2008), is sufficient to characterize the potential QTc interval prolongation of XL184. In the event that the proposed Phase 3 study in GBM is completed prior to the completion of the Phase 3 MTC study, the Sponsor proposes that, in the absence of a preclinical or clinical signal, the ECG data from the Phase 3 GBM study will be



submitted at the time of filing, and that subsequent submission of the ECG data from study XL184-301 will be acceptable. Does the Agency agree with this proposal?

**FDA:**

**Your proposal of monthly safety ECGs for the Phase 3 GBM study and a QT assessment in the Phase 3 MTC study appears acceptable if the following recommendations for XL184-301 are incorporated into the protocol.**

- **ECGs are taken in triplicate at the proposed sampling times.**
- **Additional ECGs are collected in triplicate pre-dose and 4 h post-dose on C1D15, or**
- **when XL184 is at steady-state.**
- **ECGs are read by a central reader blinded to time, treatment and subject.**
- **We recommend the following analysis of the ECG data collected:**
  - **Analysis of Central Tendency: comparisons of mean change in QTc from baseline by time for each treatment group.**
  - **Outliers Analysis: QTc increases of 60 ms over baseline and QTc values greater than 500 ms.**
  - **Collection of cardiac related AEs: for example, clinically significant morphological changes in ECG, syncope, palpitations.**
  - **Analysis of drug exposure versus QTc and baseline adjusted QTc in the subgroup of patients with PK measurements.**

*Sponsor Response:*

*The Sponsor confirms that the above recommendations are reflected in the XL184-301 protocol, per the Special Protocol Assessment (06 June 2008). As such, the Sponsor would like to request confirmation that the Agency agrees with the original proposal as outlined above and that it is not necessary to collect these data in the proposed study XL184-302.*

***Discussion:***

***FDA agrees.***

15. Rifampin is typically used as an inducer in CYP3A4 induction drug-drug interaction studies, but anticonvulsants, which are often used in patients with GBM, can also induce CYP3A4. As such, the Sponsor proposes to use an inducing anticonvulsant such as phenytoin for this study. Does the Agency agree with this proposal?

**FDA:**

**This appears acceptable.**

*Sponsor Response:*

*The Sponsor acknowledges the Agency's response.*

16. Does the Agency agree that the proposed clinical pharmacology development plan, including the proposed inclusion of normal healthy volunteers, and timing of the studies is adequate to support the pivotal clinical study and registration requirements for XL184?

**FDA: No.**

**In addition to your proposed clinical pharmacology studies, you should also conduct organ dysfunction studies (renal and/or hepatic) based on the results of your ongoing mass balance study.**

**You may not initiate your proposed clinical pharmacology studies in healthy subjects until we review the genotoxicity data. If you have not submitted the results of the genotoxicity studies, please submit the data for review.**

**All your proposed clinical pharmacology studies in addition to the organ dysfunction studies should be completed and included in your the NDA submission at the time of filing.**

Sponsor Response:

*The Sponsor agrees to conduct organ dysfunction studies (renal and/or hepatic) based on results from the mass balance study (ie, identification of the major route(s) of XL184 and metabolite elimination). A pharmacokinetic evaluation in minimally hepatically impaired subjects is planned as part of the Phase 2 randomized discontinuation study (XL184-203, SN0092); these exposure data will be used to establish a safe dose in a subsequent study in moderately hepatically impaired subjects. A renal impairment study is not anticipated based on results from the Phase 1 study (XL184-001) indicating less than 1% of parent dose is eliminated in urine.*

*Listed below are the three GLP-compliant genotoxicity studies of XL184 that have been conducted and submitted to the IND:*

*Study XL184-NC-010. Salmonella-Escherichia coli mammalian microsome reverse mutation assay with a confirmatory assay with XL184 (SN0000 Vol. 4)*

*Study XL184-NC-011. Chromosomal aberrations in cultures peripheral lymphocytes with XL184. (SN0000 Vol. 4)*

*Study XL184-NC-019. In vivo mouse bone micronucleus assay. (SN0093)*

*XL184 was shown to be negative in all three genotoxicity assays. Based on the data in the above studies, the Sponsor believes it is appropriate to conduct the proposed clinical pharmacology studies (as identified) in healthy volunteers. The Sponsor plans to initiate the first of these studies in the fourth quarter of 2009.*

Linked Applications

Sponsor Name

Drug Name / Subject

-----  
IND 72596

-----  
EXELIXIS INC

-----  
XL-184

-----  
**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KE LIU

05/28/2009

## MEETING MINUTES

**MEETING DATE:** March 6, 2008 **TIME:** 1pm **LOCATION:** room 1311

**Drug Name:** XL184 **IND:** 76,596 **Type of meeting:** EOP2

**Sponsor:** Exelixis **Meeting Request Submission Date:** 1-11-08  
**Briefing Document Submission Date:** 2-5-08

### **FDA Invitees, titles and offices:**

**Robert Justice, M.D., Division Director**  
**Ramzi Dagher, M.D., Deputy Division Director**  
**Michael Brave, M.D., Medical Officer**  
**Rajeshwari Sridhara, Ph.D., Deputy Director, Biometrics V**  
**Chris Holland, Ph.D., Statistical Reviewer**  
Doo Lee Ham, Ph.D., Pharmacology Reviewer  
**Leigh Verbois, Ph.D., Pharmacology Team Leader**  
Brian Booth, Ph.D., Deputy Director, DCP5  
**Julie Bullock, Ph.D., Acting Clinical Pharmacology Reviewer Team Leader**  
**Sophia Abraham, Ph.D., Clinical Pharmacology Reviewer**  
Sarah Pope, Ph.D., Pharmaceutical Assessment Lead  
Haripada Sarker, Ph.D., Pharmaceutical Assessment Lead  
Ravi Harapanhalli, Ph.D., Branch Chief, ONDQA  
IRT representative(s)  
**Paul Zimmerman, R.Ph., Project Manager**  
(attendees are bolded)

### **Sponsor, titles and offices**

Lisa Sauer, Associate Director, Regulatory Affairs  
John Frye, PharmD, Senior Director, Clinical Science  
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### **Meeting Objective(s):**

The objectives of this meeting include addressing the acceptability of the proposed clinical program as well as the clinical pharmacology and nonclinical plans to support the pivotal study and registration of XL184 in MTC. The purpose of this meeting is to obtain Agency feedback regarding the planned pivotal study and registration program for XL184 in medullary thyroid carcinoma (MTC). Exelixis plans to conduct an international, double-blinded pivotal Phase 3 study of XL184 randomized 2:1 (N = 405 total) against placebo in patients with unresectable, locally advanced, or metastatic MTC.

### **Background:**

XL184 is a new chemical entity that inhibits multiple receptor tyrosine kinases that promote cell growth and/or angiogenesis. The primary targets of XL184 are RET, MET, VEGFR2/KDR, and KIT. Currently, no effective therapy exists for patients with MTC.

## **QUESTIONS for DISCUSSION with FDA RESPONSE**

### **Clinical Questions**

Exelixis intends to pursue an indication for XL184 as monotherapy in the treatment of subjects with unresectable, locally advanced, or metastatic MTC. This indication would be supported by the following study: An International, Randomized, Double-Blinded, Phase 3 Efficacy Study of XL184 versus Placebo in Subjects with Unresectable, Locally Advanced, or Metastatic Medullary Thyroid Cancer

**Question regarding the registration pathway:**

1. In this Phase 3 study, Exelixis is proposing to use progression-free survival (progression as determined by an independent blinded central radiology review) as the primary endpoint. Response rate, duration of response, overall survival, and subject self-assessment and quality of life parameters will serve as secondary endpoints. Would the Agency consider this single, randomized, well-controlled study acceptable for full approval?

**FDA:**

- a. **PFS may be an acceptable endpoint in this disease setting, depending on the magnitude of the effect observed and the risk to benefit ratio. However, you should power your study or studies to show an improvement in overall survival.**

**Discussion:**

**The sponsor proposes conducting an interim analysis of survival at the time of the final analysis of PFS and a final analysis of survival will be conducted when the survival data are mature. FDA stated that this is acceptable. FDA recommended that the sponsor consider increasing the sample size to better be able to demonstrate a realistic effect on OS.**

- b. **PFS is a complex composite endpoint. The analysis may be influenced by informative censoring or imbalances in missing data and assessments between treatment arms. The protocol should clearly address these concerns and plan for sensitivity analyses using different censoring mechanisms. In addition, discrepancies between investigators and the blinded central review should be reconciled using a pre-specified algorithm. We strongly recommend that you submit this trial as a Special Protocol Assessment.**
- c. **You should provide the following in your protocol: (a) a primary analysis and one or more sensitivity analyses to evaluate the robustness of the results; (b) an adequate method for handling missing assessments during the treatment period as well as methods for censoring; (c) methodology for analyzing incomplete and/or missing follow-up visits and censoring methods; (d) inclusion of the number of deaths in patients who have been lost to follow-up during the follow-up time period.**
- d. **The acceptability of your proposed trial for full approval is a review issue and will depend upon factors such as the magnitude and statistical persuasiveness of the**

**difference in PFS between arms, the consistency of the data across secondary endpoints, and the risks associated with the use of XL184.**

**Discussion:**

**The sponsor intends to file for approval on the basis of the primary efficacy analysis of PFS and will include an interim analysis of OS. The final analysis of OS will be conducted when the data mature.**

- e. The secondary endpoints of overall survival, duration of response, and response rate are acceptable secondary endpoints. Note, however, that secondary endpoints analyses are considered supportive only if the primary analysis is positive. If you wish to claim benefit based on these endpoints, then you must include in your analysis plan a method for adjusting for the overall type I error rate for these secondary endpoints.**
- f. The acceptability of the subject self-assessment and quality of life endpoints will depend on the acceptability of the instrument being used to measure quality of life for the given patient population.**

**Discussion:**

**The sponsor plans to use thyroid specific instruments to measure symptom burden PRO. The FDA suggested that the sponsor include the validation information as part of the SPA.**

- g. For additional details regarding the primary and secondary endpoints, please refer to our final *Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* and our draft *Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.**

**Questions regarding study design:**

- 2. Exelixis is proposing to include MTC patients who have documented progressive disease (PD) at screening based on RECIST compared with a previous CT or MRI scan done within 14 months of screening. Progressive disease will be documented by an independent central radiology review. Does the Agency agree with this proposal.**

**FDA:**

**Possibly.**

- a. Given the variable natural history of patients with advanced/metastatic MTC, please explain your rationale for selecting 14 months as the interval in which progression must be documented for protocol eligibility. You may wish to consider limiting enrollment to a higher risk population (e.g., patients who progressed over a**

**shorter interval) in order to better be able to demonstrate a difference in overall survival.**

**Discussion:**

**The sponsor stated that the usual clinical practice is to obtain imaging studies on an annual basis and therefore the 14 month period was selected.**

**b. We concur with your plan for an independent central radiology review.**

3. Based upon input from key opinion leaders, a median progression-free survival (PFS) of 12 months in the XL184 treatment arm and a 50% improvement in PFS over placebo are considered clinically meaningful in the proposed study population due to the current lack of effective standard therapy in the setting of MTC. Exelixis is proposing to power the study to detect a 50% improvement in PFS (HR 0.667), with an expected median PFS of 8 and 12 months in the placebo and XL184-treated arms, respectively. A total number of 360 subjects will be randomized in a 2 to 1 ratio to XL184 and placebo, respectively. Does the Agency agree with this proposal?

**FDA:**

**Please see #1 and 2 above. The general proposal appears reasonable. Be sure to specify in your protocol and statistical analysis plan the statistical analysis test, the alpha-spending function, and all other assumptions and parameters that factor into the sample size calculations.**

4. The proposed clinical development plan for registration of XL184 in metastatic or unresectable MTC is comprised of a single pivotal trial (XL184-301), three supportive Phase 1 and 2 trials (XL184-001, XL184-201 [GBM], (b) (4) and clinical pharmacology studies evaluating food effect, mass balance and drug-drug interactions. The pivotal trial XL184-301 is currently designed with a primary endpoint of PFS and a 2-sided Type 1 error rate (alpha level) of 0.05. Does FDA agree that this alpha level in a single pivotal trial is acceptable in the context of the proposed registration strategy in this population with unmet medical need?

**FDA:**

**For a single randomized trial to support an NDA, the trial must be flawlessly executed, internally consistent and provide statistically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform. Although the proposed alpha-level is acceptable for planning purposes, the p-value associated with the primary endpoint from a single Phase III trial that would support approval would be a review issue.**

5. For the Phase 3 study, Exelixis plans a single interim analysis for efficacy to be conducted by an Independent Data Monitoring Committee (IDMC) after approximately 50% of the total expected PFS events are observed. It is anticipated that approximately 85% of the total planned subjects will have been enrolled at the time of the interim analysis. The recommendation by the IDMC to terminate the trial early for overwhelming evidence of efficacy will be based upon a stopping boundary for the primary endpoint (PFS) defined by an alpha-spending function, as well as an evaluation by the committee of the strength of the secondary efficacy and safety parameters. Exelixis plans to pursue registration if efficacy is demonstrated in this study at either the interim or final analysis. Does the Agency agree with this proposal in the context of the proposed registration strategy?

**FDA:**

- a. **We discourage claiming efficacy based on an interim PFS analysis. Consideration of PFS as the primary endpoint for demonstration of efficacy for approval of drug products is based on the magnitude of the effect and the risk benefit profile of the drug product. Because documentation of PFS assessments depends on the frequency, accuracy, reproducibility and completeness of tumor assessments, it is important that the observed magnitude of effect is robust. An interim PFS analysis may not provide an accurate or reproducible estimate of the treatment effect size due to inadequate follow-up, missing assessments, and disagreements between investigator and independent assessments. Stopping a trial based on interim PFS results which may not be verifiable after adjudication can be problematic and the trial results, in particular, may not be interpretable if the treatment in the control group was changed based on the interim results.**
  - b. **In the event that you do plan to conduct an interim efficacy analysis, we recommend that accrual be completed prior to the data lock and analysis.**
  - c. **We recommend you perform an interim analysis for OS at the time of the PFS analysis.**
6. The primary endpoint analysis of PFS will be based on progression as determined by an independent, blinded radiology review. However, during the course of the study, progression of all subjects will be determined by the investigator for the purpose of subject management. After determination of disease progression, subjects will be unblinded to the investigator, and those randomized to placebo would be offered the opportunity to cross-over to receive XL184 under a separate, open label protocol. For subjects who elect to cross over to receive XL184, the identity of their treatment on study XL184-301 will necessarily be known to Exelixis to have been placebo. Does the Agency agree with this proposal?

**FDA: Possibly.**



**Be sure to specify in your statistical analysis plan methods for dealing with subjects who cross-over to XL184 but are not deemed by the independent review committee to have met the criteria for disease progression. Note that you will also need to continue to track and collect OS data for patients who cross-over and are treated under the separate protocol. For the OS endpoint, cross-over patients should remain in the placebo treatment group for analysis.**

7. Exelixis is proposing to require magnetic resonance imaging (MRI) scans of the liver and CT scans of the neck and chest at each evaluation timepoint for tumor assessment. CT scans of the liver will be allowed whenever MRI assessment of the liver is not possible. (The same methodology will be used at each assessment for each subject.) Measurements using different modalities will be combined to evaluate response. Does the Agency agree with this proposal?

**FDA response: Yes, pending review of the SPA.**

8. Exelixis plans to submit this protocol for a Special Protocol Assessment. Is this acceptable to the Agency?

**FDA:**

**Yes. Please include with the Special Protocol Assessment materials a statistical analysis plan, case report forms, and charters for the independent radiology review committee and the independent data monitoring committee. Key elements to the committees' decision making processes should be described in these documents.**

**Question regarding the evaluation of dose and extent of exposure:**

9. To date 56 subjects (including 14 with MTC) have received XL184 in the context of the Phase 1 study XL184-001 including five subjects dosed at the recommended Phase 3 dose of 175 mg PO qd. To date, no dose-limiting toxicities have been reported at this dose level. It is estimated that an additional 20 subjects with MTC will have received the dose intended for use in the pivotal study in an expanded cohort in the Phase 1 study, XL184-001. A total of approximately 34 MTC subjects will be enrolled in this study. Does the Agency agree that this constitutes adequate clinical experience to proceed with the proposed Phase 3 pivotal study in this setting of a rare patient population and unmet medical need?

**FDA:**

**Yes, pending results in the expanded MTD cohort in patients with MTC.**

10. Approximately 240 MTC subjects will be dosed with XL184 at the 175-mg dose level (per randomization) in the proposed Phase 3 pivotal study. Additionally, subjects randomized to the placebo arm of the pivotal study may receive XL184 after documented disease progression. Approximately 30 subjects in the Phase 1 study XL184-001 will also receive XL184 at this dose and schedule. In addition, the Phase 2 studies XL184-201 (N = 46) [REDACTED] (b)(4) will evaluate the 175-mg dose of XL184 in subjects [REDACTED] (b)(4) respectively. In total, approximately 400 subjects will receive XL184 at a dose of 175 mg qd in clinical studies.

Does the Agency agree that the population exposed to XL184 at the recommended Phase 3 dose is adequate to characterize the safety profile of XL184 and to support registration?

**FDA: Yes.**

#### **Question regarding QTc Interval Characterization**

11. XL184 did not inhibit HERG channel activity when tested at 1, 10, and 30  $\mu$ M as determined by patch-clamp electrophysiology. In a cardiovascular safety pharmacology study in dogs, XL184 administration at either 150 or 1000 mg/kg had no effect on electrocardiographic parameters. No events of QTc interval prolongation from baseline have been reported in the XL184-001 Phase 1 study, which incorporated electrocardiogram (ECG) monitoring at screening (within 14 days of the first dose of XL184), Cycle 1 Day 1 (Day 1) at pre-dose, Cycle 2 Day 1 (Day 15) at pre-dose, and Cycle 3 Day 1 (Day 29) at pre-dose. ECG monitoring will be incorporated in the pivotal study at screening (within 28 days of the first dose of study drug), at pre-dose and 4 hours post-dose on Day 1 of the first three 28-day cycles, every third cycle thereafter, and at the 30-day post-treatment visit.

Does the Agency agree that the proposed ECG monitoring and QTc analyses adequately address the characterization of XL184 effects on QTc interval?

**FDA:**

**We have the following recommendations for improving the plan in order to best characterize the effect of administering XL184 on the QT interval:**

- **ECGs should be taken in triplicate at the proposed sampling times.**
- **Additional ECGs should be collected in triplicate pre-dose and 4 h post-dose on C1D15, or when XL184 is at steady-state.**
- **ECGs should be read by a central reader blinded to time, treatment and subject.**
- **We recommend the following analysis of the ECG data collected:**

- **Analysis of Central Tendency: comparisons of mean change in QTc from baseline by time for each treatment group.**
- **Outliers Analysis: QTc increases of 60 ms over baseline and QTc values greater than 500 ms.**
- **Collection of cardiac related AEs: for example, clinically significant morphological changes in ECG, syncope, palpitations.**
- **Analysis of drug exposure versus QTc and baseline adjusted QTc in the subgroup of patients with PK measurements.**

### **Clinical Pharmacology Question**

12. Exelixis plans to conduct food effect studies in parallel to the pivotal study. As the results of this study will not be available prior to initiation of the pivotal study, the current proposed pivotal study will require subjects to take XL184 (or placebo) in a fasted state. A mass-balance study to identify possible metabolites of relevance is planned to be conducted in parallel to the pivotal study. Drug-drug interactions will be evaluated in vitro prior to initiation of the pivotal study. If the results of the drug-drug interaction study warrant, more detailed studies in humans may be conducted at a later date based on in vitro results. Specific studies in subjects with renal and hepatic impairment are not planned at this time. If clinical or in vitro data suggest these studies are warranted, Exelixis will conduct them.

In addition to the available PK data from XL184-001, PK samples will be collected from all subjects in studies XL184-201 (b) (4), and from 50% of the subjects in study XL184-301. Data from four studies (XL184-001, -201, (b) (4) and -301) will be combined to estimate population PK parameters of XL184. In addition, the relationship between XL184 exposure measures (ie, AUC and Cmax) in plasma and clinical outcomes will be explored to support the dose selection. No further PK studies are planned.

Does the Agency agree that the proposed clinical pharmacology development plan and timing is adequate to support the pivotal clinical studies and registration requirements for XL184?

### **FDA:**

**You should also address the following issues in your NDA submission:**

- a. **According to 21 CFR 320.25, the bioavailability (i.e., absolute or relative) of XL184 should be assessed.**
- b. **Based on the results of the mass balance study, you should conduct a renal and/or hepatic impairment study. We recommend that you include this study in the NDA submission.**

- c. **As XL184 is a substrate for CYP3A4, we recommend that you conduct *in vivo* drug-drug interaction studies to determine the effects of potent CYP3A4 inhibitors/inducers (e.g., ketoconazole, rifampicin) on the PK of XL184.**
- d. **You should also conduct *in vitro* studies to determine whether XL184 is a substrate and/or inhibitor of P-glycoprotein efflux transporter.**

#### Nonclinical Pharmacology/Toxicology Question

13. Exelixis has conducted 14-day and 6-month toxicology studies in rats and dogs. The final reports for these studies have been filed with the Agency. Reproductive toxicology studies, including a mouse micronucleus study, and ADME studies are planned to be conducted in parallel with the pivotal studies.

Does the Agency agree that the proposed nonclinical pharmacology/ toxicology program is adequate to support registration of XL184?

**FDA: Yes, it appears adequate.**

#### **FDA Additional Comments**

##### **CMC:**

Please note the following additional CMC comments.

- a. Provide a concise pharmaceutical development report in the NDA highlighting the product development and process understanding in the delineation of critical quality attributes and critical process parameters. Also, you are encouraged to take the quality-by-design (QbD) approach to pharmaceutical development as outlined in ICH Q8 Guidance on *Pharmaceutical Development*. If appropriate, please include QbD-related information and questions in a CMC-specific meeting or request a CMC guidance meeting to discuss your QbD approach during your Phase 3 clinical studies.
- b. We recommend that for the NDA, the stability data be submitted in SAS transport format along with statistical analyses of all stability indicating attributes.

#### **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/4856fml.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](mailto: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](http://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- $\leq$ 1 Mo.		>1 Mo.- $\leq$ 2Year		>2-<12	
	12-16		17-64		$\geq$ 65	
Race:	White		Black		Asian	
	Other					

Linked Applications

Sponsor Name

Drug Name

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IND 72596

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EXELIXIS INC

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XL-184

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RAMZI N DAGHER

03/18/2008