

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203756Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 203756

SUPPL #

HFD #

Trade Name Cometriq

Generic Name cabozantinib

Applicant Name Exelixis, Inc.

Approval Date November 29, 2012

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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

YES NO

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

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

d) Did the applicant request exclusivity?

YES NO

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

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

YES NO

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

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

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

YES NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA#

NDA#

NDA#

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

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

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

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

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

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

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

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2 YES NO

Investigation #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: Gina M. Davis, M.T.
Title: Regulatory Health Project Manager
Date: November 14, 2012

Name of Office/Division Director signing form: Patricia Keegan, M.D.
Title: Director, Division of Oncology Products 2

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

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

/s/

GINA M DAVIS
11/30/2012

PATRICIA KEEGAN
11/30/2012

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 203756 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____
Division Name: DOP2/OHOP/CDER PDUFA Goal Date: _____ Stamp Date: 5/29/2012
November 29, 2012

Proprietary Name: Cometriq (IND provisional approval - NDA pending approval)

Established/Generic Name: cabozantinib

Dosage Form: capsules - 20 mg, 80 mg

Applicant/Sponsor: Exelixis

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
- (2) _____
- (3) _____
- (4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 0

(Attach a completed Pediatric Page for each indication in current application.)

Indication: _____

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

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

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
 - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- 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.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):
Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

[#] Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

^{*} Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

s page was completed by:

(See appended electronic signature page)

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.



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650.837.7000 main
650.837.8122 fax

Development
Regulatory Affairs

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

05-21-2012

Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 203756	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Cometriq Established/Proper Name: cabozantinib Dosage Form: 20 mg and 80 mg (capsules)-		Applicant: Exelixis, Inc. Agent for Applicant (if applicable): N/A
RPM: Gina Davis		Division: Division of Oncology Products 2
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>November 29, 2012</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> None

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

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

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p>	<input type="checkbox"/> Received
<p>❖ Application Characteristics ³</p>	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p> <input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input checked="" type="checkbox"/> REMS not required </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<input type="checkbox"/> Yes, dates
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other – Asco Burst

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

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

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

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

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

Yes No

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

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

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

❖ Copy of this Action Package Checklist ⁴	Yes
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s)
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	11/29/2012
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	5/21/2012
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	

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

<ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) 	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	11/29/2012
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	5/21/2012
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	
<ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) 	
<ul style="list-style-type: none"> • Most-recent draft labeling 	11/28/2012
<ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	08/23/2012 08/23/2012
<ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) 	<input checked="" type="checkbox"/> RPM 09/04/12 <input checked="" type="checkbox"/> DMEPA 09/11/12 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) 11/09/12 <input checked="" type="checkbox"/> ODPD (DDMAC) 11/08/12, 11/13/12 & 11/29/2012 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Peds./Mat. Health 10/15/2012
Administrative / Regulatory Documents	
<ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) 	09/04/2011
<ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) 	<input checked="" type="checkbox"/> Not a (b)(2) <input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>) 	<input checked="" type="checkbox"/> Included (ADD)
<ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm 	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC If PeRC review not necessary, explain: <u>Orphan Designation</u> • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) - July 25, 2012 	<input checked="" type="checkbox"/> Included

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

<p>❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)</p>	<p><input checked="" type="checkbox"/> Verified, statement is acceptable</p>
<p>❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)</p>	<p>Req. – labeling negot. 11/29/2012 T-con- clinical 11/28/2012- uploaded 11/30/2012 T- con – clinical 11/28/2012- uploaded 11/30/2012 Req. – PMR/PMC dts 11/27/2012 Req – lab negotiations 11/27/2012 T-con – clinical info. 11/26/2012 – uploaded 11/30/2012 Req – PMR/PMC lab. 11/20/2012 Proposed PMR 11/09/2012 Proposed PMC/PMR 11/01/2012 Req. – clinical info 11/01/2012 Req. – clinical info. 11/01/2012 Req. – c.pharm info 11/01/2012 Req. – N/clinical info 10/31/2012 T-con – CMC info. 10/23/2012 uploaded 11/05/2012 Req. – DEMPA info. 10/10/2012 Req. – CMC info 10/09/2012 – uploaded 10/12/2012 Req. DEMPA info 10/02/2012 uploaded 10/03/2012 Req. clinical info. 09/07/2012 Req. DEMPA info 8/30/2012 T-con – no ODAC 08/29/2012 Req. – clinical info. 08/17/2012 Req. – stats info. 08/10/2012 Req. – clinical info. 08/08/2012 Req. – clinical info. 08/08/2012 Req. – clin/stats info 08/03/2012 Req. – DMEPA info. 08/01/2012 Req. – clinical info. 08/01/2012 Filing ltr/def/lab – neg. 07/27/2012 Req. – DMEPA info 07/13/2012 Req. – stats info 07/13/2012 Req. - stats info 07/10/2012 Notice of ODAC 07/10/2012 Req. for info 07/09/2012 Ack ltr – NDA 06/11/2012 Ack ltr – rolling sub. 12/30/2011</p>
<p>❖ Internal memoranda, telecons, etc.</p>	<p>Nov. Wrp-up Mtg 11/01/2012 – uploaded 11/20/2012 (revised 12/14/2012) Oct. Monthly Tm Mtg 10/02/2012 uploaded 11/20/2012 (revised – 12/14/2012)</p>

	Sep. Monthly Tm Mtg 09/11/2012 uploaded 11/20/2012 Aug. Monthly Tm Mtg 08/16/2012 uploaded 11/20/2012 (revised 12/14/2012) July Monthly Tm Mtg 07/10/2012 uploaded 11/20/2012 Filing Meeting 06/29/2012 uploaded 11/20/2012 revised 12/14/2012 Planning Meeting 06/15/2012 uploaded - 11/20/2012 revised 12/14/2012
❖ Minutes of Meetings	
<ul style="list-style-type: none"> Regulatory Briefing (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	12/20/2011
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	03/06/2008
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	None
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
<ul style="list-style-type: none"> 48-hour alert or minutes, if available (<i>do not include transcript</i>) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/29/2012
Division Director Summary Review (<i>indicate date for each review</i>)	11/20/2012 – revised 11/28/2012
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	11/08/2012
PMR/PMC Development Templates (<i>indicate total number</i>)	8
Clinical Information⁶	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	None; refer to CDTL Review
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	11/06/2012 Filing Review 11/15/2012
<ul style="list-style-type: none"> 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>)	Clinical Review 11/06/2012 (Page 20)

⁶ Filing reviews should be filed with the discipline reviews.

❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	10/19/2012
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	Cosigned primary review on 10/19/2012
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	Cosigned primary review on 10/19/2012
Statistical Review(s) (<i>indicate date for each review</i>) –Filing Review	Filing Review 06/12/2012 Bio. Stats review 10/19/2012
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) and QT-IRT Review(s) (<i>indicate date for each review</i>)	Clinical Pharmacology – Cosigned on 11/02/2012 QT-IRT – Cosigned on 10/31/2012
Clinical Pharmacology Team Leader Review and QT-IRT Review(s) (<i>indicate date for each review</i>)	Clinical Pharmacology TL Co-signed primary 11/02/2012 QT-IRT – TL Cosigned primary on 10/31/2012
Clinical Pharmacology review and QT-IRT Review(s) (<i>indicate date for each review</i>)	Clin. Pharm. Review 11/02/2012 Clin. Pharm Filing Review 7/03/2012 QT-IRT Review 10/31/2012
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None

Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	Cosigned primary review on 11/06/2012
• Supervisory Review(s) (<i>indicate date for each review</i>)	Cosigned primary review on 11/06/2012
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	Nonclinical Review 11/06/2012 Filing Review – 06/28/2012
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)	
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)	CMC - 11/14/2012 (Branch Chief) CMC (DS & DP) TL Co-signed 11/06/2012 Biopharmaceuticals TL – Cosigned on 10/29/2012
• Product quality review(s) including ONDQA biopharmaceuticals reviews (<i>indicate date for each review</i>)	CMC Reviews DS 11/06/2012 DP 11/06/2012 Filing Reviews DS 06/28/2012 DP 06/28/2012 Biopharmaceutical Review 10/29/2012 Filing Rev 6/29/2012
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (<i>indicate date of each review</i>) <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (<i>indicate date of each review</i>)	Microbiology Reviews TL Co-signed 10/16/2012 Primary Review 10/11/2012 Micro. Filing Review 06/27/2012
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>)	See page 175 of the CMC review
<input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>)	
<input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>)	

❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) (date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites ⁷)	Date completed: July 23, 2012 <input checked="" type="checkbox"/> Acceptable
<input type="checkbox"/> BLAs: TB-EER (date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation (check box only, do not include documents)	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

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

Appendix to Action Package Checklist

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

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

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

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

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

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

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

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

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

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

/s/

GINA M DAVIS
12/14/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 28, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756; Exelixis; Cometriq (cabozantinib); Teleconference; carton and container negotiations – NDC numbers

Teleconference

Sponsor Attendees:

Gisela Schwab, MD, Chief Medical Officer
Yifah Yaron, MD, PhD, Clinical Research
Colin Hessel, Biostatistics and Data Management
JoAnn Wilson, PhD, CMC
Steve Lacy, PhD, Nonclinical Development
Dana Aftab, PhD, Translational Research
Kirk Rosemark, Regulatory Affairs
Scott Garland, Chief Commercial Officer
Lisa Sauer, Regulatory Affairs

FDA Attendees:

Patricia Keegan, M.D.	Director, Division of Oncology Products 2
Suzanne Demko, P.A.-C	Medical team lead, Division of Oncology Products 2
Whitney Helms, Ph.D.	Supervisor, Division of Hematology Oncology Toxicology
Karen Jones	Chief, Project Management Staff, Division of Oncology Products 2
James Schlick, Pharm.D.	Office of Surveillance and Epidemiology
Li-Shan Hsieh, Ph.D.	CMC Reviewer, Office of New Drug Quality Assessment
Nallaperum Chidambaram, Ph.D.	Supervisor, Office of New Drug Quality Assessment
Gina Davis, M.T.	Regulatory Health Project Manager

Background/Discussion

FDA requested a teleconference with Exelixis to discuss the package insert and the carton and container presentation with respect to the NDC number and how it would be displayed. Exelixis agreed to display the NDC numbers on the cartons and not on the individual blister cards. This issue may be re-visited under a supplemental NDA.

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

/s/

GINA M DAVIS
11/30/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 28, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756; Exelixis; Cometriq (cabozantinib); Teleconference; Labeling Negotiations

Teleconference

Sponsor Attendees:

Lisa Sauer, Regulatory Affairs

FDA Attendees:

Suzanne Demko, P.A.-C

Gina Davis, M.T.

Medical team lead, Division of Oncology Products 2

Regulatory Health Project Manager

Background/Discussion

FDA requested a teleconference with Exelixis to discuss the package insert for the NME Cometriq (cabozantinib). Editorial changes were discussed and the FDA's counter-proposal to the Cometriq (cabozantinib) package insert was sent to Exelixis via electronic (email) communication.

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/s/

GINA M DAVIS
11/30/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 26, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756; Exelixis; Cometriq (cabozantinib); Teleconference; PMC/PMR negotiations

Teleconference

Sponsor Attendees:

Gisela Schwab, MD, Chief Medical Officer
Yifah Yaron, MD, PhD, Clinical Research
Colin Hessel, Biostatistics and Data Management
JoAnn Wilson, PhD, CMC
Steve Lacy, PhD, Nonclinical Development
Dana Aftab, PhD, Translational Research
Kirk Rosemark, Regulatory Affairs
Keith Watson, Project Management
Lisa Sauer, Regulatory Affairs

FDA Attendees:

Patricia Keegan, M.D.	Director, Division of Oncology Products 2
Jeffrey Summers, M.D.	DDS, Division of Oncology Products 2
Suzanne Demko, P.A.-C	Medical team lead, Division of Oncology Products 2
Ruthann Giusti, M.D.	Medical Officer, Division of Oncology Products 2
Whitney Helms, Ph.D.	Supervisor, Division of Hematology Oncology Toxicology
Margot Brower, Ph.D.	Supervisor, Division of Hematology Oncology Toxicology
James Schlick, Pharm.D.	Office of Surveillance and Epidemiology
Yuan Li Shen, Ph.D.	Biostatistics Reviewer, DBV
Hong Zhao, Ph.D.	Team Lead, Division of Clinical Pharmacology V
Jun Yang, Ph.D.	Team Lead, Division of Clinical Pharmacology V
Liang Zhou, Ph.D.	Team Lead, Office of New Drug Quality Assessment
Gina Davis, M.T.	Regulatory Health Project Manager

Background/Discussion

FDA requested a teleconference with Exelixis to discuss the timelines for the Postmarketing Requirements (PMRs) and Postmarketing Commitment (PMC) associated with the NME Cometriq (cabozantinib). Exelixis proposed a single-dose healthy volunteer study for the clinical pharmacology PMR. It was considered acceptable by the clinical pharmacology team.

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/s/

GINA M DAVIS
11/30/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 27, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756; Exelixis – Cometriq (cabozantinib)

Dear Ms. Sauer,

Please refer to your May 21, 2012, New Drug Application (NDA), received on May 29, 2012, for your product cabozantinib. We are currently reviewing your submission and have the following comment and request for additional information.

Enclosed are our counter-proposal to the Cometriq (cabozantinib) package insert, patient information sheet and carton and container as well as questions regarding the dates for the nonclinical PMRs. Please review as soon as possible and ensure that the instructions for taking Cometriq on the carton and container are consistent with the package insert.

We will make ourselves available to you if necessary as we plan to take action on Wednesday, November 28, 2012. Please send us a copy of ASCO burst as it will need to be modified.

If you have any additional questions or concerns please contact me.

All the best,

Gina

Gina M. Davis, M.T.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Nonclinical PMRs

1. [REDACTED] (b) (4)

The dates that we have proposed for the 2-year rat carcinogenicity are April, 2013 for the SPA submission, and October, 2016 for the final report submission. (b) (4)

2. [REDACTED] (b) (4)
[REDACTED] . The dates that we have proposed for the transgenic mouse are: June, 2013 for the SPA submission, and October, 2015 for the final report submission.

Note that if cabozantinib is a positive carcinogen in either the rat or mouse study, an additional carcinogenicity study in the 2nd species is not needed.

3. The pre- and post-natal reproductive toxicology study should follow ICH S5A standard protocol. [REDACTED] (b) (4)

The date that we have proposed is October, 2014 for final report submission of this pre- and post-natal reproductive study.

4. The dates you have proposed for the completion of the *in vitro* mutagenicity assay of the M4 metabolite are acceptable.

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/s/

GINA M DAVIS
11/27/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 27, 2012

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 203756 – Exelixis – Cometriq (cabozantinib); PMC/PMR timelines

Dear Ms. Sauer,

Please refer to your May 21, 2012, New Drug Application (NDA), received on May 29, 2012, for your product cabozantinib. We are currently reviewing your submission and note that you have proposed timelines for the following Post Market Requirements (PMRs) and Post Market Commitment (PMC).

Provide the agreed upon dates to the specific PMRs and the PMC listed below.

1970-1 A rodent carcinogenicity study in the mouse designed according to “FDA Guidance for Industry-Carcinogenicity Study Protocol Submissions”. Submit the carcinogenicity protocol for Special Protocol Assessment prior to initiating the study.

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

SPA Submission: MO /YR
Final Protocol Submission: MO/YR
Study Completion: MO/YR
Final Report Submission: MO/YR

1970-2 A rodent carcinogenicity study in the rat designed according to “FDA Guidance for Industry-Carcinogenicity Study Protocol Submissions”. Submit the carcinogenicity protocol for Special Protocol Assessment prior to initiating the study.

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

SPA Submission: MO /YR
Final Protocol Submission: MO/YR
Study Completion: MO/YR
Final Report Submission: MO/YR

1970-3 A pre- and post-natal reproductive toxicology study designed according to “ICH Guidance for Industry S5a: Detection of Toxicity to Reproduction for Medicinal Products.”

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

Final Protocol Submission: MO/YR
Study Completion: MO/YR
Final Report Submission: MO/YR

1970-4 An *in vitro* mutagenicity assay of the M4 metabolite (monohydroxy sulfate).

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

Study Completion: MO/YR
Final Report Submission: MO/YR

1970-5 A randomized dose-comparison trial in patients with progressive metastatic medullary thyroid cancer comparing the safety and activity of oral cabozantinib 140 mg daily to a biologically active and potentially safer lower daily cabozantinib dose. The trial will be designed to test non-inferiority of the lower dose to the approved dose for effect on progression-free survival effect and to assess the comparative safety of the two doses.

Safety assessments will include evaluation for all labeled adverse reactions and the analysis plan will provide comparisons of the incidence and severity of the following adverse reactions of cabozantinib: hemorrhage, gastrointestinal and non-gastrointestinal perforations and fistulas, hypertension, diarrhea, oral mucositis/stomatitis, and palmar-plantar erythrodysesthia (PPE) syndrome.

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

Submit Final Protocol: MO/YR
Trial Completion: MO/YR
Final Report Submission: MO/YR

1970-6 A clinical trial designed according to “FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function—Study Design, Data Analysis and Impact on Dosing and Labeling”. The frequency and duration of plasma sampling should be sufficient to accurately estimate relevant pharmacokinetic parameters for cabozantinib. A data analysis plan must be included in the protocol. The number of patients enrolled in each of the hepatic function cohorts should be sufficient to reliably detect exposure differences. The trial results should allow for a determination on dosage adjustment recommendations in the label.

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

Submit Final Protocol: MO/YR
Trial Completion: MO/YR

Final Report Submission: MO/YR

1970-7 A drug-drug interaction clinical trial to evaluate if gastric pH elevating agents alter the bioavailability and the steady-state exposure of cabozantinib. The trial may be conducted in a gated manner, first evaluating the effect of a proton pump inhibitors (PPIs) on the steady state exposure of cabozantinib. In the event that concomitant administration of a PPI has a large effect on cabozantinib steady state exposure, H2 antagonists and antacids will be subsequently evaluated. The number of subjects enrolled in the trial should be sufficient to detect exposure differences. The trial results should allow for a determination on how to dose cabozantinib with regard to concomitant gastric pH elevating agents.

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

Submit Final Protocol: MO/YR
Trial Completion: MO/YR
Final Report Submission: MO/YR

1970-8 Submit the results of the protocol-specified final analysis of overall survival, along with datasets and analysis programs, from Protocol XL184-301.

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

Study Completion: MO/ YR
Final Report Submission: MO/ YR

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
11/27/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 26, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756 – Exelixis – Cometriq (cabozantinib); Request for Clinical Information

Dear Ms. Sauer,

Please refer to your May 21, 2012, New Drug Application (NDA), received on May 29, 2012, for your product cabozantinib. We are currently reviewing your submission and have the following comment and request for additional information.

We are unable to replicate the data you provided in tables 1 and 2. Please provide the jump scrip used to derive these tables from the ae.xpt data file using the variable CTCAE rather than the derived categories for all grades and grade 3-4 toxicities

Please review the aforementioned comment as we wish to discuss this issue at this afternoon's teleconference.

All the best,
Gina

Gina M. Davis, M.T.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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GINA M DAVIS
11/26/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 21, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756 – Exelixis – Cometriq (cabozantinib); FDA counter-proposal to the Cometriq (cabozantinib) label

Dear Ms. Sauer,

Please refer to your May 21, 2012, New Drug Application (NDA), received on May 29, 2012, for your product cabozantinib. We are currently reviewing your submission and have the following comments and requests for additional information.

Enclosed is FDA's counter proposal to your November 2, 2012, amendment proposing changes to the package insert for Cometriq (cabozantinib).

Please review our proposal and provide a response by close of business Friday, November 23, 2012.

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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GINA M DAVIS
11/21/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 20, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756; Exelixis – Cometriq (cabozantinb); Proposed PMC/PMR Language

Dear Ms. Sauer,

Please refer to your May 21, 2012, New Drug Application (NDA), received on May 29, 2012, for your product cabozantinib. We are currently reviewing your submission and require the following Post Market Requirement (PMR). This list is provided to you in draft format and additional PMRs or Post Marketing Commitments (PMCs) may be required.

We note that Exelixis will be required to provide reasonable timelines for completion of the PMRs and PMC including dates for submission of the final study protocol, trial completion date and submission of the final study report. Exelixis is required to exercise due diligence to ensure that these timelines can be met, including anticipating expected accrual and event rates, as well as administrative other potential delays. Please note that PMRs are not negotiable.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of carcinogenicity and teratogenicity.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(1) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 1970-1 A rodent carcinogenicity study in the mouse to evaluate the potential for serious risk of carcinogenicity. Submit the carcinogenicity protocol for Special Protocol Assessment prior to initiating the study.

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

SPA Submission	MO /YR (i.e., JUNE 2012)
Final Protocol Submission	MO/YR
Study Completion:	MO/20XX
Final Report Submission:	MO/20XX

- 1970-2 A long-term (2 year) rodent carcinogenicity study in the rat to evaluate the potential for serious risk of carcinogenicity. Submit the carcinogenicity protocol for Special Protocol Assessment prior to initiating the study.

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

SPA Submission	MO /YR (i.e., JUNE 2012)
Final Protocol Submission	MO/YR
Study Completion:	MO/20XX
Final Report Submission:	MO/20XX

- 1970-3 A pre- and post-natal reproductive toxicology study to evaluate the potential for teratogenic effects on neonates..

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

Final Protocol Submission:
Study Completion: MO/20XX
Final Report Submission: MO/20XX

- 1970-4 An *in vitro* mutagenicity assay of the M4 metabolite (monohydroxy sulfate).

Study Completion: MO/20XX
Final Report Submission: MO/20XX

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of potential toxicity from altered GI absorption and to assess a known serious risk of excessive toxicity at the studied dose and to identify an unexpected, serious risk of an adverse effect on overall survival.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

- 1970-5 A randomized dose-comparison trial in patients with progressive metastatic medullary thyroid cancer comparing the safety and activity of oral cabozantinib 175 mg daily to a biologically active but lower daily cabozantinib dose. The trial will be designed to test non-inferiority of the lower dose for PFS and to assess the comparative safety of the two doses.

Safety assessments will include evaluation for all adverse reactions and the analysis plan will provide comparisons of the incidence and severity of the following adverse reactions of cabozantinib: hemorrhage, gastrointestinal and non-gastrointestinal perforations and fistulas, hypertension, diarrhea, oral mucositis/stomatitis, and palmar-plantar erythrodysesthia (PPE) syndrome.

Submit Final Protocol: MO/YR
Trial Completion: MO/20XX
Final Report Submission: MO/20XX

- 1970-6 A clinical trial according to “FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function–Study Design, Data Analysis and Impact on Dosing and Labeling”. The frequency and duration of plasma sampling should be sufficient to accurately estimate relevant pharmacokinetic parameters for cabozantinib. A data analysis plan must be included in the protocol. The number of patients enrolled in each of the hepatic function cohorts should be sufficient to reliably detect exposure differences. The trial results should allow for a determination on dosage adjustment recommendations in the label.

Submit Final Protocol: MO/YR
Trial Completion: MO/20XX
Final Report Submission: MO/20XX

- 1970-7 A drug-drug interaction clinical trial to evaluate if gastric pH elevating agents alter the bioavailability and the steady-state exposure of cabozantinib. The trial may be conducted in a gated manner, first evaluating the effect of a proton pump inhibitors (PPIs) on the steady state exposure of cabozantinib. In the event that concomitant administration of a PPI has a large effect on cabozantinib steady state exposure, a H2 antagonists and an antacids will be subsequently evaluated. The number of subjects enrolled in the trial should be sufficient to detect exposure differences. The trial results should allow for a determination on how to dose cabozantinib with regard to concomitant gastric pH elevating agents.

Submit Final Protocol: MO/YR
Trial Completion: XXXXXX 20XX
Final Report Submission: XXXXXX 20XX

Submit the protocols to your IND 113446, with a cross-reference letter to this NDA. Submit all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: “Required Postmarketing Protocol Under 505(o)”, “Required Postmarketing Final Report Under 505(o)”, “Required Postmarketing Correspondence Under 505(o)”.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

1970-8 Submit the results of the protocol-specified final analysis of overall survival, along with datasets and analysis programs, from ProtocolXL184-301.

The timetable you submitted on DATE, states that you will conduct this study according to the following schedule:

Trial Completion: XXXXXX 20XX
Final Report Submission: XXXXXX 20XX

Submit clinical protocols to your IND 113446 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol**,” “**Postmarketing Commitment Final Report**,” or “**Postmarketing Commitment Correspondence**.”

Please provide responses by Friday, November 23, 2012, by 1:00 PM (PT). If you have any additional questions or concerns please feel free to contact me.

All the best,

Gina

Gina M. Davis, M.T.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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GINA M DAVIS
11/20/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Memorandum

Date: November 15, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756; Exelixis – Cometriq (cabozantinib) – Clinical request for additional information

Teleconference

Sponsor Attendees:

Gisela Schwab, MD	Chief Medical Officer
Yifah Yaron, MD, PhD	Clinical Research
Colin Hessel	Biostatistics and Clinical Data Management
Bruce Ashton	Clinical Data Management
Keith Watson	Project Management
Lisa Sauer	Regulatory Affairs
Kirk Rosemark	Regulatory Affairs

FDA Attendees:

Ruthann Giusti, MD	Medical Officer, Division of Oncology Products 2
Gina Davis, MT	Regulatory Health Project Manager

Background

On November 16, 2012, the Division of Oncology Products 2, held a teleconference with Exelixis, Inc., to discuss the relationship between cross validating adverse reactions and laboratory values submitted in the labeling of the NME Cometriq (cabozantinib).

Discussion

DOP 2 requested Exelixis explain coordination between adverse events and laboratory data and how it's clinically meaningful.

Exelixis stated that high grade laboratory values may not be noted as an adverse event. Laboratory values are useful indicators from a biologic standpoint. Exelixis does not make a correlation between laboratory values or adverse events.

DOP 2 stated that the laboratory values are not CTCAE criteria for grade 3 and above and requested that Exelixis provide direction for using the laboratory database to select the most severe reaction.

DOP 2 requested that Exelixis create a toxicity table noting grade 3/4 laboratory adverse events based on laboratory data selecting the most severe toxicity using the following laboratory values based on CTCAE criteria (using # and %):

ALK
ALT
AST
Hypocalcaemia
Hypocalcaemia
Hypermagnesium
Hypomagnesium
Hypokalemia
Hyperkalemia
Hypoalbuminemia
Hyperalbuminemia
Neutropenia
Thrombocytopenia
white blood cells

DOP 2 also requested that Exelixis provide the following;

- written description of variables used in the database.
- defined criteria used to grade hypothyroidism.

DOP 2 requested that Exelixis provide a table regarding hypertension in the label. CTCAE (version 4) was used and is inadequate. DOP2 stated that the CJC definition for hypertension should be followed.

Action Items

Exelixis agreed to provide the requested information by Monday, November 18, 2012.

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/s/

GINA M DAVIS
11/27/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 9, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756; Exelixis – Cometriq (cabozantinb); PMR language

Dear Ms. Sauer,

Please refer to your May 21, 2012, New Drug Application (NDA), received on May 29, 2012, for your product cabozantinib. We are currently reviewing your submission and require the following Post Market Requirement (PMR). This list is provided to you in draft format and additional PMRs or Post Marketing Commitments (PMCs) may be required.

We note that Exelixis will be required to provide reasonable timelines for completion of this PMR including dates for submission of the final study protocol, trial completion date and submission of the final study report. Exelixis is required to exercise due diligence to ensure that these timelines can be met, including anticipating expected accrual and event rates, as well as administrative other potential delays.

PMR

Nonclinical

1. Conduct an *in vitro* mutagenicity assay to determine the potential genetic toxicity of the M4 metabolite (monohydroxy sulfate).

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/s/

GINA M DAVIS
11/09/2012

NDA: 203756
November 1, 2012

November Wrap-Up Meeting

Product: Cometriq (cabozantinib) capsules
Submission Date: May 21, 2012
Received Date: May 29, 2012
PDUFA Date: November 29, 2012
Sponsor: Exelixis, Inc.

Proposed Indication: For the treatment of patients with progressive, unresectable, locally advanced or metastatic medullary thyroid cancer

Current Review Team for NDA 203756:

Patricia Keegan, M.D., Director DOP2
Gina Davis, M.T., Regulatory Health Project Manager
Karen Jones (CPMS)
Ruthann Giusti, M.D., Medical Officer
Suzanne Demko, C- P.A., (TL and CDTL)
Yuan Li Shen, Ph.D., Statistics
Kun He, Ph.D., Statistics (TL)
Jun Yang, Ph.D., Clinical Pharmacology
Hong Zhao, Ph.D., Clinical Pharmacology (TL)
Margaret Brower, Ph.D., Non-Clinical
Whitney Helms, Ph.D., Nonclinical (TL)
William (Mike) Adams, Ph.D., Product
Li Shan Hsieh, Ph.D. Product
Liang Zhou, Ph.D., Product (TL)
Nallaperumal Chidambaram, Ph.D., Branch Chief
Sarah Pope Miksinski, Ph.D., Acting Division Director
Jewell Martin, M.S., Product (ONDQA RPM)
Angelica Dorantes, Ph.D., Biopharmaceutics TL
Minerva Hughes, Ph.D., Biopharmaceutics Reviewer
Denise Miller, Ph.D. Microbiology Reviewer
Roy Blay, OSI Inspector
Mahesh Ramanadham, Facilities Inspector, PharmD/M.B.A.

Labeling Negotiations for Cometriq (cabozantinib) were conveyed to the sponsor on October 26, 2012. Proposed PMCs/PMRs will be conveyed to the sponsor on November 1, 2012.

Discussion during the Meeting:

Team Reviews

Clinical

Review to be completed shortly.

Nonclinical Review

Review to be completed shortly.

Clinical Pharmacology

Review is complete and in DARRTs.

CMC Reviews

DS and DP – nearing completion and to be uploaded in DARRTs shortly and no further information is required from the sponsor.

Biopharmaceutical Review

Review is in DARRTs and know further information is required from the sponsor.

Microbiology

Review is complete and in DARRTs.

Inspections

Facilities

Inspections have been completed and are acceptable.

OSI

Inspections have been completed and are acceptable.

OSE

DMEPA

Review is complete and in DARRTs.

DRISK

To be completed shortly and uploaded in DARRTs.

PMHS

Review completed and in DARRTs.

PMCs/PMRs

PMC/PMR negotiations to be sent to the November 1, 2012 for the following disciplines;

Clinical

Nonclinical

Clinical Pharmacology

Labeling

Labeling negotiations began on July 27, 2012 (provided in the filing letter). Counter-proposals were sent by Exelixis on August 7, 2012, and August 10, 2012. The Division's most recent counter-proposal was sent on October 26, 2012.

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/s/

GINA M DAVIS
12/14/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 1, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756; Exelixis – Cometriq (cabozantinb); Request for Additional Information

Dear Ms. Sauer,

Please refer to your May 21, 2012, New Drug Application (NDA), received on May 29, 2012, for your product cabozantinib. We are currently reviewing your submission and have the following comment and request for additional information.

On page 78/248 of the XL184-301 Clinical study report dated May 9, 2012, the figure showing patient disposition indicates that 214 patients were screened who did not meet the eligibility criteria for this protocol. Please provide a breakdown showing which criteria were not met for these patients, or provide direction to requested data in the submission.

Please provide a response to the aforementioned comments by 2:00 PM (EST), Monday, November 5, 2012. If you have any additional questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
11/01/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 1, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756; Exelixis – Cometriq (cabozantinb); Request for Additional Information

Dear Ms. Sauer,

Please refer to your May 21, 2012, New Drug Application (NDA), received on May 29, 2012, for your product cabozantinib. We are currently reviewing your submission and have the following comment and request for additional information.

Please provide a safety analysis of events by severity (All Grades and Grades 3-4) for the following events:

- PPE
- Diarrhea
- Fatigue
- Asthenia
- weight decrease
- oral pain
- Stomatitis
- Decreased appetite

For oral pain, please include the following preferred terms:

- Oral Pain
- Oropharyngeal Pain
- Glossitis
- Burning Mouth Syndrome
- Glossodynia

For stomatitis, please include the following preferred terms:

- Stomatitis
- Aphthous Stomatitis
- Mouth Ulceration
- Mucosal Inflammation

Please provide a breakdown separately for adverse events with onset occurring while the patient was treated at the starting dose (175 mg;L-malate salt weight base) and with adverse events with

onset occurring while the patient was treated at the first dose-level reduction (125 mg;L-malate salt weight base)

Please provide a response to the aforementioned comments by 2:00 PM (EST), Monday, November 5, 2012. If you have any additional questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
11/01/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 1, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756; Exelixis – Cometriq (cabozantinib); Proposed PMC/PMRs language

Dear Ms. Sauer,

Please refer to your May 21, 2012, New Drug Application (NDA), received on May 29, 2012, for your product cabozantinib. We are currently reviewing your submission and propose the following Post Market Commitments (PMC) and Post Market Requirements (PMR). This listing is provided to you in draft format and additional PMRs or PMCs may be required. We note that Exelixis will be required to provide reasonable timelines for completion of these PMRs and PMCs including dates for submission of the final study protocol, trial completion date and submission of the final study report. Exelixis is required to exercise due diligence to ensure that these timelines can be met, including anticipating expected accrual and event rates, as well as administrative other potential delays.

Based on the observation that 80% of patients enrolled on XL184-301 required at least one dose level reduction and that within this trial, dose intensity did not appear to be associated with a reduction in progression free survival (PFS), FDA concludes that the treatment dose for cabozantinib has not been optimized and that a lower dose may be equally efficacious and less toxic and may lead to a labeling change.

PMRs

Nonclinical

1. There is a concern that chronic exposure to cabozantinib could cause additional cancers in patients with medullary thyroid cancer administered cabozantinib, based on the expected extended survival (5 years or longer after first exposure to cabozantinib), and extended dosing duration of this patient population. Based on this consideration, two rodent carcinogenicity studies, a long-term (2-year) rat study and a mouse study need to be conducted to assess the potential for cabozantinib to cause carcinogenicity.
2. Based on the expected extended survival, and extended dosing duration of this patient population, as well as the pharmacological mechanism of action (e.g. inhibition of MET and VEGF pathways which may result in altered bone development in neonates), pre- and post-natal reproduction studies will be needed.

Clinical

3. Conduct a randomized dose-comparison, non-inferiority trial in which patients with progressive metastatic medullary thyroid cancer will be randomized to receive oral cabozantinib 140 mg or 80 mg daily. A primary endpoint will be progression-free survival with overall response rate as a secondary endpoint. The trial will be designed to retain 50% of the effect size determined in trial XL184-301 as the non-inferiority margin. The study will also assess between arm differences in the incidence of a composite safety endpoint incorporating adverse events which led to cabozantinib dose reduction in $\geq 5\%$ of patients treated on the cabozantinib arm in XL184-301, that is: palmar-plantar erythrodysesthesia syndrome, weight decrease, decreased appetite, fatigue, diarrhea, stomatitis, asthenia and nausea. The study arms will also be compared with respect to differences in the number of dose reductions and delayed doses and the incidence of a composite index of toxicities associated with VEGF inhibition, including: hemorrhage, gastrointestinal and non-gastrointestinal perforation, fistula and abscess formation, hypertension/hypertensive crisis, arterial and venous thrombosis, proteinuria, wound complications, osteonecrosis and RPLS.

Clinical Pharmacology

4. Conduct a clinical trial to determine the appropriate dose of cabozantinib in patients with hepatic impairment. Submit the final protocol for FDA review before conducting the trial.
5. Conduct a clinical trial to evaluate if proton pump inhibitors, H₂ antagonists and antacids alter the bioavailability of cabozantinib. You may study the worst case scenario first, and then determine if further studies on other drugs are necessary. The study results should allow for a determination on how to dose cabozantinib with regard to these gastric pH elevating agents. Submit the final protocol for FDA review before conducting the trial.

PMC

Clinical

6. Submit the results of the final analysis of overall survival data from the randomized clinical trial of cabozantinib 175 mg vs. placebo in progressive metastatic medullary thyroid cancer (XL184-301).

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/s/

GINA M DAVIS
11/01/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: November 1, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756; Exelixis – Cometriq (cabozantinb); Request for Additional Information

Dear Ms. Sauer,

Please refer to your May 21, 2012, New Drug Application (NDA), received on May 29, 2012, for your product cabozantinib. We are currently reviewing your submission and have the following comment and request for additional information.

As recommended by the pharmacology reviewer, please tighten and revise the limits for GTIs' in the drug product specification to match with that in the drug substance specification.

Please provide a response to the aforementioned comment by 2:00 PM (EST), Friday, November 2, 2012. If you have any additional questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
11/01/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 31, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756; Exelixis – Cometriq (cabozantinb); Request for Additional Information

Dear Ms. Sauer,

Please refer to your May 21, 2012, New Drug Application (NDA), received on May 29, 2012, for your product cabozantinib. We are currently reviewing your submission and have the following comment and request for additional information.

Address the following IR and submit the response to the IND:

Identify whether the acid metabolite (EXEL-5366) studied for pharmacological activity in Study # XL184-Disc-002 is the monohydroxy sulfate metabolite.

Please provide a response to the aforementioned comment by 2:00 PM (EST), Thursday, November 1, 2012. If you have any additional questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
10/31/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 26, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756 – Exelixis – Cometriq (cabozantinib); FDA counter-proposal to the Cometriq (cabozantinib) label

Dear Ms. Sauer,

Please refer to your May 21, 2012, New Drug Application (NDA), received on May 29, 2012, for your product cabozantinib. We are currently reviewing your submission and have the following comments and requests for additional information.

Enclosed is FDA's counter proposal to your August 10, 2012, amendment proposing changes to the package insert for Cometriq (cabozantinib).

Please review our proposal and provide a response by Friday, November 2, 2012. If you have any questions or concerns please contact me.

All the best,

Gina

Gina M. Davis, M.T.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

58 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

GINA M DAVIS
10/26/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 23, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756; Exelixis; Cometriq (cabozantinib); Teleconference; CMC specifications

Teleconference

Sponsor Attendees:

Khalid Shah, PhD.	CMC
Bih Hsu, PhD.	CMC
Gisela Schwab, M.D.	Chief Medical Officer, Executive VP
JoAnn Wilson, Ph.D.	CMC
Shigang Zhang, Ph.D.	CMC
Jing Yuan, Ph.D.	CMC
Steve Lacy, Ph.D.	Nonclinical
Kirk Rosemark	Regulatory
Lisa Sauer	Regulatory

FDA Attendees:

William M. Adams	CMC
Liang Zhou, Ph.D.	CMC
Nallaperum Chidambaram, Ph.D.	CMC
Margaret Brower, Ph.D.	Nonclinical
Whitney Helms, Ph.D.	Nonclinical
Suzanne Demko, P.A.-C	Medical team lead
Ruthann Giusti, M.D.	Medical Officer
Jeffrey Summers, M.D.	DDS
Gina Davis, M.T.	Regulatory Health Project Manager

Background

FDA requested a teleconference with Exelixis to discuss the batch analysis data and stability specifications submitted in the New Drug Application (NDA) for the new molecular entity Cometriq (cabozantinib). The teleconference was held on October 23, 2012.

Discussion

FDA requested clarification regarding the data for genotoxic impurities in drug substance lot 0904672 provided in NDA section 3.2.S.4.4, table 7. The table indicates that the lot was used in a safety study and that the reported values represent retesting results. FDA asked the applicant to identify the methods used to obtain the data. Exelixis indicated that the methods were those proposed in the drug substance release specification. FDA acknowledged the response.

FDA requested clarification regarding the stability specification for drug substance provided in NDA section 3.2.S.7.1, table 7. The stability specification criteria for impurities are much larger than those proposed in the release specification. Exelixis stated that this table presents the stability specification when the study was started, however they are using the criteria proposed in the release specification to reach stability conclusions. FDA acknowledged the response and requested that a revised stability specification be submitted.

Action Item

Exelixis agreed to submit the requested stability specification to the NDA.

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/s/

GINA M DAVIS
11/05/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 10, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756; Exelixis – Cometriq (cabozantinb); Advice and Information Request from the Biopharmaceutical and Division of Medication Error Prevention and Analysis (DMEPA)

Dear Ms. Sauer,

Please refer to your May 21, 2012, New Drug Application (NDA), received on May 29, 2012, for your product cabozantinib. We are currently reviewing your submission and have the following comment and request for additional information

Please provide updated stability specifications and stability data including current blister stability data. In addition, you should institute 3 month and 9 month testing points for commercial batches at real time storage in their proposed post-approval stability protocols.

Please address the aforementioned comments by Wednesday, October 17, 2012. If you have any questions or concerns please contact me at (301) 796-0704.

Thank you,
Gina

Gina M. Davis, MT
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
10/10/2012



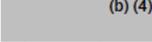
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 9, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756; Exelixis – Cometriq (cabozantinb); Advice and Information

Dear Ms. Sauer,

Please refer to your May 21, 2012, New Drug Application (NDA), received on May 29, 2012, for your product cabozantinib. We are currently reviewing your submission and have the following comments and requests for additional information.

1. Regarding the description of the manufacturing process and process controls (NDA section 3.2.S.2.2):
 - a.  (b) (4)
 - b.  (b) (4)
 - c.  (b) (4)
2. Regarding the controls for raw materials, reagents and solvents (NDA section 3.2.S.2.3):
 - a. For each designated starting material and the key component; specify what is tested on each lot for acceptance versus what is accepted from supplier's certificate of analysis. Also, specify the limit of quantitation (QL) for each impurity detected by the various HPLC methods.
 - b. For regulatory starting material  (b) (4), identify the methods for  (b) (4) and specify the QL for each of these methods.
 - c. For regulatory starting material  (b) (4) either provide a commitment to the proposed synthesis and resulting impurity profile which support the proposed acceptance specification or describe how future suppliers of this material will be qualified.

- d. Specify how a lot of drug substance is designated as (b) (4) and whether additional testing is performed on this lot.
 - e. Specify the grade of (b) (4)
 - f. Specify the grade and composition of (b) (4) used.
 - g. Specify whether (b) (4) If yes, then describe the recovery process and propose an acceptance specification.
3. Process validation protocol VP075 for (b) (4) (NDA section 3.2.S.2.5) indicates that raw material (b) (4) material is used, however it is not described in NDA sections 3.2.S.2.2 and 3.2.S.2.3. Propose a specification (test methods and acceptance criterion) for raw material (b) (4) and indicate the amount of this material that is introduced into (b) (4)
 4. Please explain the discrepancy between the amount of (b) (4) that are described for (b) (4) (section 3.2.S.2.4) and IPC#1, where a (b) (4) indicated.
 5. Provide a copy of the particle size distribution plot obtained by method MTD313 for each of the NDA representative and presentation lots.
 6. Regarding your proposed release specification in section 3.2.S.4.1:
 - a. Revise the calculation for Assay for XL184 Freebase to correct for organic impurities, inorganic impurities, and residual organic solvents and water in the test sample and in the reference standard.
 - b. Revise the limit for (b) (4) to a level observed in the process B-2 lots used in the NDA primary stability studies and provide an updated specification table.
 7. Regarding description of your proposed analytical methods (NDA section 3.2.S.4.2):
 - a. Explain why (b) (4) is not addressed in the system suitability criteria for (b) (4) method 11-11-SP-2272, and specify column temperature range.
 - b. Describe the procedure and system suitability criteria in method 505115001-GTIH1 for switching UV detection from (b) (4)
 8. Regarding submitted stability information:
 - a. Genotoxic impurities are known to form at an accelerated rate when drug substance is stored above room temperature. Revise the storage statement to (b) (4)

- b. The submitted stability data supports a retest period of (b) (4). We recommend that you revise the initial retest period to (b) (4).
- c. Revise your proposed post approval stability protocol to include testing at the 3 and 9 month time points.

Please address the aforementioned comments by Friday, October 19, 2012. If you have any questions or concerns please contact me at (301) 796-0704.

Thank you,
Gina

Gina M. Davis, MT
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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GINA M DAVIS
10/12/2012

NDA: 203756
October 2, 2012

Monthly Team Meeting – October

Product: Cometriq (cabozantinib) capsules
Submission Date: May 21, 2012
Received Date: May 29, 2012
PDUFA Date: November 29, 2012
Sponsor: Exelixis, Inc.

Proposed Indication: For the treatment of patients with progressive, unresectable, locally advanced or metastatic medullary thyroid cancer

Current Review Team for NDA 203756:

Patricia Keegan, M.D., Director DOP2
Gina Davis, M.T., Regulatory Health Project Manager
Karen Jones (CPMS)
Ruthann Giusti, M.D., Medical Officer
Suzanne Demko, C- P.A., (TL and CDTL)
Yuan Li Shen, Ph.D., Statistics
Kun He, Ph.D., Statistics (TL)
Jun Yang, Ph.D., Clinical Pharmacology
Hong Zhao, Ph.D., Clinical Pharmacology (TL)
Margaret Brower, Ph.D., Non-Clinical
Whitney Helms, Ph.D., Nonclinical (TL)
William (Mike) Adams, Ph.D., Product
Li Shan Hsieh, Ph.D. Product
Liang Zhou, Ph.D., Product (TL)
Nallaperumal Chidambaram, Ph.D., Branch Chief
Sarah Pope Miksinski, Ph.D., Acting Division Director
Jewell Martin, M.S., Product (ONDQA RPM)
Angelica Dorantes, Ph.D., Biopharmaceutics TL
Minerva Hughes, Ph.D., Biopharmaceutics Reviewer
Denise Miller, Ph.D. Microbiology Reviewer
Roy Blay, OSI Inspector
Mahesh Ramanadham, Facilities Inspector, PharmD/M.B.A.

Review Status:

- Priority Review - confirmation (6 month clock)
- Categorical Exclusion requested
- Requested full waiver of pediatric studies - Orphan Designation granted on November 29, 2010 – product is exempt from PRE
- The clinical development of cabozantinib has been conducted under INDs 113446 and (b) (4)

Manufacturing\Clinical inspections - Dates of inspections – current status:

- All manufacturing/facility site inspections are complete and acceptable.

Office of Scientific Inspections (DSI)

Foreign Inspections
Italy – currently ongoing
Germany – scheduled (tentative completion)
October 19, 2012

All inspections are complete, however; OSI is still awaiting inspection reports from two of the clinical sites as well as the sponsor. There may be some issues regarding the sponsor inspection with respect to monitoring, source documentation, oversight, informed consent and SAE reporting. OSI is awaiting written responses from the sponsor for final assessment.

Next Monthly Team Meetings

- November 1, 2012 (November Team Meeting\Wrap-up Meeting)

Recent Information

-  (b) (4)
No actions will be taken at this time.
- 120-day safety update has been submitted including interim analysis of OS.

Discussion

No Discussion occurred.

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/s/

GINA M DAVIS
12/14/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: October 2, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756; Exelixis – Cometriq (cabozantinb); Recommendations for the Carton and Container

Dear Ms. Sauer,

Please refer to your May 21, 2012, New Drug Application (NDA), received on May 29, 2012, for your product cabozantinib. We are currently reviewing your carton and container for the new molecular entity (NME) cabozantinib and have the following requests for additional information.

Container Labels and Carton Labeling for 60 mg, 100 mg, 140 mg Blister Cards, and 20 mg Bottle

1. Revise the presentation of the proprietary name from all upper case letters (COMETRIQ) to title case (Cometriq) to improve readability.
2. Ensure the established name is at least ½ the size of the proprietary name and has prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printer features per 21 CFR 201.10(g)(2).

.Carton Labeling and Container Label for 140 mg Dose

3. The (b)(4) color used to highlight the 140 mg dose may look similar to the orange color of the 80 mg capsule. To ensure patients and healthcare providers do not associate the (b)(4) color used to highlight the dose with the orange 80 mg capsule color, change the (b)(4) color on the labels and labeling to a color that is not similar to the orange or grey capsule colors. Additionally, chose a color that is not at all similar to the colors used to highlight the daily dose or product strength on the other Cometriq labels and labeling.

Container Label for 20 mg Bottle

4. The (b)(4) color used to highlight the product strength on 20 mg bottle is similar to the orange color of the 80 mg capsule. To ensure patients and healthcare providers do not associate the (b)(4) color used to highlight the product strength with the orange 80 mg capsule color, change the (b)(4) color on the label to a color that is not similar to the orange or grey capsule colors. Additionally, chose a color that is not at all similar to the colors used to highlight the daily dose on the other Cometriq labels and labeling.

5. Revise the statement [REDACTED] (b) (4) to “Take on an empty stomach (at least 1 hour before or 2 hours after eating).”

Blister Card for 60 mg, 100 mg, 140 mg Dose

6. Please ensure that dosing instructions on the blister card are legible font size
7. Add the statement “Daily Dose Pack” prominently and include it in the color block with the total daily dose. Remove the asterisks which follow the dose statement. Immediately below the statement “Daily Dose Pack”, add the appropriate statement(s) indicating the number of capsules and product strengths in each row of the blister pack, and ensure the statement(s) appear inside the color block. Below is an example for the 140 mg daily dose pack.

<p>140 mg Daily Dose Pack Each row contains a 140 mg daily dose comprised of:</p> <ul style="list-style-type: none">• one 80 mg orange capsule and• three 20 mg grey capsules
--

8. Remove the statements [REDACTED] (b) (4) located below the dose presentation on the principal display panel.
9. Revise the statement “Each blister card contains a 7-day supply...” to read “Each blister card contains a 7 day supply of capsules for patients taking a XXX mg daily dose.”
10. Revise the statement “Record the date of the first dose in the space provided.” to read “Record the date of the first dose in the space provided below.” Additionally, relocate the box to record the date of first dose to follow this statement, delete the statement that is currently to the left of the box (Record Date of First Dose) and delete all associated superscript symbols.
11. Ensure that each blister card uses the alternating light and dark shades of gray to help separate the rows to ensure the patient is taking the correct set of capsules each day.
12. To help ensure patients take the correct capsules, place the product strength of each capsule next to each blister on the card. This will provide an additional safeguard for the patient.
13. Revise the statement under Dosing Instructions “Take all capsules in one row...” to “Take all capsules in one row on an empty stomach (at least 1 hour before or 2 hours after eating) once each day.”

14. Revise the current net quantity layout:

XX Capsules

Total Quantity of XX mg capsules: X

Total Quantity of XX mg capsules: X

to the following:

60 mg Blister Card

Each blister card contains:

Twenty-one 20 mg capsules

100 mg Blister Card

Each blister card contains:

Seven 80 mg capsules

Seven 20 mg capsules

140 mg Blister Card

Each blister card contains:

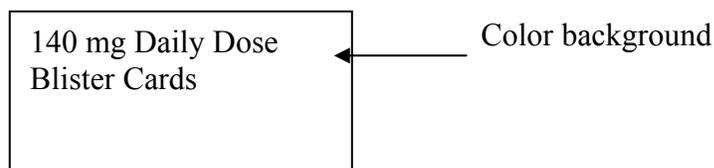
Seven 80 mg capsules

Twenty-one 20 mg capsules

15. Include a bar code on each blister pack in accordance with 21 CFR 201.25.

Carton Labeling for 60 mg, 100 mg, and 140 mg Dose

16. Add the statement “Daily Dose Blister Cards” prominently and include it in the color block with the daily dose each place it occurs on the carton. Additionally, remove the asterisk after the dose. For example:



17. Revise the statement “Each blister card contains a 7-day supply...” to read “The blister cards in this carton are for patients prescribed a XXX mg daily dose.” Additionally, increase the prominence of this statement.
18. For each place it occurs on the carton, remove the asterisks at the beginning of the statement (b) (4)
19. Revise to include National Drug Code (NDC) numbers on each carton.

Storage of Product

20. Please ensure that the following information is included on the blister packs, container and carton labels.

- Store Cometriq at 25°C (77°F); excursions are permitted from 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].

Please address the aforementioned comments by Wednesday, October 10, 2012. If you have any questions or concerns please contact me at (301) 796-0704.

Thank you,
Gina

Gina M. Davis, MT
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
10/03/2012

NDA: 203756
September 11, 2012

Monthly Team Meeting – September

Product: Cometriq (cabozantinib) capsules
Submission Date: May 21, 2012
Received Date: May 29, 2012
Goal Date:
PDUFA Date: November 29, 2012
Sponsor: Exelixis, Inc.

Proposed Indication: For the treatment of patients with progressive, unresectable, locally advanced or metastatic medullary thyroid cancer

Staff members present at the September 11, 2012, monthly meeting; Suzanne Demko, Ruthann Giusti, Whitney Helms, Margaret Brower, Li Shan Hsieh, Mike Adams, Nallaperumal Chidambaram, Hong Zhao, Jun Yang, Denise Miller, Minverva Hughes, Gina Davis

Current Review Team for NDA 203756:

Patricia Keegan, M.D., Director DOP2
Gina Davis, M.T., Regulatory Health Project Manager
Karen Jones (CPMS)
Ruthann Giusti, M.D., Medical Officer
Suzanne Demko, C- P.A., (TL and CDTL)
Yuan Li Shen, Ph.D., Statistics
Kun He, Ph.D., Statistics (TL)
Jun Yang, Ph.D., Clinical Pharmacology
Hong Zhao, Ph.D., Clinical Pharmacology (TL)
Margaret Brower, Ph.D., Non-Clinical
Whitney Helms, Ph.D., Nonclinical (TL)
William (Mike) Adams, Ph.D., Product
Li Shan Hsieh, Ph.D. Product
Liang Zhou, Ph.D., Product (TL)
Nallaperumal Chidambaram, Ph.D., Branch Chief
Sarah Pope Miksinski, Ph.D., Acting Division Director
Jewell Martin, M.S., Product (ONDQA RPM)
Angelica Dorantes, Ph.D., Biopharmaceutics TL
Minerva Hughes, Ph.D., Biopharmaceutics Reviewer
Denise Miller, Ph.D. Microbiology Reviewer
Roy Blay, OSI Inspector
Mahesh Ramanadham, Facilities Inspector, PharmD/M.B.A.

Review Status:

- Priority Review - confirmation (6 month clock)
- Categorical Exclusion requested

- Requested full waiver of pediatric studies - Orphan Designation granted on November 29, 2010 – product is exempt from PRE
- The clinical development of cabozantinib has been conducted under INDs 113446 and (b) (4)

Manufacturing\Clinical inspections - Dates of inspections – current status:

- All manufacturing/facility site inspections are complete and acceptable.

Office of Scientific Inspections

- OSI is scheduled to inspect three clinical sites
 - Domestic Inspection
 - Ohio – August 17, 2012 - complete and acceptable
 - Foreign Inspections
 - Italy – currently ongoing
 - Germany – scheduled (tentative completion) October 19, 2012

Monthly Team Meetings

- October 2, 2012 (October Team Meeting)
- November 1, 2012 (November Team Meeting\Wrap-up Meeting)

Midcycle Meeting (Outcome)

- Determined that there was no need for cabozantinib to be discussed at the November 2012, ODAC Meeting. This information was conveyed to the sponsor on August 28, 2012.
- Nonclinical and CMC discussions regarding GTI's are ongoing.
- Biopharm – The proposed dissolution acceptance criterion is not acceptable. FDA recommends that Exelixis change their dissolution acceptance criterion.
- DEMPA - Recommending Exelixis assign each carton a NDC number and each blister pack will contain a bar code.
- Recommendation – Work with sponsor regarding drug presentation.

Labeling Meetings

- September 13, 2012 – Third Labeling Meeting - to discuss the following Sections: Clinical Sections - Dosage and Administration, Clinical Studies, (Nonclinical, DMEPA and PMH)
- October 1, 2012 – Fourth Labeling Meeting - to discuss the following Sections: Dosage Forms and Strengths, Description, How Supplied/Storage and Handling, CMC, DMEPA, (Clinical Pharmacology [?]) - DMEPA/CMC to review carton and container.

- October 2, 2012 – Labeling Meeting - To discuss the following sections; Drug Interactions, Use in Specific Populations, Overdosage (Clinical Pharmacology, Nonclinical, PMH)
- October 15, 2012 – Fifth Labeling Meeting – to discuss the following Sections: Dosage Forms and Strengths, Description, How Supplied/Storage and Handling, CMC, DMEPA, (Clinical Pharmacology [?])
- October 23, 2012 - Sixth Labeling Meeting – Extra Meeting

PMRs

Clinical Pharmacology

- Renal Impairment

Nonclinical

- Carcinogenicity Studies
- Reprotoxicity Studies

QT-IRT

- Cardiac Signal

SUMMARY OF SEPTEMBER MONTHLY MEETING

Discipline Review Feedback

CMC

Drug Substance - Information/Request memo will be sent to the sponsor, regarding drug substance, once the comments are sent to the RPM.

Drug Product - No issues.

Biopharmaceuticals – Awaiting response to the August 30, 2012, information request.

Nonclinical – Not sure of GTI's will provide information at a later date.

Clinical Pharmacology – No issues.

Microbiology – No issues.

Clinical – Awaiting response to the September 7, 2012, information request.

Information/Request

- Exelixis was notified, via teleconference, that their NME cabozantinib will not be discussed at the November 2012, ODAC Meetings (August 29, 2012).
- Biopharm – The proposed dissolution acceptance criterion is not acceptable. FDA recommends that Exelixis change their dissolution acceptance criterion (request sent on August 30, 2012).
- DEMPA - Recommending Exelixis assign each carton a NDC number and each blister pack will contain a bar code (request sent on August 30, 2012).
- Clinical – Provide the autopsy report/additional information concerning patient 44033003 enrolled on XL184-301 who was treated with cabozantinib and died of hemorrhage (request sent on September 7, 2012).

Responses to the aforementioned requests have not been received to date.

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

/s/

GINA M DAVIS
11/20/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 7, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756 – Exelixis – Cometriq (cabozantinib); Request for Clinical Information

Dear Ms. Sauer,

Please refer to your May 21, 2012, New Drug Application (NDA), received on May 29, 2012, for your product cabozantinib. We are currently reviewing your submission and have the following comments and requests for additional information.

Provide the autopsy report/additional information concerning patient 44033003 enrolled on XL184-301 who was treated with cabozantinib and died of hemorrhage. The nature of the hemorrhage is not clear from the case report form. We need additional information concerning the site of bleeding and the nature of the event.

Please address the aforementioned request, as soon as possible. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

GINA M DAVIS
09/07/2012

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 203756 BLA#	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE- N/A
Proprietary Name: Cometriq Established/Proper Name: cabozantinib Dosage Form: capsules Strengths: 20 mg , 80 mg		
Applicant: Exelixis, Inc. Agent for Applicant (if applicable):		
Date of Application: May 21, 2012 Date of Receipt: May 29, 2012 Date clock started after UN:		
PDUFA Goal Date: November 29, 2012		Action Goal Date (if different):
Filing Date: July 28, 2012		Date of Filing Meeting: June 29, 2012
Chemical Classification: (1,2,3 etc.) (original NDAs only) Type 1 NME		
Proposed indication(s)/Proposed change(s): For the treatment of progressive, unresectable, locally advanced, or metastatic medullary thyroid cancer.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>		Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input checked="" type="checkbox"/> Fast Track <input checked="" type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product):				
List referenced IND Number(s): IND 113446 and IND (b)(4)				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:			X	
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>			<p>X</p>																	
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? Check the <i>Electronic Orange Book</i> at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1451 1349 1587"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															<p>X</p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</p>		<p>X</p>																		

<p>If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?</p> <p><i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i></p>			X	
<p>Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>)</p> <p>If yes, # years requested:</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>		X		
<p>Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?</p>		X		
<p>If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?</p> <p><i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i></p>			X	

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

1

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

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
Applications in “the Program” (PDUFA V) (NME NDAs/Original BLAs)	YES	NO	NA	Comment
Was there an agreement for any minor application components to be submitted within 30 days after the original submission?			X	
<ul style="list-style-type: none"> If yes, were all of them submitted on time? 			X	
Is a comprehensive and readily located list of all clinical sites included or referenced in the application?			X	
Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?			X	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?				
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			

<p><i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i></p> <p><i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i></p>				
Clinical Trials Database	YES	NO	NA	Comment
<p>Is form FDA 3674 included with authorized signature?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i></p> <p><i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i></p>	X			
Debarment Certification	YES	NO	NA	Comment
<p>Is a correctly worded Debarment Certification included with authorized signature?</p> <p><i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i></p> <p><i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i></p>	X			
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	X			
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i></p>			X	

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		X		Orphan Designation
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>			X	
<p>If studies or full waiver not included, is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included?</p> <p><i>If no, request in 74-day letter</i></p>			X	
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)?</p> <p><i>If no, request in 74-day letter</i></p>				
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i></p>			X	
Proprietary Name	YES	NO	NA	Comment
<p>Is a proposed proprietary name submitted?</p> <p><i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i></p>	X			
REMS	YES	NO	NA	Comment
<p>Is a REMS submitted?</p> <p><i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i></p>		X		
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide)			

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

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

	<input type="checkbox"/> Carton labels <input type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	X			
Is the PI submitted in PLR format? ⁴	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>			X	
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>			X	
If representative labeling is submitted, are all represented SKUs defined?			X	

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

<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	X			Consult submitted to QT/IRT to review cardiac safety report for Study XL184-301-ECG-001.
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): December 14, 2010 <i>If yes, distribute minutes before filing meeting</i>	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): December 21, 2011 <i>If yes, distribute minutes before filing meeting</i>	X			Final Meeting Minutes issued on January 6, 2011
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: June 29, 2012

BLA/NDA/Supp #: 203756

PROPRIETARY NAME: Cometriq (provisional granted under IND - under NDA review)

ESTABLISHED/PROPER NAME: cabozantinib

DOSAGE FORM/STRENGTH: capsules – 20mg and 80 mg

APPLICANT: Exelixis, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): For the treatment of progressive, unresectable, locally advanced, or metastatic medullary thyroid cancer.

BACKGROUND:

On June 10, 2005, Exelixis, Inc submitted an Investigational New Drug Application (IND) for their investigational product XL184, assigned IND (b) (4) Orphan drug designation was granted on November 29, 2010 and fast track designation was granted on April 8, 2011. (b) (4)

(b) (4) assigned IND 113446 for the indication of medullary thyroid cancer and transferred to the Division of Oncology Products 2

Exelixis requested to submit a rolling NDA submission which was granted by the Division of Oncology Products 1. The last portion containing the clinical module and CMC stability data was received on May 29, 2012.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Gina Davis	Y
	CPMS/TL:	Karen Jones	N
Cross-Discipline Team Leader (CDTL)	Suzanne Demko, P.A. - C		Y
Clinical	Reviewer:	Ruthann Giusti, M.D.	N
	TL:	Suzanne Demko, P.A.-C	Y

Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:	N/A	
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	N
	TL:		
Clinical Pharmacology	Reviewer:	Jun Yang, Ph.D.	Y
	TL:	Hong Zhao, Ph.D.	Y
Biostatistics	Reviewer:	Yuan Li Shen, Ph.D.	N
	TL:	Kun He, Ph.D.	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Margaret Brower, Ph.D.	N
	TL:	Whitney Helms, Ph.D.	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Li Shan Hsieh, Ph.D. – DP Reviewer William M. Adams, Ph.D. – DS Reviewer (Liang Zhou CMC team lead – in attendance) Janice Brown in attendance Biopharmaceuticals Reviewer – Minerva Hughes, Ph.D	N Y Y
	TL:	Liang Zhou, PhD. Janice Brown, Ph.D.	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	Denise Miller	N
	TL:		

CMC Labeling Review	Reviewer:	Li Shan Hsieh, Ph.D. William M. Adams, Ph.D.	N Y
	TL:	Janice Brown, Ph.D.	Y
Facility Review/Inspection	Reviewer:	Mahesh Ramandham, OMPQ TL	Y
OSE/DMEPA (proprietary name)	Reviewer:	James Schlick	Y
	TL:	Todd Bridges	Y
OSE/DRISK (REMS)	Reviewer:	N/A	
	TL:	N/A	
Bioresearch Monitoring (OSI)	Reviewer:	Roy Blay	Y
	TL:	Janice Pohlman	N
Other Reviewers and Attendees	Jewell Martin, Product (ONDQA RPM) Sue Kang, (OSE RPM) Karen Munoz, OPDP, Consumer Reviewer Karen Dowdy, PLT Janine Best- PMH Nintin Mehrotra – QT-IRT		

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments: No Comments</p>	<input type="checkbox"/> Not Applicable
CLINICAL	
<p>Comments: The clinical team requested additional information be provided regarding financial disclosure and radiological assessments.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input checked="" type="checkbox"/> Review issues for 74-day letter

<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: November 7, 2012 <input type="checkbox"/> NO <input checked="" type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE

<p>Comments: Information request from the stats team were sent to the sponsor on July 10 and July 13, 2012.</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments: No comments</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Biopharmaceuticals</p> <p>Comments: Biopharmaceutical comments sent to the sponsor on July 9, 2012.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments: No Comments</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments: (b) (4) inspection - capsule manufacturing site started on (b) (4) – complete. (b) (4) inspection – (b) (4) has been assigned to district office – no dates determined. (b) (4) – The drug substance testing facility inspection is acceptable. (b) (4) – The drug substance manufacturer was inspected in (b) (4) and is currently under review – CDER/OC.</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments: No comments.</p>	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Richard Pazdur, M.D. Date of Mid-Cycle Meeting August 28, 2012 21st Century Review Milestones Filing Action July 28, 2012, 74 day letter – August 11, 2012</p> <p>Comments: The review team discussed the following during the filing meeting:</p> <ol style="list-style-type: none"> 1. The review team agreed to review this submission as a priority review. 2. A mid-cycle meeting was scheduled for August 28, 2012. 3. Standing monthly meetings have been scheduled from July – October (Wrap- up Meeting – November 2, 2012). 4. Labeling meetings have been scheduled for July - October 2012. 5. Clinical sites have been selected for inspections, inspections are being scheduled. 6. DP manufacturing sites have been inspected and are close to completion. 7. The Division requested additional information be provided regarding financial disclosure and radiological assessments – submitted by sponsor. 8. Biopharmaceutical comments were sent to the sponsor on July 9, 2012– dissolution issues. 9. Statistical comments were sent to the sponsor on July 10 and July 13, 2012. 	

REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.</p> <p><input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): Labeling issues identified.</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review</p> <p><input checked="" type="checkbox"/> Priority Review</p>
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in “the Program”)
<input type="checkbox"/>	<p>BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]</p>
<input type="checkbox"/>	Other

Appears this way on original

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/s/

GINA M DAVIS
08/31/2012

KAREN D JONES
09/04/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 30, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756; Exelixis – Cometriq (cabozantinb); Advice and Information Request from the Biopharmaceutical and Division of Medication Error Prevention and Analysis (DMEPA)

Dear Ms. Sauer,

Please refer to your May 21, 2012, New Drug Application (NDA), received on May 29, 2012, for your product cabozantinib. We are currently reviewing your submission and have the following comments and requests for additional information from the Biopharmaceutical and DMEPA teams.

Biopharmaceuticals

1. Your proposed dissolution acceptance criterion of $Q = \text{[redacted]}^{(b) (4)}$ is not supported by the data submitted and is not acceptable. FDA recommends an acceptance criterion of $Q = \text{[redacted]}^{(b) (4)}$ at 15 minutes for your cabozantinib 20 mg and 80 mg capsule products. Provide a revised drug product regulatory specification table, revised stability protocol, and revised method protocols with the aforementioned dissolution acceptance criterion change.

DEMPEA

2. Although your intentions at this time are to distribute your product through specialty pharmacies, your distribution plans may change in the future and include non-specialty pharmacies. Healthcare practitioners, including those in specialty pharmacies, are accustomed to a NDC number on each level of packaging of a product. The NDC provides a unique number which identifies the labeler, drug, and package size of every product available for sale or use in the U.S. It's important that you include a NDC on the carton labeling of your proposed product to help ensure patients are dispensed the quantity of product intended by their healthcare provider. Additionally, assigning a NDC number to each carton should not be a costly or lengthy process. We maintain that each carton should be assigned a NDC number. We also request you confirm that each blister pack will contain a bar code in accordance with 21 CFR 201.25.

Please address the aforementioned comments by Thursday, September 13, 2012. If you have any questions or concerns please contact me at (301) 796-0704.

Thank you,

Gina

Gina M. Davis, MT
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
08/30/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 29, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756; Exelixis; Cometriq (cabozantinib); Teleconference

Teleconference

Sponsor Attendee:

Kirk Rosemark Vice President, Regulatory Affairs

FDA Attendee:

Gina Davis, M.T. Regulatory Health Project Manager

Discussion

On August 29, 2012, Kirk Rosemark (authorized regulatory contact for NDA 203756) was notified that the new molecular entity (NME) Cometriq (cabozantinib) has been removed from the agenda for the November 8 and November 9, 2012, Advisory Committee Meeting.

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/s/

GINA M DAVIS
08/29/2012



NDA 203756

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Exelixis, Inc.
210 East Grand Ave.
South San Francisco, CA 94083

ATTENTION: Kirk Rosemark, RAC
Vice President, Regulatory Affairs

Dear Mr. Kirk:

Please refer to your New Drug Application (NDA) dated May 21, 2012, received May 29, 2012, submitted under section 505 (b)(1) of the Federal Food, Drug, and Cosmetic Act for Cabozantinib Capsules, 20 mg and 80 mg.

We also refer to your May 30, 2012, correspondence, received May 31, 2012, requesting review of your proposed proprietary name, Cometriq. We have completed our review of the proposed proprietary name, Cometriq and have concluded that it is acceptable.

The proposed proprietary name, Cometriq, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your May 30, 2012, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Gina Davis at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

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

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/s/

KELLIE A TAYLOR on behalf of CAROL A HOLQUIST
08/23/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 17, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756 – Exelixis – Cometriq (cabozantinib); Requesting Information from the Division of Medication Error Prevention and Analysis

Dear Ms. Sauer,

Please refer to your May 21, 2012, New Drug Application (NDA), received on May 29, 2012, for your product cabozantinib. We are currently reviewing your submission and have the following comment and request for additional information.

Please provide narratives for the following patients on the placebo arm as soon as possible.

14183005
44013001
44113004
48063002
97023007
32013011
39043003
97043001

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
08/17/2012

NDA: 203756
August 16, 2012

Monthly Team Meeting – August

Product: Cometriq (cabozantinib) capsules
Submission Date: May 21, 2012
Received Date: May 29, 2012
Sponsor: Exelixis, Inc.

Proposed Indication: For the treatment of patients with progressive, unresectable, locally advanced or metastatic medullary thyroid cancer

Current Review Team for NDA 203756:

Patricia Keegan, M.D., Director DOP2
Gina Davis, M.T., Regulatory Health Project Manager
Karen Jones (CPMS)
Ruthann Giusti, M.D., Medical Officer
Suzanne Demko, C- P.A., (TL and CDTL)
Yuan Li Shen, Ph.D., Statistics
Kun He, Ph.D., Statistics (TL)
Jun Yang, Ph.D., Clinical Pharmacology
Hong Zhao, Ph.D., Clinical Pharmacology (TL)
Margaret Brower, Ph.D., Non-Clinical
Whitney Helms, Ph.D., Nonclinical (TL)
William (Mike) Adams, Ph.D., Product
Li Shen Hsieh, Ph.D. Product
Liang Zhou, Ph.D., Product (TL)
Janice Brown, Ph.D. Product (Acting BC)
Sarah Pope Miksinski, Ph.D., Product TL
Jewell Martin, M.S., Product (ONDQA RPM)
Angelica Dorantes, Ph.D., Biopharmaceutics TL
Minerva Hughes, Ph.D., Biopharmaceutics Reviewer
Denise Miller, Ph.D. Microbiology Reviewer
Roy Blay, OSI Inspector
Mahesh Ramanadham, Facilities Inspector, PharmD/M.B.A.

SUMMARY OF AUGUST MONTHLY MEETING

Midcycle Meeting

- The Midcycle Meeting is scheduled for Tuesday, August 28, 2012, please have your slides to Suzanne Demko (CDTL) by Tuesday, August 21, 2012.

ODAC – Currently we are scheduled for ODAC – Tentatively scheduled for November 9, 2012 (possibly November 8, 2012 - date and time not yet finalized).

- Exelixis has been notified that the NME has been placed on the agenda for the November 9, 2012, ODAC (may change to November 8, 2012).
- Names of identified SGE's were due on July 18, 2012 (initial contact has been made)

Questions to be considered now or in the near future

- Will you expect to have a guest speaker?
- Will you expect to have a separate stat presentation?
- Will you expect to have other presentations (e.g., safety?)
- Will you need DSARM (Drug Safety and Risk Management AC) or RCAC (Risk Communication AC) representation at the meeting?

ODAC Practice Sessions @ OHOP Staff meetings (Monday/Friday) (dates for entire team – slides for ODAC - due November 2, 2012)

- October 15, 2012 – ODAC Practice Session #1 – Division Level
- October 22, 2012 – ODAC Practice Session #2 – Division Level
- October 26 (Friday) - ODAC Practice Session - Office level
- October 30, 2012 – ODAC Practice Session # 4 – Division Level

Labeling Meetings

- August 29, 2012 – Second Labeling Meeting – to discuss the following Sections: Clinical Sections - Indications and Usage, Dosage and Administration, Over Dosage, Contraindications, Adverse Reactions, Warnings and Precautions.
- September 13, 2012 – Third Labeling Meeting - to discuss the following Sections: Clinical Sections - Dosage and Administration, Clinical Studies, Drug Interactions, Use in Specific Populations, Overdosage (clinical pharmacology, Nonclinical, DMEPA and PMH) **Due scheduling conflicts it would be helpful to have clinical Pharmacology go first followed by DMEPA.**
- October 1, 2012 – Fourth Labeling Meeting - to discuss the following Sections: Dosage Forms and Strengths, Description, How Supplied/Storage and Handling, CMC, DMEPA, (Clinical

Pharmacology [?]) - DMEPA/CMC to review carton and container.

- October 15, 2012 – Fifth Labeling Meeting – to discuss the following Sections: Dosage Forms and Strengths, Description, How Supplied/Storage and Handling, CMC, DMEPA, (Clinical Pharmacology [?])
- October 23, 2012 - Sixth Labeling Meeting – Extra Meeting

Additional Questions or Concerns

PMR – nonclinical – Exelixis was advised to submit plans to conduct carcinogenicity studies as PMR.

Discussion

Team was informed that the filing letter, containing preliminary labeling negotiations, was sent on July 27, 2012.

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/s/

GINA M DAVIS
12/14/2012

Varney, Deanne

From: Varney, Deanne
Sent: Friday, August 10, 2012 9:19 AM
To: 'Isauer@exelixis.com'
Cc: Davis, Gina
Subject: NDA 203756 - Statistical Information Request

Hello Dr. Sauer,

I am sending this on behalf of your Regulatory Project Manager for NDA 203756, Ms. Gina Davis. The statistical team has the following request for clarification. Please provide a response via email to Gina Davis at your earliest convenience, followed by a submission to your NDA.

On page 39 of the CSR, you indicated that amendment 2 was implemented after 295/330 subjects were enrolled in the study. However, FDA obtained 100 patients who had randomization date (RANDDT) after amendment 2 (dated 9/24/10). Please clarify how these 35 patients enrolled after amendment 2 can be extracted from the current submitted data.

Thank you,
Deanne

Deanne Varney
Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Phone: 301-796-0297

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/s/

DEANNE R VARNEY
08/10/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 8, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756 – Exelixis – Cometriq (cabozantinib); Request for statistical information

Dear Ms. Sauer,

Please refer to your May 21, 2012, New Drug Application (NDA), received on May 29, 2012, for your product cabozantinib. We are currently reviewing your submission and have the following comment and request for additional information.

On page 39 of the CSR, you indicated that amendment 2 was implemented after 295/330 subjects were enrolled in the study. However, FDA obtained 100 patients who had randomization date (RANDDT) after amendment 2 (dated 9/24/10). Please clarify how these 35 patients enrolled after amendment 2 can be extracted from the current submitted data

If you have any additional questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
08/08/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 8, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756 – Exelixis – Cometriq (cabozantinib); Request for clinical information

Dear Ms. Sauer,

Please refer to your May 21, 2012, New Drug Application (NDA), received on May 29, 2012, for your product cabozantinib. We are currently reviewing your submission and have the following comment and request for additional information.

We have reviewed your Monday, August 6, 2012, electronic (email) communication and have the following comment.

The updated analysis may involve not only the updated OS data (timing and event indicators), but also the other data (tumor assessments date, last treatment date, last visit date, date cutoff date, end of study visit page, dates that patients took anti-cancer therapy etc) for updating the timing of the censoring. Basically, the SAS program that derived the OS analyses and the corresponding baseline data has been submitted in the current submission. The proposed submission of the updated OS analysis (including only the analysis dataset and the SAS program that produces the results) may be acceptable provided that Exelixis documents what data have been updated (including what cutoff date is used) and incorporated into this updated OS analyses.

If you have any additional questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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GINA M DAVIS
08/08/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 3, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756 – Exelixis – Cometriq (cabozantinib); Request for Clinical and Statistical Information

Dear Ms. Sauer,

Please refer to your May 21, 2012, New Drug Application (NDA), received on May 29, 2012, for your product cabozantinib. We are currently reviewing your submission and have the following comments and requests for additional information.

FDA was not able to duplicate the numbers presented in Tables 34-36. Please submit the corresponding SAS programs (including programs that created the derived variables) to confirm the results of the biomarker (Calcitonin and CEA) analyses which appear in these tables in the final study report for XL184,-301 (Section 11.4.10.1.2, page 134 and on).

Please address the aforementioned request, by Friday, August 10, 2012. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
08/03/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 1, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756 – Exelixis – Cometriq (cabozantinib); Requesting Information from the Division of Medication Error Prevention and Analysis

Dear Ms. Sauer,

Please refer to your May 21, 2012, New Drug Application (NDA), received on May 29, 2012, for your product cabozantinib. We are currently reviewing your submission and have the following comment and request for additional information.

The Division of Medication Error Prevention and Analysis (DMEPA) has received the applicant's July 20, 2012, response regarding the NDC information for Cometriq. DMEPA specifically notes the Applicant's rationale for not assigning an NDC number to the carton of four blister cards. However, DMEPA still requests that the Applicant assign a separate NDC number to each carton for billing and ordering purposes. Although the blister card is the individual unit for sale, pharmacies will most likely order the carton of four blister cards from their wholesaler and dispense a 28 day supply (one carton). Hence, an NDC number for the carton will help simplify and minimize confusion with ordering and billing in pharmacies.

Please address the aforementioned request, by Wednesday, August 8, 2012. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
08/01/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: August 1, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756 – Exelixis – Cometriq (cabozantinib); Request for Clinical Information

Dear Ms. Sauer,

Please refer to your May 21, 2012, New Drug Application (NDA), received on May 29, 2012, for your product cabozantinib. We are currently reviewing your submission and have the following comments and requests for additional information.

Please provide the complete protocol deviation log from the Trial Master File from clinical protocol XL4-301 for verification with a complete listing of protocol violations by patient showing the ID#, Treatment Group, and all protocol deviations for each subject.

Please address the aforementioned request, by Friday, August 3, 2012. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
08/01/2012



NDA 203756

FILING COMMUNICATION

Exelixis, Inc.
Attention: Lisa Sauer
Director, Regulatory Affairs
210 East Grand Avenue
South San Francisco, CA 94083

Dear Ms. Sauer:

Please refer to your New Drug Application (NDA) dated May 21, 2012, received May 29, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Cometriq (cabozantinib).

We also refer to your amendment dated July 13, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is November 29, 2012.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by November 1, 2012.

During our filing review of your application, we identified the following potential review issues:

1. Provide an updated analysis of survival in the 120-day safety update.
2. There is one discrepancy in the censoring date for patient 33033003: the PDDT_IRC (a reviewer's derived variable) date is 11/3/2010, but your derived variable KMDT_IRC date is 6/3/2009 (see listing below). Please note that we had the same last tumor

assessment date (lastoadt=lta_irc). Please clarify why your KMDT_IRC for patient 33033003 is the same as the RANDDT.

PFS

			P	K	K	l			e
			D	M	M	a	L		1
			D	D	C	s	T	R	3
			T	T	S	t	A	A	0 8
		T	—	—	—	o	—	N	A —
O		R c	I	I p I		a	I	D	D i
b	P	T h	R	R f R		d	R	D	T r
s	T	R k	C	C s C		t	C	T	x c
1	33033003	1 2	03NOV2010	03JUN2009	1 1	03NOV2010	03NOV2010	03JUN2009	. .

3. You indicated in the July 13, 2012, response to FDA’s July 10, 2012, information request that the dataset OAVND and LEVND were not derived by SAS programs. Due to the lack of a more systematic way to demonstrate the adequacy of the variable derivation from the raw data, we request several programmatically derived variables be created and any discrepancy between the values (CR, PR, SD, PD or UK) from these programmatically derived variables versus the corresponding variables provided by Perceptive, if available, be explained. These variables should include the following:
 - a. Sum of the longest diameters, percent change of the longest diameters for each time point (or visit) -- possibly to be compared with OAPCCHBA and OATPSLD from dataset OAVND.
 - b. Response based on the target lesions for each time point (or visit) as defined on page 91 of 1484 of the CSR. – possibly to be compared with OAOVUTPA (or OATARESP ?) from dataset OAVND.
 - c. Overall Response based on the target lesions, non-target lesions and new lesions as shown on page 92 of 1484 of the CSR – (not sure what is the corresponding variable in dataset OAVND).

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application. During our preliminary review of your submitted labeling, we have identified the following labeling format issues (see comments below and attached draft package insert label):

Highlights

4. Highlights must reference the section(s) or subsection (s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary. Please address this in Indications and Usage, Dosage and Administration and Adverse Reactions sections.
5. The Highlights Limitation Statement must appear in bold font.
6. The Highlights product title must be bolded.
7. Initial U.S. Approval in Highlights must be placed immediately beneath the product title, bolded, and include the verbatim statement “Initial U.S. Approval followed by the 4 digit year. Please insert the year in the label.
8. Insert white space between the last sentence in Adverse Reactions and the first sentence describing where to report Adverse Reactions.
9. The Patient Counseling Information Statement must appear as the following statement, bolded and in quotation marks, “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**” as it has been determined that your label contains a patient package insert and not a Medication Guide.
10. FDA approved patient labeling should not be a subsection of Section 17.
11. The review team has determined that a Boxed Warning to address gastrointestinal and other enterovisceral perforations, surgery and wound healing complications, and hemorrhage adverse reactions is needed for the label. Please be sure to incorporate the following formatting requirements in the Boxed Warning:
 - a. All text must be bolded.
 - b. The Boxed Warning must have a centered heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (see attached revised draft package insert)
 - c. The Boxed Warning must always have the verbatim statement “***See full prescribing information for complete boxed warning.***” centered immediately beneath the heading.
 - d. The Boxed warning must be limited in length to 20 lines (this does not include the heading and statement ““***See full prescribing information for complete boxed warning.***”)

- e. Use sentence case for summary (a combination of upper case and lower case letters typical of that used in a sentence).
12. A horizontal line must appear between the TOC from the FPI.

Table of Contents (TOC)

13. Include Boxed Warning in the TOC. Note that the section headings and subheadings (including title of the Boxed warning) must match the headings and subheadings in the Full Prescribing Information (FPI) and that the same title for the Boxed warning that appears in the Highlights and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and be bolded.

Full Prescribing Information

14. If no Contraindications are known, this section must state “none”. Provide data indentifying all cases of hypersensitivity to the cabozantinib capsules or any other components of Cometriq capsules. If no cases exist, delete this comment from the label.
15. Section 17, Patient Counseling Information currently states “See FDA approved Medication Guide.” Your label does not contain a Medication Guide. Change the sentence to read, “See FDA-approved patient labeling (Patient Information and Instructions for Use)”.
16. Avoid unnecessary bolding of headings within subsections (as noted in Section 12.0, subsection 12.2).

We also have the following preliminary comments (that are not formatting comments) on your proposed labeling.

In the Full Prescribing Information, please address the following:

Section 6.0 – Adverse Reactions – Clinical Trials Experience – Subsection 6.1

17. Revise Table 1 and Table 2 such that the column header contains the total number of patients in each arm and the data in the columns is expressed only in percentages of the patient totals. Round percents to the nearest whole number. Report frequencies occurring in less than 1% as “<1”.

Include only those adverse reactions occurring with a between arm difference (Cometriq-placebo) >5% for all grades combined or >2% for grades 3 and 4 combined. Using these criteria, (b) (4) would not be included in the adverse reactions table.

18. Report laboratory adverse events in Table 2 using medical terminology and do not duplicate the MedDRA terms for these event in Table 1.
19. Provide adverse event terms in US English, not British English (e.g. Palmar-Plantar Erythrodysesthesia Syndrome –PPES).
20. [REDACTED] (b) (4) with events described as “changes in hair color” in Table 1 and provide a detailed description of these events.
21. Report data for the incidence of hypertension according to guidelines and definitions suggested in the 2003 (7th) report of the Joint National Committee (JNC 7) rather than using the MedDRA classification. The JNC7 definition is based on the average of two or more properly measured readings at each of two or more visits after initial screen:

Normal Blood Pressure	Systolic	< 120 mmHg and Diastolic < 80 mmHg
Pre-hypertension	Systolic	120 – 139 mm Hg or Diastolic 80 – 89 mmHg

Hypertension

Stage	1:	Systolic 140-159 mmHg or Diastolic 90-99 mmHg
Stage	2:	Systolic ≥ 160 or Diastolic ≥ 100 mmHg

22. Add [REDACTED] (b) (4) to Table 2.

Drug Interactions – Section 7.0 – Subsection

23. [REDACTED] (b) (4)

Use in Specific Populations – Section 8.0 – Subsection 8.5

24. Sufficient data has not been provided with respect to hepatic impairment. If there are no data, delete this subsection. Similarly, if insufficient data has been obtained per the guidance (reference) to determine whether there is increased risk in subpopulations, this should be stated.

Overdosage – Section 10.0

25. Provide data on patients, including adverse reactions observed, for any patient exposed to one or more daily doses of more than 140 mg. Indicate if no data is available on overdosage.

We request that you resubmit labeling that addresses these issues by August 10, 2012. The resubmitted labeling will be used for further labeling sessions.

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

PROMOTIONAL MATERIAL

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

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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and patient PI (as applicable), 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.

Because the drug for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Gina Davis, Regulatory Project Manager, at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

23 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

PATRICIA KEEGAN
07/27/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 13, 2012

From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 203756 – Exelixis – Cometriq (cabozantinib); Request for Information

Dear Ms. Sauer,

Please refer to your May 21, 2012, New Drug Application (NDA), received on May 29, 2012, for your product cabozantinib. We are currently reviewing your submission and have the following comments and requests for additional information.

We note that you have included placeholders for the National Drug Code (NDC) number on the blister packs but not on the cartons. We ask that you submit blister pack labels and carton labeling for all packaging configurations with the complete NDC numbers included as soon as possible.

If you have any questions or concerns please contact me at (301) 796-0704.

All the best,
Gina

Gina M. Davis, M.T.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
07/13/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 13, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756 – Exelixis – Cometriq (cabozantinib); Request for Stats Information

Dear Ms. Sauer,

Please refer to your May 21, 2012, New Drug Application (NDA), received on May 29, 2012, for your product cabozantinib. We are currently reviewing your submission and have the following comments and requests for additional information.

1. FDA was not able to follow or re-run the SAS program KM.SAS due to minimum documentation. After spot check of the program, FDA noted the following issues:
 - a. FORMATS.XPT is not complete. Many format items were not found (or loaded) during the run in the .XPT file which caused difficulty in reading the SAS data.
 - b. Variables were not included in some of the data. For example, variables LASAXDT and TXSTDT were not included in the dataset ASAX.
 - c. There were DS.XPT data in the both raw and analysis data. Exelixis should clearly document which data was used in the calculation.
2. Note that FDA used the following code to read FORMATS, please revise if Exelixis used different approach :

```
libname formats xport \\Cdsesub5\evsprod\NDA203756\0002\m5\datasets\xl184-301\tabulations\legacy\raw\formats.xpt";  
libname an 'C:\Documents and Settings\xxx\  
My Documents\BLA_2012\cabozantinib\XL184-301';  
  
proc copy in=formats out=an; ;  
run;  
  
proc format cntlin=an.formats cntlout=formats library=an; run;
```

Please submit the missing pieces or clarify the issues indicated above. Also, FDA would like to request a clear documentation for the KM.SAS program. Please submit the required pieces in 5 business days.

NDA 203756

Page 2

If you have any questions or concerns please contact me at (301) 796-0704.

All the best,

Gina

Gina M. Davis, M.T.

Regulatory Health Project Manager

Division of Oncology Products 2

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
07/13/2012

NDA: 203756

Monthly Team Meeting – July Meeting – July 10, 2012

Product: Cometriq (cabozantinib) capsules
Submission Date: May 21, 2012
Received Date: May 29, 2012
Sponsor: Exelixis, Inc.

Proposed Indication: For the treatment of patients with progressive, unresectable, locally advanced or metastatic medullary thyroid cancer

Current Review Team for NDA 203756:

Patricia Keegan, M.D., Director DOP2
Gina Davis, M.T., Regulatory Health Project Manager
Karen Jones (CPMS)
Ruthann Giusti, M.D., Medical Officer
Suzanne Demko, C- P.A., (TL and CDTL)
Yuan Li Shen, Ph.D., Statistics
Kun He, Ph.D., Statistics (TL)
Jun Yang, Ph.D., Clinical Pharmacology
Hong Zhao, Ph.D., Clinical Pharmacology (TL)
Margaret Brower, Ph.D., Non-Clinical
Andrew McDougal, Ph.D., Non-Clinical
Whitney Helms, Ph.D., Nonclinical (TL)
William (Mike) Adams, Ph.D., Product
Li Shen Hsieh, Ph.D. Product
Liang Zhou, Ph.D., Product (TL)
Janice Brown, Ph.D. Product (Acting BC)
Sarah Pope Miksinski, Ph.D., Product TL
Jewell Martin, M.S., Product (ONDQA RPM)
Angelica Dorantes, Ph.D., Biopharmaceutics TL
Minerva Hughes, Ph.D., Biopharmaceutics Reviewer
Denise Miller, Ph.D. Microbiology Reviewer
Roy Blay, OSI Inspector
Mahesh Ramanadham, Facilities Inspector, PharmD/M.B.A.

A standard **reminder** that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss.

Review Status:

- Priority Review - confirmation (6 month clock)
- Categorical Exclusion requested
- Requested full waiver of pediatric studies - Orphan Designation granted on November 29, 2010 – product is exempt from PREA

- The clinical development of cabozantinib has been conducted under INDs 113446 and (b) (4)

SUMMARY OF JULY MONTHLY MEETING

Manufacturing inspection site(s) selected/Dates of inspections:

- (b) (4) inspection – capsule manufacturing site inspection started on (b) (4) is acceptable.
- (b) (4) – Drug Substance Tester (b) (4) inspection – (b) (4) – No firm inspection date from (b) (4) however, the pre-approval manager expects the inspection to be completed before the end of July.
- (b) (4) – The drug substance testing facility inspection is acceptable - as noted at the June 29, 2012, filing meeting.
- (b) (4) - Drug Substance Manufacturer - Found acceptable by the International Division within OMPQ, however the status has not yet been updated in EES – status to be updated shortly.

ODAC – Currently we are scheduled for ODAC – November 6- 7, 2012 (date and time not yet finalized).

- Exelixis has been notified that the NME has been placed on the agenda for the November 6-7, 2012, ODAC
- Names of identified SGE's will be due on July 18, 2012 (initial contact has been made)

Questions to be considered now or in the near future

- Will you expect to have a guest speaker?
- Will you expect to have a separate stat presentation?
- Will you expect to have other presentations (e.g., safety?)
- Will you need DSARM (Drug Safety and Risk Management AC) or RCAC (Risk Communication AC) representation at the meeting?

ODAC Practice Sessions @ OHOP Staff meetings (Monday/Friday) (dates for entire team – slides for ODAC - due November 2, 2012)

- October 19 (Friday)
- October 22 (Monday)
- October 26 (Friday)
- October 29 (Monday)

Labeling Meeting

- Labeling meeting scheduled on Thursday, July 12, 2012 to discuss the following; Clinical Sections – Indication and Usage, Dosage and Administration, Over Dosage, Contraindications, Adverse Reactions, Warnings and Precautions

Information/Request – Deficiencies

- The biopharmaceuticals team has identified dissolution issues that were conveyed to the sponsor on July 9, 2012.

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/s/

GINA M DAVIS
11/20/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 10, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756 – Exelixis – Cometriq (cabozantinib); Request for Stats Information

Dear Ms. Sauer,

Please refer to your May 21, 2012, New Drug Application (NDA), received on May 29, 2012, for your product cabozantinib. We are currently reviewing your submission and have the following comments and requests for additional information.

Please provide SAS programs that created datasets OAVND and LEVND from the raw (CRF) data or point to the location where these programs may be present in the current submission.

Please address the aforementioned request, by Friday, July 13, 2012. If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
07/10/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 10, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756 – Exelixis – Cometriq (cabozantinib); Oncologic Drug Advisory Committee (ODAC)

Dear Ms. Sauer:

Please refer to your May 21, 2012, New Drug Application (NDA), received on May 29, 2012, for your product cabozantinib.

Please note that your new molecular entity, Cometriq (cabozantinib), is tentatively scheduled for the November 6 -7, 2012, Oncologic Drug Advisory Committee (ODAC).

If we decide to go forth with our plans for ODAC we will notify you promptly. The information provided in this memo is not public and should not be disclosed until published via the Federal Registry.

If you have any questions or concerns please contact me.

All the best,
Gina

Gina M. Davis, M.T.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
07/10/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: July 9, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756; Exelixis; cabozantinib; identified deficiencies

Dear Ms. Sauer,

Please refer to your May 21, 2012, New Drug Application (NDA), received on May 29, 2012, for your product cabozantinib. We are currently reviewing your submission and have the following comments and requests for additional information.

1. Your dissolution method development summary is incomplete. Provide the following additional information to support your position that the proposed method (USP 2, 0.01N HCl with 0.5% Triton X-100 at 75 rpm) is discriminating and the acceptance criterion ($Q = \text{(b)(4)}$) is meaningful for product quality assurance.
 - a. Rationale for using two different approaches for determining saturation solubility ((b)(4))
 - b. Complete dissolution profile data (individuals, mean, RSD, and plots) for each surfactant type and amount ((b)(4)) tested for method development. The minimum amount of surfactant to achieve sink conditions and robust dissolution performance is recommended. Solubility is not the only determinant of performance with respect to surfactant selection; other factors such as micelle structure, excipient interactions, etc., should also be considered. Include the 10 minute sampling time point in your analysis for adequate profile sampling.
 - c. Complete dissolution profile data (individuals, mean, and RSDs) supporting the evaluation and selection of the proposed testing apparatus and paddle speed.
 - d. A summary of the meaningful process or product variations that could impact in vivo performance for which the proposed method and acceptance criterion are adequate to detect and reject, as per USP <1092>, for optimal quality assurance.
 - e. A science and data-based justification for the proposed acceptance criterion of $Q = \text{(b)(4)}$ when your dissolution data could support a criterion of $Q = \text{(b)(4)}$ at 15 minutes using the proposed method. Include in your response descriptive statistics (mean, min, max, RSDs) for pooled dissolution data from the bio-batches and primary registration stability batches at 15 and 30 minutes by dosage strength and testing time (T0, 3, 6 months, etc.), and an estimation of the dissolution pass rate for lots at stage 1, stage 2, and stage 3 applying your proposed acceptance criterion as well as criterion of $Q = \text{(b)(4)}$ at minutes.

2. Dissolution method validation studies should address the variation associated with different profile time points. As per your protocol, QM4334.01, dissolution profile sampling is performed at 15, 30, 45, and 60 minutes. In addition, your proposed sampling specification time point is (b) (4) Thus, the robustness and intermediate precision attributes of the method should address performance at the 15 and 30 minute sampling time points. Provide the validation test data on the variation associated with the 15 and 30 minute sampling time points.
3. It is noted in the dissolution method validation report, KCM-2011-0543-ANA, that the mean percent recovery for the low concentration accuracy standard was below the pre-specified 97% acceptance limit for one analyst. It appears that re-sampling was performed two additional times until one of the three samples prepared met the 97% passing threshold. The perception of “testing to pass” is concerning. Provide a copy of the investigation report INV2009-0060-L and your scientific rationale why the method should be considered valid for its intended use, despite the findings.
4. Provide copies of the HPLC chromatograms supporting your conclusions on the specificity of the dissolution test method, as noted in validation report KCM-2011-0543-ANA.

Please provide responses to the aforementioned comments by Wednesday, August 1, 2012. If you have any questions or concerns please contact me at (301) 796-0704.

Thank you,
Gina

Gina M. Davis, MT
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

GINA M DAVIS
07/09/2012

**Filing Meeting
June 29, 2012**

NDA: 203756

Product: Cometriq (cabozantinib) capsules
Submission Date: May 21, 2012
Received Date: May 29, 2012
Sponsor: Exelixis, Inc.

Proposed Indication: For the treatment of medullary thyroid cancer

Current Review Team for NDA 203756:

Patricia Keegan, M.D., Director DOP2
Gina Davis, M.T., Regulatory Health Project Manager
Karen Jones (CPMS)
Ruthann Giusti, M.D., Medical Officer
Suzanne Demko, C- P.A., (TL and CDTL)
Yuan Li Shen, Ph.D., Statistics
Kun He, Ph.D., Statistics (TL)
Jun Yang, Ph.D., Clinical Pharmacology
Hong Zhao, Ph.D, Clinical Pharmacology (TL)
Margaret Brower, Ph.D., Non-Clinical
Andrew McDougal, Ph.D., Non-Clinical
Whitney Helms, Ph.D., Nonclinical (TL)
William (Mike) Adams, Ph.D., Product
Li Shen Hsieh, Ph.D. Product
Liang Zhou, Ph.D., Product (TL)
Janice Brown, Ph.D. Product (Acting BC)
Sarah Pope Miksinski, Ph.D., Product TL
Jewell Martin, M.S., Product (ONDQA RPM)
Angelica Dorantes, Ph.D., Biopharmaceutics TL
Minerva Hughes, Ph.D., Biopharmaceutics Reviewer
Denise Miller, Ph.D. Microbiology Reviewer

A standard **reminder** that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss.

Review Status:

- Priority Review - confirmation (6 month clock)
- Categorical Exclusion requested
- Requested full waiver of pediatric studies - Orphan Designation granted on November 29, 2010 – product is exempt from PREA
- The clinical development of cabozantinib has been conducted under INDs 113446 and (b) (4)

Agenda Items:

Discuss Filing Issues by Primary Discipline

Please be prepared to discuss any significant filing issues for day 74 letter. The filing template is available on the 21st Century website.

<http://inside.fda.gov:9003//Drugs/21stCenturyReview/ucm034190.htm>

1. **Discuss Filing Issues by Primary Discipline**

Clinical

Clinical site inspection sites(s) selected/Dates of inspections

OSI – The OSI consult has been completed by the clinical team and is in DARRTs. The Division is requesting inspections of three sites one domestic (Ohio), and to foreign (Italy and Germany).

OSI informed the Division on June 28, 2012, that the inspections will not be complete until mid October.

Nonclinical

Exelixis was advised in December 2011 to submit plans to conduct carcinogenicity studies as a PMR. The PMR has not been submitted.

Statistics

No issues. - Application is filable.

Clinical Pharmacology

CMC

Potential Concerns:

- The proposed name needs to be evaluated (salt vs. free base)

- Information/Request regarding the dissolution method needs to be addressed (Clinical Pharmacology may offer assistance?)
- Total impurities and individual impurity acceptance criteria for DS should be evaluated.
- Genotoxicity impurity (b) (4) specifications will be further evaluated by the CMC and Nonclinical teams.

Manufacturing inspection site(s) selected/Dates of inspections:

- (b) (4) inspection – capsule manufacturing site inspection started on (b) (4) and is complete.
- (b) (4) inspection – (b) (4) has been assigned to the district office – no date has been determined.
- (b) (4) – The drug substance testing facility inspection is acceptable.
- (b) (4) – The drug substance manufacturer was inspected in (b) (4) and is currently under review – CDER/OC.

Biopharmaceutical

Issues with dissolution method as noted in the CMC section.

Microbiology

No issues. - Application is filable.

Regulatory

**Please bring a copy of your Filing review (draft) and any interim deliverables needed. Please note your filing review will need to be uploaded and signed off on in DARRTs prior to day 60 (July 27, 2012).

2. Dates Milestone Letters Must Issue (6-month priority review clock)

Milestone	6 month review
Acknowledgment Letter	Mailed June 11, 2012
Filing Action Letter •Do we have any filing issues that we should discuss today? •Do we need to have teleconference with the Applicant before the filing meeting? •If the filing issues are not identified, we will need to send a “Notification of Review Status” letter.	July 27, 2012
Deficiencies Identified Letter (74 Day Letter)	August 11, 2012
Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner’s Target date)	November 1, 2012
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	November 8, 2012
Review Target Due Dates: <i>Primary Review Due</i> <i>Secondary Review Due</i> <i>CDTL Review Due</i> <i>Division Director Review Due</i> <i>Office Director Review Due/Sign-Off</i>	November 1, 2012 November 5, 20 12 November 8, 2012 November 19, 2012 November 29, 2012
Compile and circulate Action Letter and Action Package	November 8, 2012
FINAL Action Letter Due	November 29, 2012

3. Potential Consults/Collaborative Reviewers Needed:

OPDP	Carole Broadnax- professional reviewer Karen Munoz- consumer reviewer Olga Salis – RPM
OSE	Sue Kang-OSE RPM Sean Bradley-OSE RPM TL DMEPA/CMC/DDMAC to review carton/container, and patient labeling James Schlick-Proprietary Name Review
OMP/DMPP	Barbara Fuller – Patient labeling TL Karen Dowdy – Patient labeling reviewer
Maternal Health	Janine Best-Reviewer Melissa Tassinari Carrie Ceresa
Facility/OMPQ	Mahesh Ramanadham
QT-IRT	Consult submitted to QT-IRT for review of study XL184-301.ECG.001. Reviewer to be assigned. Nitin Mehrotra Monica Fiszmon
OSI	Roy Blay assigned by Janice Pohlman – assigned sites selected but inspection can not be completed until mid October 2012
Pediatric Page/PeRC	Full Waiver Requested – Orphan Designation granted on November 29, 2010 – exempt from PREA
Patient Labeling Team	Patient Package Insert
SEALD	Consult submitted
SGE's or Patient Representatives - if AC is scheduled (presently tentative)	?

Are there any additional consults we need?

4. Upcoming Internal Team Meetings:

July Team Meeting	July 10, 2012
August Team Meeting	August 16, 2012
September Team Meeting	September 11, 2012
October Team Meeting	October 2, 2012
November Team Meeting	November 2, 2012 (Wrap- up Meeting)

- **Mid-Cycle Meeting:** Scheduled for August 28, 2012
- **Labeling Meetings (suggested section groupings): Dates to be announced**
 - a. _____ (Clinical Sections: Indications and Usage, Dosage and Administration, Over Dosage, Contraindications, Adverse Reactions, Warnings and Precautions)
 - b. _____ (Clinical Sections: Dosage and Administration, Clinical Studies, Drug Interactions, Use in Specific Populations, Overdosage, (Clinical Pharmacology and Nonclinical Toxicology) DMEPA PMHC)
 - c. _____ (Dosage Forms and Strengths, Description, How Supplied/Storage and Handling, CMC DMEPA, (Clinical Pharmacology (?])

**Include DMEPA/CMC during this labeling meeting to review carton and container.
 - d. _____ (Highlights, Indications and Usage, Patient Counseling Information/Patient Package Insert)
- **Wrap- Up Meeting:** November 2, 2012

5. **Applicant Orientation Presentation:** held June 22, 2012

6. **ODAC Needed/Not Needed:** Tentatively scheduled for November 7, 2012 if needed

Target AC date:

If not needed, for an original NME or BLA application, include the reason in the RPM filing review memo. For example:

- this drug/biologic is not the first in its class
- the clinical study design was acceptable
- the application did not raise significant safety or efficacy issues
- the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease

Will we be going to Advisory Committee- (To be decided at the filing meeting)
If so, we will need a planning meeting and _____ practice sessions (SGEs – Consultants).

7. Miscellaneous Items or Issues:

- a. CMC/Jewell Martin will assist with the following consults:
- Establishment (EES)/Coordinate Inspections
 - Environmental Analysis: Request for Categorical Exclusion
 - Labeling

Summary

The team agreed that the NDA was acceptable for filing. Biopharmaceuticals will have comments to be relayed to the sponsor.

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/s/

GINA M DAVIS
12/14/2012

**Planning Meeting
June 15, 2012**

NDA: 203756

Product: Cometriq (cabozantinib) capsules
Submission Date: May 21, 2012
Received Date: May 29, 2012
Sponsor: Exelixis

Proposed Indication: For the treatment of medullary thyroid cancer

Current Review Team for NDA 203756:

Patricia Keegan, M.D., Director DOP2
Gina Davis, M.T., Regulatory Health Project Manager
Karen Jones (CPMS)
Ruthann Giusti, M.D., Medical Officer
Suzanne Demko, C- P.A., (TL and CDTL)
Yuan Li Shen, Ph.D., Statistics
Kun He, Ph.D., Statistics (TL)
Jun Yang, Ph.D., Clinical Pharmacology
Hong Zhao, Ph.D, Clinical Pharmacology (TL)
Margaret Brower, Ph.D., Non-Clinical
Andrew McDougal, Ph.D., Non-Clinical
Whitney Helms, Ph.D., Nonclinical (TL)
William (Mike) Adams, Ph.D., Product
Li Shen Hsieh, Ph.D. Product
Liang Zhou, Ph.D., Product (TL)
Janice Brown, Ph.D. Product (Acting BC)
Sarah Pope Miksinski, Ph.D., Product TL
Jewell Martin, M.S., Product (ONDQA RPM)
Angelica Dorantes, Ph.D., Biopharmaceutics TL
Minerva Hughes, Ph.D., Biopharmaceutics Reviewer
Denise Miller, Ph.D. Microbiology Reviewer

A standard **reminder** that all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss.

Agenda Items:

1. Review Status:

- Priority Review - confirmation (6 month clock)
- Categorical Exclusion requested
- Requested full waiver of pediatric studies
- The clinical development of cabozantinib has been conducted under INDs 113446 and (b) (4)

2. Dates Milestone Letters Must Issue (6-month priority review clock)

Milestone	6 month review
Acknowledgment Letter	Mailed June 11, 2012
Filing Action Letter •Do we have any filing issues that we should discuss today? •Do we need to have teleconference with the Applicant before the filing meeting? •If the filing issues are not identified, we will need to send a “Notification of Review Status” letter.	July 27, 2012
Deficiencies Identified Letter (74 Day Letter)	August 11, 2012
Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner’s Target date)	October 29, 2012
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	November 5, 2012
Review Target Due Dates: <i>Primary Review Due</i> <i>Secondary Review Due</i> <i>CDTL Review Due</i> <i>Division Director Review Due</i> <i>Office Director Review Due/Sign-Off</i>	November 5, 2012 November 8, 20 12 November 15, 2012 November 29, 2012 N/A

Compile and circulate Action Letter and Action Package	November 15, 2012
FINAL Action Letter Due	November 29, 2012

3. Potential Consults/Collaborative Reviewers Needed:

OPDP	Carole Broadnax- professional reviewer Karen Munoz- consumer reviewer Olga Salis – RPM
OSE	Sue Kang-OSE RPM Sean Bradley-OSE RPM TL DMEPA/CMC/DDMAC to review carton/container, and patient labeling Risk Management Plan (REMs - ?) James Schlick-Proprietary Name Review
OMP/DMPP	Barbara Fuller – Patient labeling TL Karen Dowdy – Patient labeling reviewer
Maternal Health	Janine Best-Reviewer Melissa Tassinari Carrie Ceresa
Facility/OMPQ	Mahesh Ramanadham
QT-IRT	Consult submitted to QT-IRT for review of study XL184-301.ECG.001. Reviewer to be assigned.
OSI	Roy Blay assigned by Janice Pohlman - need to select sites (clinical).
Pediatric Page/PeRC	Full Waiver Requested
Patient Labeling Team	Medication Guide
SEALD	Consult submitted
SGE's or Patient Representatives	?

Are there any additional consults we need?

4. Upcoming/TBD Internal Team Meetings:

- **Filing Meeting:** Scheduled for June 29, 2012

- a. Please bring Filing review (TL signature) and Interim Deliverables. Please be prepared to identify significant filing issues for day 74 letter. The template is available on the 21st Century website. <http://inside.fda.gov:9003/ProgramsInitiatives/Drugs/21stCenturyReview/ucm034190.htm>

- **Mid-Cycle Meeting:** Scheduled for August 28, 2012.
- **Labeling Meetings (suggested section groupings): When should we begin labeling meetings?**
 - a. _____ (Clinical Sections: Indications and Usage, Adverse Reactions, Warnings and Precautions)
 - b. _____ (Clinical Sections: Dosage and Administration, Clinical Studies, Drug Interactions, Use in Specific Populations, Overdosage, Contraindications, References)
 - c. _____ (Dosage Forms and Strengths, Description, How Supplied/Storage and Handling, Nonclinical Sections, Clinical Pharmacology, Nonclinical Toxicology)
**Include OSE/CMC during this labeling meeting to review carton and container.
 - d. _____ (Highlights, Indications and Usage, Patient Counseling Information)
- **Team Meetings and PMR/PMC Working Meetings:**
 - **Do we want to schedule monthly team meetings?**
 - **Do we want to schedule separate PMC/PMR meetings?**
- **Wrap- Up Meeting:** TBD

5. **Applicant Orientation Presentation:** to be held on June 22, 2012

6. **ODAC Needed/Not Needed:**

Target AC date: November 29, 2012

If not needed, for an original NME or BLA application, include the reason in the RPM filing review memo. For example:

- *this drug/biologic is not the first in its class*
- *the clinical study design was acceptable*
- *the application did not raise significant safety or efficacy issues*
- *the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease*

If needed, we plan on going to Advisory Committee- we will need a planning meeting and _____practice sessions.

7. Miscellaneous Items or Issues:

- a. OSI inspections are needed, when does clinical/stats team need to pick the sites that will be inspected. **Do we need any preclinical study site Audits?
Sites selected by _____.
- b. CMC/Jewell Martin will assist with the following consults:
 - **Establishment (EES)/Coordinate Inspections**
 - **Environmental Analysis: Request for Categorical Exclusion**
 - **Labeling**

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/s/

GINA M DAVIS
12/14/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: June 13, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 203756; Exelixis; Cometriq (cabozantinib); Application Orientation Presentation; Advice and Information Memorandum

Dear Mr. Rosemark,

The Division of Oncology Products 2 has scheduled Exelixis' Application Orientation Presentation for June 22, 2012, from 10:00 AM – 11:00 PM (EST). Please send me the names of all staff members that will be present at this presentation. I am including a foreign visitor form to be filled out by all non-US citizens. Please send this information to me by Friday, June 15, 2012.

I have also included a form that will assist your team with your presentation. We ask that your team consist of no more than 10 members (to include a member of your data management team).

Per our March 16, 2012, electronic (email) communication, the FDA strongly encourages participation in the Office of Scientific Investigations (OSI) pilot program and notes that Exelixis should ensure that data identified in Parts I, II and III of the previously provided attachments (see January 6, 2012, final meeting minutes) are included in the application.

If you have any additional questions or concerns please contact me.

Thank you,
Gina

Gina M. Davis, MT
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosures:
Foreign Visitor Form
OHOP General Advice and Application Orientation Presentation Meetings

FOREIGN VISITOR DATA REQUEST FORM

VISITORS FULL NAME (First, Middle, Last)	
GENDER	
COUNTRY OF ORIGIN/CITZENSHIP	
DATE OF BIRTH (MM/DD/YYYY)	
PLACE OF BIRTH (city and country)	
PASSPORT NUMBER COUNTRY THAT ISSUED PASSPORT ISSUANCE DATE: EXPIRATION DATE:	
VISITOR ORGANIZATION/EMPLOYER	
MEETING START DATE AND TIME	
MEETING ENDING DATE AND TIME	
PURPOSE OF MEETING	
BUILDING(S) & ROOM NUMBER(S) TO BE VISITED	
WILL CRITICAL INFRASTRUCTURE AND/OR FDA LABORATORIES BE VISITED?	
HOSTING OFFICIAL (name, title, office/bldg, room number, and phone number)	
ESCORT INFORMATION (If different from Hosting Official)	

OHOP's General Advice for Application Orientation Presentation Meetings

Within 45 days after arrival of a new NDA, original BLA or efficacy supplement, FDA may hold an Application Orientation Presentation meeting with you for purposes of orienting the review team to the content and format of the application. Preferably, the meeting would take place as soon as possible once the application has been submitted so that the review team can become familiar with your application.

Below are comments, which are intended to help in your presentation preparation. This list is not inclusive of all issues that you should consider in preparing for your presentation, but highlights areas of interest to OHOP. These are general comments and we acknowledge that individual applications have unique characteristics. We also acknowledge that information needed to support a new NDA or original BLA will differ from an efficacy supplement. If you believe some comments are inapplicable to your application and therefore your presentation and/or you believe that other information is relevant, adjust your presentation accordingly.

Application Orientation Presentation meetings are generally one hour in length, including time for discussion and Q & A (approximately 35-40 minutes of presentation and 25-20 minutes for discussion). The primary focus of the presentation should be on clinical (with clinical sections presented first) with highlights of other sections to follow (i.e., 1-2 slides for remaining sections).

Administrative:

1. Sponsor attendees
2. Presentation outline or Agenda. Should list sections included in submission.

Background and Application Specifics:

3. Proposed indication(s) and current indication(s), if efficacy supplement. Dosing recommendation from proposed labeling.
4. Drug/biologic characteristics, including what makes the drug/biologic unique, mechanism of action.
5. Listing of registration trial(s), to support marketing/licensing application, as well as Phase 1 and Phase 2 trials to support application.
6. Statement of whether you plan to seek approval under 21 CFR 314.510, Subpart H/21 CFR 601.41, Subpart E (i.e., accelerated approval) or full approval. If accelerated approval, design of the confirmatory trial(s) that will be ongoing at the time of accelerated approval and a timetable of when confirmatory trial(s) will be completed and final clinical study report(s) submitted.
7. Regulatory history, including the following:
 - Orphan Drug designation, Fast Track designation
 - Foreign Regulatory history: Where/when approved and for what indications, whether there are pending applications with foreign regulators, Risk management plans in foreign countries.
 - Key Outcomes from FDA Interactions
 - EOP2 Meeting

- Special Protocol Assessment Correspondence: any agreements/disagreements on primary endpoints and key secondary endpoints, statistical analysis plan
- Pre-NDA/BLA meeting
- Other pertinent meetings/communications with FDA marking agreements/disagreements between you and the Agency

Summary Content of NDA/BLA/Efficacy Supplement Sections:

8. Clinical: Key findings from registration trials – Demographics of subjects and baseline characteristics, outcomes from primary and secondary endpoints, safety findings (most frequently reported adverse events, serious adverse events). Safety findings should also be presented from trials in other phases. NOTE: For demographics, you should address whether your study(s) represent ethnic minorities and whether study population is reflective of the U.S. population in which the drug/biologic is intended to be used.

You should also present results of the following, as appropriate:

- Clinical study sites (foreign or domestic)
- Biomarker development for population selection (if applicable)
- Assay validation (if applicable)

120-day Safety update: Plans for 120-day Safety update, including how many additional patients will be included in safety update and from which studies.

9. Statistics: Study design, description of planned analyses, efficacy analyses, safety analyses, subpopulation analyses of safety and efficacy (age, sex, race, concurrent therapy, number of prior treatments, region/country), length of follow-up, handling of missing data
10. CMC: Manufacturing site locations and dates when available for inspection, brief summary of manufacturing process, comparability of drug substance and drug product after major manufacturing changes, characterization, controls, stability, status of drug master files, discuss any novel excipients, state if application is Quality by Design (ICH Q8, Q9, Q10)
 - For BLAs: Immunogenicity results, validated assay method, and manufacturing schedule for DS and DP.
11. Nonclinical: Brief summary of toxicology studies and findings, genetic toxicology, QT studies, effect on fertility or reproduction, carcinogenicity studies (if needed), qualification of drug impurities
12. Clinical Pharmacology: Exposure response relationship supporting dose selection, pharmacogenomics-related issues, Description/listing of PK studies, PK characteristics (metabolic pathway, metabolites, $t_{1/2}$, ADME, PK in special populations, drug-drug interactions).
13. If a Risk Evaluation and Mitigation Strategy (REMS) is included, you should briefly identify the risks to be addressed, list the goals of the REMS, and outline the REMS components (e.g. Medication Guide, Communication Plans and/or Elements to Assure Safe Use (ETASU)).
14. Risk/benefit profile for drug/biologic
15. Summary
16. Q & A

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/s/

GINA M DAVIS
06/13/2012



NDA 203756

NDA ACKNOWLEDGMENT

Exelixis, Inc.
Attention: Lisa Sauer
Director, Regulatory Affairs
210 East Grand Avenue
South San Francisco, CA 94083

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: Cometriq (cabozantinib) capsules, 20 mg, 80 mg

Date of Application: May 21, 2012

Date of Receipt: May 29, 2012

Our Reference Number: NDA 203756

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 July 28, 2012, 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 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

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. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Gina Davis, Regulatory Project Manager, at (301) 796- 0704.

Sincerely,

{See appended electronic signature page}

Karen D. Jones
Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

KAREN D JONES
06/11/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 16, 2012
From: Gina Davis, RPM DOP 2/OHOP/CDER/FDA
Subject: IND 113446; Exelixis, Incorporated; FDA response to requested information

Dear Ms. Sauer,

Please refer to your Investigational New Drug Application (IND) for your investigational product cabozantinib.

Please also refer to your February 27, 2012, amendment requesting clarification of information provided to you at the December 20, 2012, pre-IND/pre-NDA meeting. We have reviewed your submission and have the following comments:

Exelixis Comment

The Sponsor has investigated the option of providing PDFs of the radiologic scans from Study XL184-301 (via the Independent Radiology Facility), and has identified several challenges with this approach.

When digital imaging is converted into the Adobe PDF format, there is a loss of not only image quality, but also functionality in the use of the image. The major benefit of digital imaging viewed electronically is the ability to manipulate the image itself for optimal analysis. The conversion takes a high quality image and will convert it to a PDF file, however it is then locked "as-is". The diagnostic value of such an option would be very low, and could lead to the PDF raising further questions as opposed to answering them.

It is estimated that, for each image at each subject visit, there would be approximately 100 slices per scan image (100 pdf files per image), with multiple scan images per visit.

The scans (at the IRF) are not currently in PDF format. If specific scans are requested, time will be required to convert all the requested images. Because providing radiographic images as PDF files has challenges and provides sub-optimal representation of these images, and in light of the Guidance for Industry, Standards for Clinical Trial Imaging Endpoints (August 2011), the Sponsor proposes to not provide any radiographic images as PDF files, and instead (as recommended in the guidance), all images and IRF assessments will be available on-site at the IRF.

1. Does the Agency agree that PDF files of radiologic scans will not need to be provided?

FDA Response: Please review the enclosures. If you have any additional questions or concerns regarding datasets, please send them to: cdcr-edata@fda.hhs.gov.

Regarding the requested SAS programs supporting the Phase 3 Study XL184-301 and the ISS (Summary of Clinical Safety) (discussed in Questions 8, 11, 12):

2. Do the SAS programs need to be executable, or is FDA's primary purpose to use them as reference to review the logic and algorithms?

FDA Response: *FDA's primary purpose is to review the algorithms. Do not submit the executable programs. Submit the original SAS codes including any macros used in the programs. Provide the name(s) of the program(s) that generated the results in table caption for each table in your clinical reports.*

3. If FDA plans to run the programs, the following information is needed:

- a. what platform (UNIX, Windows, etc.) does FDA use?
- b. what version of SAS?
- c. can FDA give guidance as to any directory structure requirements or constraints?

FDA Response: *Please see our response to question 2.*

And lastly, information regarding a pilot program with the Office of Scientific Investigations (OSI) was appended to the meeting minutes.

4. The Sponsor would like to ask whether the information requested in the context of this pilot program is a requirement, or if this is optional. This was not discussed during the December 20 meeting.

FDA Response: *Participation in the pilot program is voluntary but strongly encouraged. Even if you choose not to participate in the pilot, you should ensure that the data identified in Parts I, II, and III of the attachment are included in the application. For example, Parts I and II requests general study-related information and specific Clinical Investigator information that directly assist FDA in preparing for clinical site inspection assignments, and assist in preparation of Background Materials to be used by FDA field investigators conducting on-site inspections. Part III requests specific datasets from the key pivotal study(ies) the conduct of which is expected to be assessed by FDA.*

If you have any additional questions or concerns please contact me.

All the best,
Gina

Gina M. Davis
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research
Gina.Davis@fda.hhs.gov

IND 113446

Page 3

Enclosures:

End of Phase 2 – General Advice for Planned Marketing Applications
Additional DOP 2 CDISC Guidance

DOP2's End-of-Phase 2 General Advice for Planned Marketing Applications

NDA and BLA applications must comply with all applicable statutes and regulations (e.g. 21 CFR 314, 21 CFR Part 201, and 21 CFR Parts 600 and 601). In addition, FDA has published many guidance documents (available at: www.fda.gov/RegulatoryInformation/Guidances/default.htm) that contain important information necessary for preparing a complete, quality application.

CDER strongly encourages IND sponsors and NDA applicants to consider the implementation and use of data standards for the submission of applications. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies.

Please refer to following draft Guidance for Industry in order to ensure that you properly collect and submit standardized study data:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>.

Additionally, the **Study Data Standards Common Issues Document** can be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm> The purpose of the document is to highlight important aspects of CDISC and STDM datasets that should be addressed by the Sponsor/Applicant regarding submission of CDISC data in support of an application for registration.

In addition to the information and guidance provided at the above FDA link and CDISC links contained therein, the Division Oncology Products 2 (DOP2) has attached a separate document that details additional Oncology Specific domains and variables that we request be used for all oncology submissions.

Based on our experience with marketing applications, the following tables focus on specific areas of an application and are intended to help you plan and prepare for submitting a quality application. These comments do not include all issues you need to consider in preparing an application, but highlight areas where we have seen problems and/or issues that can delay our timely review of applications. These are general comments; if you believe some are inapplicable to your planned application we encourage you to provide justification and discuss it with us.

NDA/BLA content and format
CLINICAL
1) Original versions of all protocols, statistical analysis plans, Data Safety Monitoring Board (DSMB) and adjudication committee charters, and all amendments.
2) Minutes of all DSMB and efficacy endpoint review/adjudication committee meetings.
3) Investigator instructions that may have been produced in addition to the protocol and investigator brochure
4) All randomization lists and, if used, IVRS datasets (in SAS transport format)

5) All datasets used to track adjudications (in SAS transport format)
<p>6) A Reviewers Guide to the data submission that includes, but is not limited to the following:</p> <ol style="list-style-type: none"> a) description of files and documentation b) description of selected analysis datasets c) key variables of interest, including efficacy and safety variables d) SAS codes for sub-setting and combining datasets e) coding dictionary used f) methods of handling missing data g) list of variable contained in every dataset h) listing of raw data definitions i) analysis data definitions j) annotated CRF (the annotated CRF should contain links connecting to the document that defines the variable name and lists the data sets that contain the specific item) k) documentation of programs
<p>7) Clinical study report(s) for all trials (should follow the ICH E3 Structure and Content of Clinical Study Reports guidance www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129456.pdf).</p>
<p>8) <u>Pediatric Studies:</u></p> <p>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 exempt (i.e. orphan designation), waived or deferred. We request that you submit a pediatric plan that describes development of your product to provide important information on the safe and effective use of in the pediatric population where it may be used. If the product will not be used in pediatric populations your application must include a specific waiver request with the NDA submission, including supporting data. A request for deferral, must include a pediatric plan, certification of the grounds for deferring the assessments, and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time.</p>
<p>9) <u>Quantitative Safety Analysis Plan (QSAP):</u></p> <p>The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. When unanticipated safety issues are identified the QSAP may be amended. At a minimum the Safety Analysis Plan should address the following components:</p> <ol style="list-style-type: none"> a) Study design considerations (See: FDA Guidance to Industry: Premarketing Risk Assessment, www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf). b) Safety endpoints for Adverse Events of Special Interest (AERI) c) Definition of Treatment Emergent Adverse Event (TEAE) d) Expert adjudication process (Expert Clinical Committee Charter or Independent Radiology Review Charter)) e) Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP) f) Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity

analyses considered.
<p>10) Integrated summaries of safety and effectiveness (ISS/ISE) as required by 21 CFR 314.50 and in conformance with the following guidance documents:</p> <p>a) Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf</p> <p>b) Cancer Drug and Biological Products-Clinical Data in Marketing Applications www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071323.pdf</p>
11) Perform SMQs on the ISS adverse event data that may further inform the safety profile for your investigational agent, and include the results in the ISS report
12) A statement that the manufacturing facilities are ready for inspection upon FDA receipt of the application
13) A chronology of prior substantive communications with FDA and copies of official meeting/telecom minutes.
<p>14) <u>References:</u> There should be active links from lists of references to the referenced article.</p>
Studies, Data And Analyses
15) Provide a table listing all of the manufacturing facilities (e.g. drug product, drug substance, packaging, control/testing), including name of facility, full address including street, city, state, country, FEI number for facility (if previously registered with FDA), full name and title, telephone, fax number and email for on-site contact person, the manufacturing responsibility and function for each facility, and DMF number (if applicable).
<p>16) Provide a table with the following columns for each of the completed Phase 3 clinical trials:</p> <p>a) Site number b) Principle investigator c) Location: City State, Country d) Number of subjects screened e) Number of subjects randomized f) Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites for inspection) g) Number of protocol violations (Major, minor, including definition)</p>
17) Provide an assessment of safety as per the Guidance for Industry: Premarketing Risk Assessment (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf).
<p>18) Provide detailed information, including a narrative (data listings are not an acceptable substitute for a narrative), for all patients who died while on study or who terminated study drug or participation in the study prematurely including those categorized as other, lost to follow up, physician decision, or subject decision. Narrative summaries should contain the following components:</p> <p>a) subject age and gender b) signs and symptoms related to the adverse event being discussed</p>

- c) an assessment of the relationship of exposure duration to the development of the adverse event
- d) pertinent medical history
- e) concomitant medications with start dates relative to the adverse event
- f) pertinent physical exam findings
- g) pertinent test results (for example: lab data, ECG data, biopsy data)
- h) discussion of the diagnosis as supported by available clinical data
- i) a list of the differential diagnoses, for events without a definitive diagnosis
- j) treatment provided
- k) re-challenge and de-challenge results (if performed)
- l) outcomes and follow-up information
- m) an informed discussion of the case, allowing a better understanding of what the subject experienced.

19) Provide complete case report forms (CRFs) for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events. You should be prepared to supply any additional CRFs with a rapid turnaround upon request.

20) Provide reports for any autopsies conducted on study.

21) For patients listed as discontinued to due “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated. In addition, the verbatim description from the CRF should be included as a variable in the adverse event data set.

22) Regulations require that the safety and effectiveness data be presented for subgroups including “by gender, age, and racial subgroups”. Therefore, as you are gathering your data and compiling your application, we request that you include this data and pertinent analysis

23) The clinical information contained in the NDA/BLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP) 6010.3 (www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm080121.pdf). To facilitate the review, we request you provide analyses and discussion, where applicable, that will address the items in the template, including:

- a) Other Relevant Background Information – important regulatory actions in other countries or important information contained in foreign labeling.
- b) Exposure-Response Relationships – important exposure-response assessments.
- c) Less common adverse events (between 0.1% and 1%).
- d) Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
- e) Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
- f) Marked outliers and dropouts for laboratory abnormalities.
- g) Analysis of vital signs focused on measures of central tendencies.
- h) Analysis of vital signs focused on outliers or shifts from normal to abnormal.
- i) Marked outliers for vital signs and dropouts for vital sign abnormalities.

- j) A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the “investigations” SOC or in a SOC pertaining to the specific abnormality. For example, all AEs coded as “hyperglycemia” (SOC metabolic) and “low blood glucose” (SOC investigations) should be tabulated. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.
- k) Overview of ECG testing in the development program, including a brief review of the nonclinical results.
- l) Standard analyses and explorations of ECG data.
- m) Overdose experience.
- n) Analysis and summary of the reasons and patterns of discontinuation of the study drug. Identify for each patient the toxicities that result in study discontinuation or dose reduction.
- o) Explorations for:
 - i) Possible factors associated with a higher likelihood of early study termination; include demographic variables, study site, region, and treatment assignment.
 - ii) Dose dependency for adverse findings, which should be supported by summary tables of the incidence of adverse events based on the cumulative dose and the average dose administered.
 - iii) Time dependency for adverse finding, which should be supported by analyses summarizing the length of time subjects experience adverse events and whether recovery occurs during treatment.
 - iv) Drug-demographic interactions
 - v) Drug-disease interactions
- p) Drug-drug interactions
 - i) Dosing considerations for important drug-drug interactions.
 - ii) Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

24) Marketing applications must include the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Provide all appropriate data as well as a clinical study report for any study performed to evaluate QT/QTc prolongation.

Financial Disclosure Information

25) Marketing applications must include certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies, including those at foreign sites, covered by the regulation. This requires that investigators provide information to the sponsor during the course of the study and after completion. See Guidance for Industry - Financial Disclosure by Clinical Investigators (www.fda.gov/RegulatoryInformation/Guidances/ucm126832.htm).

Physician’s Labeling Rule

Highlights

- 1) Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and

Implementation Guidance]
2) The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
3) The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]
4) The drug name must be followed by the drug’s dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]
5) The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement “See full prescribing information for complete boxed warning.” Refer to 21 CFR 201.57(a) (4) and to www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom).
6) For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line (“margin mark”) on the left edge. [See 21 CFR 201.57(d) (9) and Implementation Guidance]. Recent major changes apply to only 5 sections (Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions).
7) The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights: (a) “(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”
8) Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.
9) Refer to 21 CFR 201.57 (a) (11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
10) A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a) (11)].
11) Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights
12) The Patient Counseling Information statement must appear in Highlights and must read “See 17 for PATIENT COUNSELING INFORMATION.” [See 21 CFR 201.57(a)(14)]
13) A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a) (15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.
14) A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]
Table of Contents
15) The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]
16) The Contents section headings must be in bold type. The Contents subsection headings must be

indented and not bolded. [See 21 CFR 201.57(d)(10)]
17) Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.
18) Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
19) When a subsection is omitted, the numbering does not change [see 21 CFR 201.56(d) (1)]. For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows: 8.1 Pregnancy 8.3 Nursing Mothers (<i>not 8.2</i>) 8.4 Pediatric Use (<i>not 8.3</i>) 8.5 Geriatric Use (<i>not 8.4</i>)
20) When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading “Full Prescribing Information: Contents” must be followed by an asterisk and the following statement must appear at the end of the Contents: “*Sections or subsections omitted from the Full Prescribing Information are not listed.”
Full Prescribing Information (FPI)
22) Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
23) Other than the required bolding [See 21 CFR 201.57(d) (1), (d) (5), and (d) (10)], use bold print sparingly. Use another method for emphasis such as italics or underline.
24) Do not refer to adverse reactions as “adverse events.” Please refer to the “Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format” (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf).
25) The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [see Use in Specific Populations (8.4)] not See Pediatric Use (8.4). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf]
26) Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
27) Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]
28) The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling

Information section to give it more prominence.
29) There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.
30) The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.
31) If the “Rx only” statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.
32) Refer to www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format.
33) Refer to the Institute of Safe Medication Practices’ website (http://www.ismp.org/Tools/abbreviationslist.pdf) for a list of error-prone abbreviations, symbols, and dose designations.

Additional DOP2 CDISC Guidance

The following two tables identify variables and domains that the division uses in conducting standardized analyses on data for marketing or licensing applications. Following the tables is a description of the Tumor Identification (TU), Tumor Results (TR), Response (RS), domains and variables therein. These are provided because DOP2 uses these domains and variables in analysis tools developed by FDA. These domains and variables will be added to the CDISC implementation guide in the near future, however, we request that you implement the use of this SDTM format with all your upcoming submissions.

Please use the draft CDISC *Oncology Disease-Specific Therapeutic Area Supplement to the SDTM Implementation Guide* (<http://www.cdisc.org/sdtm>) for submitting tumor identification, results, and response data to DOP2 as soon as they become available.

Please follow the guidance as provided in the CDER Data Standards Issues Document that can be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

Table 1: Variables that DOP2 requires for analyses of OS, PFS, RR, Disposition, and Adverse Reactions

Domain	Variable Name	Variable Label	Required Variable Values	Currently Available	CDISC Core	CDISC Data Type	CDISC Code List
ADSL	STRATA<N>	Based on definition of strata variable	0,1	No		Num	0,1
AE	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
AE	AEBODSYS	Body System or Organ Class	--	Yes	Exp	Char	
AE	AEDECOD	Dictionary-Derived Term	--	Yes	Req	Char	
AE	AETOXGR	Standard Toxicity Grade	--	Yes	Perm	Char	
AE	AESTDTC	Start Date/Time of Adverse Event	--	Yes	Exp	Char	ISO 8601
CM	CMCAT	Category for Medication	ANTI-CANCER	Yes	Perm	Char	--
CM	CMDECOD	Standardized Disposition Term	--	Yes	Perm	Char	NCOMPLT (Completion/Reason for Non-Completion)

CM	CMENDTC	End Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
CM	CMSTDTC	Start Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
CM	CMSTDY	Study Day of Start of Medication	--	Yes	Perm	Num	--
CM	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
DM	AGE	Age	--	Yes	Req	Num	--
DM	AGEU	Age Units	--	Yes	Exp	Char	AGEU
DM	ARM	Description of Planned Arm	--	Yes	Req	Char	--
DM	ACTARM		--	New			--
DM	ARMCD	Planned Arm Code	--	Yes	Req	Char	--
DM	COUNTRY	Country	--	Yes	Req	Char	ISO 3166 3- char. code
DM	DTHDTC	Date of Death	--	New		Char	ISO 8601
DM	DTHFL	Subject Death Flag	Y	New		Char	--
DM	ETHNIC	Ethnicity	--	Yes	Perm	Char	--
DM	RACE	Race	--	Yes	Exp	Char	--
DM	RFPENDTC	Date/Time of End of Participation	--	New		Char	ISO 8601
DM	SEX	Sex	--	Yes	Req	Char	M, F, U
DM	SITEID	Study Site Identifier	--	Yes	Req	Char	--
DM	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
DS	DSCAT	Category for Disposition Event	PROTOCOL MILESTONE	Yes	Perm	Char	DSCAT
DS	DSDECOD	Standardized Disposition Term	DEATH, RANDOMIZED, LOST TO FOLLOW-UP, ALIVE, ADVERSE EVENT, PROGRESSIVE DISEASE	Yes	Req	Char	NCOMPLT (Completion/Reason for Non-Completion)
DS	DSDTC	Date/Time of Collection	--	Yes	Perm	Char	ISO 8601

DS	DSSCAT	Subcategory for Disposition Event	STUDY DISCONTINUATION, TREATMENT DISCONTINUATION, STUDY TERMINATION	Yes	Perm	Char	--
DS	DSSTDTC	Start Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
DS	DSSTDY	Study Day of Start of Disposition Event	--	Yes	Perm	Num	--
DS	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
EX	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
EX	EXSTDTC	Start Date/Time of Treatment	--	Yes	Exp	Char	ISO 8601
EX	EXENDTC	End Date/Time of Treatment	--	Yes	Perm	Char	ISO 8601
LB	LBLFL	Baseline Flag	Y	Yes	Exp	Char	NY
LB	LBNRIND	Reference Range Indicator	HIGH, LOW	Yes	Exp	Char	--
LB	LBTEST	Lab Test or Examination Name	--	Yes	Req	Char	--
LB	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
MH	MHDECOD	Dictionary-Derived Term	--	Yes	Perm	Char	--
MH	MHENDTC	End Date/Time of Medical History Event	--	Yes	Perm	Char	ISO 8601
MH	MHSTDTC	Start Date/Time of Medical History Event	--	Yes	Perm	Char	ISO 8601
MH	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
RS	RSACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
RS	RSDTC	Date/Time of Response Assessment	--	Yes	Exp	Char	ISO 8601

RS	RSEVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
RS	RSSTAT	Response Assessment Status	NOT DONE	Yes	Perm	Char	ND
RS	RSSTRESC	Response Assessment Result in Std Format	CR or COMPLETE RESPONSE, PR or PARTIAL RESPONSE, SD or STABLE DISEASE, PD or PROGRESSIVE DISEASE, NE or NOT EVALUABLE	Yes	Exp	Char	--
RS	RSTESTCD	Response Assessment Short Name	OVRLRESP, looks for TGRES, NTGRES & BESTRESP	Yes	Req	Char	--
RS	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
RS	VISIT	Visit name	Must contain "UNSCH" for unscheduled	Yes	Perm	Char	
SV	SVSTDTC	Start Date/Time of Visit	--	Yes	Exp	Char	ISO 8601
SV	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
TA	ANCHDTC	Anchor date of assessment schedule	Variable in ADSL - no name determined	NEW		Char	
TA	MAXPRD	Maximum length of assessment schedule		NEW		Char	ISO 8601 Duration
TA	MINPRD	Minimum length of assessment schedule		NEW		Char	ISO 8601 Duration
TA	STOFFSET	Start time from anchor date		NEW		Char	ISO 8601 Duration
TA	TGTPRD	Length of assessment schedule		NEW		Char	ISO 8601 Duration
TR	TRACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
TR	TRDTC	Date/Time of Tumor Measurement	--	Yes	Exp	Char	ISO 8601
TR	TREVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL

TR	TRLINKID	Link ID	--	Yes	Exp	Char	--
TR	TRLNKGRP		--	NEW		Char	--
TR	TRSTAT	Tumor Assessment Status	NOT DONE	Yes	Perm	Char	ND
TR	TRSTRESC	Character Result/Finding in Std. Format	If TRTESTCD equals "TUMSTATE" Looks for PRESENT, ABSENT, UNEQUIVOCAL PROGRESSION	Yes	Exp	Char	--
TR	TRSTRESN	Numeric Result/Finding in Std. Format	--	Yes	Exp	Num	--
TR	TRTESTCD	Tumor Assessment Short Name	LDIAM, TUMSTATE, Looks for SUMLDIAM	Yes	Exp	Char	--
TR	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
TS	DCUTDTC	Data cut off date	--	New		Char	ISO 8601
TS	TSPARMCD	Trial Summary Parameter Short Name	PSSDDUR, PSCDUR	New	Req	Char	--
TS	TSVAL	Parameter Value	ISO Duration	New	Req	Char	--
TU	TUACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
TU	TUDTC	Date/Time of Tumor Identification	--	Yes	Exp	Char	ISO 8601
TU	TUEVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
TU	TULINKID	Link ID	--	Yes	Exp	Char	--

TU	TULOC	Location of Tumor	--	Yes	Exp	Char	LOC
TU	TUMETHOD	Method of Identification	--	Yes	Exp	Char	
TU	TUSTRESC	Tumor Identification Result Std. Format	NEW	Yes	Exp	Char	
TU	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--

Please ensure that the following domains and variables are included in your CDISC data submissions. Although the CDISC Implementation guide lists many variables as permissible, in order for DOP2 to conduct efficient and timely reviews of the clinical trial data, most permissible variables should be considered as required variables. Please consult with the division on any permissible variables that you intend not to include in your data files so we can determine the impact this will have on the review process and the acceptability of the omission.

Table 2: Additional variables in SDTM and ADaM that are necessary for efficient review

DOMAIN	VARAIBLE	DATA TYPE
ADaM		
ADSL	STUDYID	C
ADSL	USUBJID	C
ADSL	TRT01A	C
ADSL	TRT01P	C
ADSL	ARM	C
ADSL	AGE	N
ADSL	AGEGR1	C
ADSL	SEX	C
ADSL	RACE	C
ADSL	TRTEDT	N
ADSL	TRTEDTM	N
ADSL	TRTSDT	N
ADSL	TRTSDTM	N
ADSL	DEATHDSC	C
SDTM		
AE	STUDYID	C
AE	USUBJID	C
AE	AEDECOD	C
AE	AEBODSYS	C
AE	AEREL	C
AE	AESEV	C
AE	AETOXGR	C

AE	AESTDTC	C
AE	AEENDTC	C
AE	AESTDY	N
AE	AEENDY	N
AE	AEDUR	C
CM	STUDYID	C
CM	USUBJID	C
CM	CMDECOD	C
CM	CMSTDTC	C
CM	CMENDTC	C
CM	CMENDY	N
CM	CMSTDY	N
CM	CMDUR	C
DM	STUDYID	C
DM	USUBJID	C
DM	AGE	N
DM	SEX	C
DM	RACE	C
DM	ARM	C
DM	RFENDTC	C
DM	RFSTDTC	C
DS	STUDYID	C
DS	USUBJID	C
DS	DSDECOD	C
DS	DSCAT	C
DS	DSSTDTC	C
DS	DSSTDY	N
EX	STUDYID	C
EX	USUBJID	C
EX	EXTRT	C
EX	EXDOSE	N
EX	EXSTDTC	C
EX	EXENDTC	C
EX	EXSTDY	N
EX	EXENDY	N
EX	EXDUR	C
LB	STUDYID	C
LB	USUBJID	C
LB	LBTEST	C
LB	LBSTRESN	N
LB	LBSTNRHI	N
LB	LBSTNRLO	N
LB	LBDTC	C
LB	LBDY	N
MH	STUDYID	C
MH	USUBJID	C
MH	MHDECOD	C
MH	MHBODSYS	C

VS	STUDYID	C
VS	USUBJID	C
VS	VSTEST	C
VS	VSSTRESN	N
VS	VSDTC	C
VS	VSDY	N

CDISC Oncology Domains

Introduction

Assessment of the change in tumor burden is an important feature of the clinical evaluation of cancer therapeutics: both tumor shrinkage (objective response) and disease progression are useful endpoints in cancer clinical trials⁽¹⁾. RECIST (Response Evaluation Criteria in Solid Tumors)⁽²⁾ has been widely adopted in solid tumor clinical trials where the primary endpoints are objective response or progression and is accepted by regulatory authorities as an appropriate guideline for these assessments. The SDTM domains presented here were developed with RECIST Criteria in mind. However, the domains are intended to represent data collected in clinical trials where tumors are identified and then repeatedly measured/assessed at subsequent timepoints and used in an evaluation of response(s). As such these domains would be equally applicable for criteria other than RECIST e.g. Chesson classification⁽³⁾ in the assessment lymphomas, or, MacDonald Response⁽⁴⁾ in the assessment of malignant gliomas.

The tumor assessment package consists of three SDTM domains based on the SDTM Findings Observation Class. The three domains are related but each domain has a distinct purpose:

TU (Tumor Identification): The TU domain represents data that uniquely identifies tumors. The tumors are identified by an investigator and/or independent assessor and in RECIST terms this equates to the identification of Target, Non-Target or New tumors. A record in the TU domain contains the following information: a unique tumor ID value; anatomical location of the tumor; method used to identify the tumor; role of the individual identifying the tumor; and timing information.

TR (Tumor Results): The TR domain represents quantitative measurements and/or qualitative assessments of the tumors identified in the TU domain. These measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. A record in the TR domain contains the following information: a unique tumor ID value; test and result; method used; role of the individual assessing the tumor; and timing information.

Clinically accepted evaluation criteria expect that a tumor identified by the tumor ID is the same tumor at each subsequent assessment. The TR domain does not include anatomical location information on each measurement record because this would be a duplication of information already represented in TU. This duplication of data was a deciding factor in multi-domain approach to representing this data.

RS (Response): The RS domain represents the response evaluation determined from the data in TR. Data from other sources (in other SDTM domains) might also be used in an assessment of response for example, MacDonald Response Criteria includes a neurological aspect.

New variables:

--LINKID – The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). Therefore a new ID variable --LINKID is being proposed in order to support the linking requirements. The --LINKID variable is specifically designed to support a relrec dataset to dataset relationship. Values of LINKID could concatenate values of other variables when more than one variable are needed to do join data rows.

--ACPTFL – The Acceptance Flag identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.

--EVALID – The Evaluator Specified variable is used in conjunction with TREVAL to provide an additional level of detail. When multiple assessors play the role identified in TREVAL, values of EVALID will attribute a row of data to a

particular assessor. For example TREVAL="INDEPENDENT ASSESSOR" and TREVALID="RADIOLOGIST 1". The --EVALID variable is not subject to Controlled Terminology. When --EVALID is populated --EVAL must also be populated.

References:

- (1) E.A. Eisenhauer,*, P. Therasse, et al. [New response evaluation criteria in solid tumours: Revised RECIST guideline \(version 1.1\)](#) *EUROPEAN JOURNAL OF CANCER* 45 (2009) 228–247
- (2) RECIST Criteria - <http://www.eortc.be/recist/>
- (3) Bruce D. Cheson, Beate Pfistner, et al. [Revised Response Criteria for Malignant Lymphoma](#) *Journal of Clinical Oncology*. Vol 25 Number 5 Feb 10 2007
- (4) DR Macdonald, TL Cascino, et al. [Response criteria for phase II studies of supratentorial malignant glioma](#) *Journal of Clinical Oncology*, Vol 8, 1277-1280

1. Oncology Domains:

1.1. TUMOR IDENTIFICATION - TU

tu.xpt, Tumor Identification - Findings, Version 3. x.x One record per identified tumor per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	TU	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App.C2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
TUSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
TUGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TUREFID	Reference ID	Char		Identifier	Internal or external identifier. Example:	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TUSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TULINKID	Link ID	Char		Identifier	Identifier used to link identified tumors to the assessment results over the course of the study.	Exp	
TUTESTCD	Tumor Identification Short Name	Char	*	Topic	Short name of the TEST in TUTEST. TUTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: TUMIDENT, NEWTUMOR. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
TUTEST	Tumor Identification Test Name	Char	*	Synonym Qualifier	Verbatim name of the test for the tumor/lesion identification. The value in TUTEST cannot be longer than 40 characters. Examples: Tumor Identification, New Tumor Identified. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
TUCAT	Category for Tumor Identification	Char		Grouping Qualifier	Used to categorize tumors.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
TUSCAT	Sub-Category for Tumor Identification	Char		Grouping Qualifier	A further classification of the TUTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TUORRES	Tumor Identification Result	Char	*	Result Qualifier	Result of the Tumor identification. Examples: When TUTESTCD=TUMIDENT (Tumor Identification), values of TUORRES might be: TARGET or NON-TARGET. When TUTESTCD=NEWTUMOR the value of TUORRES might be: Y When TUTESTCD=BENIGNAB the value of TUORRES might be: BENIGN RENAL LESIONS	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TUSTRESC	Tumor Identification Result Std. Format	Char	*	Record Qualifier	Contains the result value for all findings copied from TUORRES.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TUNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the Tumor Identification.	Perm	SDTM 2.2.3
TULOC	Location of the Tumor	CHAR	(LOC)	Record Qualifier	Used to specify the anatomical location of the identified tumor. Example: Gastrointestinal Tract. Note: When anatomical location is broken down and collected as distinct pieces of data that when combined provide the overall location information (e.g. organ / laterality /location / sub-location) then the additional information should added as supplemental qualifiers. See Assumption 3	Exp	SDTMIG 2.2.3
TUMETHOD	Method of Identification		*	Record Qualifier	Method used to identify the tumor. Examples: X-ray, MRI, CT-Scan.	Exp	SDTMIG 2.2.3
TUEVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST This column can be left <i>Null</i> when the Investigator provides the complete set of data in the domain. However the column should contain no <i>Null</i> values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TUEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with TUEVAL to provide an additional level of detail. When multiple assessors play the role identified in TUEVAL, values of TUEVALID will attribute a row of data to a particular assessor. TUEVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2.. The TUEVALID variable would not be subject to CDISC Controlled Terminology. See Assumption 5.	Perm	
TUACPTFL	Accepted Record Flag	Char	*	Record Qualifier	In cases where more than one independent assessor (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide independent assessments at the same timepoint this flag identifies the record that is considered to be the accepted assessment.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISITDY	Planned Study Day of Visit	Num		Timing		Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TUDTC	Date/Time of Tumor Identification	Char	ISO 8601	Timing		Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TUDY	Study Day of Tumor Identification	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.1. ASSUMPTIONS FOR THE TUMOR IDENTIFICATION DOMAIN MODEL

TU Definition: The TU domain represents data that uniquely identifies tumors. The tumors are identified by an investigator and/or independent assessor and in RECIST terms this equates to the identification of Target, Non-Target or New tumors. A record in the TU domain contains the following information: a unique tumor ID value; anatomical location of the tumor; method used to identify the tumor; role of the individual identifying the tumor; and timing information.

1. The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REPID & SPID) are needed (see examples). The --LINKID variable is used for values that support a relrec dataset to dataset relationship and to provide a unique code for each identified tumor.
2. The values of TUTESTCD and TUTEST will be relatively simple and will either represent that the Tumor is identified and categorized at screening or that the Tumor is identified as New (has appeared since the Screening assessment).

Proposed TUTESTCD / TUTEST values for this domain:

TUTESTCD	TUTEST
TUMIDENT	Tumor Identification
NEWTUMOR	New Tumor Identified
BENIGNAB	Benign Abnormality
TUSPLIT	Tumor Split or Divided
TUMERGE	Tumor Merged or Coalesced

During the course of a trial when a new Tumor (or lesion) is identified information about that new tumor may be collected to different levels of detail. The following three scenarios represent the most commonly seen data collection methods employed when a new Tumor (or lesion) is identified. The scenarios set out below are not intended to be exhaustive. The sponsor must decide the appropriate collection method based on their analysis needs or internal processes and it is possible that a sponsor's chosen method is not reflected in the scenarios presented below.

- a. The occurrence of a New Tumor is the sole piece of information that a sponsor collects because this is a sign of disease progression and no further details are required. In such cases a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y".
- b. The occurrence of a New Tumor and the anatomical location of that newly identified Tumor are the only collected pieces of information. In this case it is expected that a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y", and the TULOC variable would be populated with the anatomical location information (the additional location variables may be populated depending on the level of detail collected).
- c. A sponsor might record the occurrence of a New Tumor to the same level of detail as Target and Non-Target Tumors. In this case the occurrence of the new tumor and the anatomical location information, and also measure the New Tumor. In this case it is expected that a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y", and the identifier, TULINKID, would all be populated. The measurement/assessment of the New Tumor would be recorded in the TR domain.

3. TUCAT and TUSCAT have been included as they are standard domain variables however these columns would generally not be needed and so the variables are not included in the accompanying examples.
4. Anatomical Location information might be collected in a number of ways the simplest way is as a long text string and in these cases the text string is captured in the TULOC variable. However, anatomical location might also be collected through a number of distinct and separate variables (that might possibly be subject to controlled terminology) and in such cases the additional information would be recorded in the following Supplemental Qualifiers:

QNAM	QLABEL	Definition
TUSUBLOC	Sub-location of the Tumor	Anatomical location information with more specificity than a gross location
TULOCDET	Detailed Location Information	Detailed anatomical location information that would include details such as: direction (Superior, Posterior); relative direction (Proximal, Distal); axes (Dorsoventral, Mediolateral); planes (Sagittal, Coronal); and any other divisions or sub-anatomy information.
TUORGAN	Organ Affected	Actual Body Organ location of the tumor. This is more specific than Body Organ Class
TULAT	Tumor Location Laterality	Lateral location used to distinguish Right & Left sides. For example if a Tumor was located in the "Right Lung" then the TULOC and QNAM.TULAT values would be TULOC=LUNG; QNAM.TULAT=RIGHT.

5. The Acceptance Flag variable (TUACPTFL) identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.
6. The Evaluator Specified variable (TUEVALID) is used in conjunction with TUEVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the TUEVAL variable. For example TUEVAL="INDEPENDENT ASSESSOR" and TUEVALID="RADIOLOGIST 1". The TUEVALID variable is not subject to Controlled Terminology. TUEVAL must also be populated when TUEVALID is populated.
7. The following proposed supplemental Qualifiers would be used to represent information regarding previous irradiation of a tumor when that information is known:

QNAM	QLABEL	Definition
PREVIR	Previously Irradiated	Indication of previous irradiation to a tumor.
PREVIRP	Irradiated then Subsequent Progression	Indication of documented progression subsequent to irradiation.

TUMOR RESULTS - TR

tr.xpt, Tumor Results - Findings, Version 3..x x One record per tumor measurement/assessment per tumor per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	TR	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App, 2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
TRSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
TRGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TRREFID	Reference ID	Char		Identifier	Internal or external identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TRSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4
TRLINKID	Link ID	Char		Identifier	Identifier used to link the assessment result records to the tumor identification record.	Exp	
TRTESTCD	Tumor Assessment Short Name	Char	*	Topic	Short name of the TEST in TRTEST. TRTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: LDIAM, DIAM. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
TRTEST	Tumor Assessment Test Name	Char	*	Synonym Qualifier	Verbatim name of the test or examination used to obtain the measurement or finding. The value in TRTEST cannot be longer than 40 characters. Examples: LONGEST DIAMETER, LONGEST PERPENDICULAR, AXIAL THICKNESS, VOLUME, AREA. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
TRCAT	Category for Tumor Assessment	Char	*	Grouping Qualifier	Used to categorize assessments. Examples: Measurement Categorical	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
TRSCAT	Sub-Category for Tumor Assessment	Char		Grouping Qualifier	A further classification of the TRTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TRORES	Result or Finding in Original Units	Char		Result Qualifier	Result of the Tumor measurement/assessment as originally received or collected.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRORESU	Original Units	Char	(UNIT)	Variable Qualifier	Original units in which the data were collected. The unit for TRORES. Example: mm	Exp	SDTMIG 2.2.3 SDTMIG 4.1.3.2
TRSTRESC	Character Result/Finding in Std Format	Char		Record Qualifier	Contains the result value for all findings, copied or derived from TRORES in a standard format or standard units. TRSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in TRSTRESN	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRSTRESN	Numeric Result/Finding in Standard Units	Num		Result Qualifier	Used for continuous or numeric results or findings in standard format; copied in numeric format from TRSTRESC. TRSTRESN should store all numeric test results or findings.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRSTRESU	Standard Units	Char	(UNIT)	Variable Qualifier	Standardized unit used for TRSTRESN.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.3.2 SDTMIG 4.1.5.1
TRSTAT	Tumor Assessment Status	Char	(ND)	Result Qualifier	Used to indicate a measurement was not done, or a tumor measurement was not taken. Should be Null if a result exists in TRORES.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
TRREASND	Reason Tumor Measurement Not Performed	Char		Record Qualifier	Describes why a measurement or test was not performed. Examples: BROKEN EQUIPMENT or SUBJECT REFUSED. Used in conjunction with TRSTAT when value is NOT DONE.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
TRNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the Tumor measurement or assessment.	Perm	SDTM 2.2.3
TRMETHOD	Method used to identify the Tumor		*	Record Qualifier	Method used to measure the tumor. Examples: X-ray, MRI, CT-Scan.	Exp	SDTMIG 2.2.3

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TREVAL	Evaluator	Char	(EVAL)	Record Qualifier	<p>Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST</p> <p>This column can be left <i>Null</i> when the Investigator provides the complete set of data in the domain. However the column should contain no <i>Null</i> values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR</p>	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.4
TREVALID	Evaluator Specified	Char		Variable Qualifier	<p>The Evaluator Specified variable is used in conjunction with TREVAL to provide an additional level of detail. When multiple assessors play the role identified in TREVAL, values of TREVALID will attribute a row of data to a particular assessor. TREVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The TREVALID variable would not be subject to CDISC Controlled Terminology. Note TREVAL must also be populated when TREVALID is populated. See Assumption 4</p>	Perm	
TRACPTFL	Accepted Record Flag	Char	*	Record Qualifier	<p>In cases where more than one independent assessor (e.g. where TREVALID has values of "RADIOLOGIST 1" & "RADIOLOGIST 2") provide independent assessments at the same timepoint this flag identifies the record that is considered to be the accepted assessment.</p>	Perm	
VISITNUM	Visit Number	Num		Timing	<ol style="list-style-type: none"> Clinical encounter number. Numeric version of VISIT, used for sorting. 	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	<ol style="list-style-type: none"> Protocol-defined description of clinical encounter. May be used in addition to VISITNUM and/or VISITDY. 	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISITDY	Planned Study Day of Visit	Num		Timing		Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TRDTC	Date/Time of Tumor Measurement	Char	ISO 8601	Timing		Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TRDY	Study Day of Tumor Measurement	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.2. ASSUMPTIONS FOR THE TUMOR RESULTS DOMAIN MODEL

TR Definition: The TR domain represents quantitative measurements and/or qualitative assessments of the tumors identified in the TU domain. These measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. A record in the TR domain contains the following information: a unique tumor ID value; test and result; method used; role of the individual assessing the tumor; and timing information.

- The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). The --LINKID variable is used for values that support a relrec dataset to dataset relationship and to provide a unique code for each identified tumor. TRLINKID is a required variable as the records in the TR domain must relate back to an identification record in TU.
- TRTESTCD / TRTEST values for this domain (this is for illustration purposes these values will be published as Controlled Terminology):

TRTESTCD	TRTEST
AREA	Area
AXTHICK	Axial Thickness
DIAM	Diameter
LDIAM	Longest Diameter
LMAXSP	Major Axis Axial Plane, Long Diameter Target
LPERP	Longest Perpendicular
METVOLNO	Average Metabolic SUV
MJAX3SP	Major Axis 3D (All Planes)

MNAX3SP	Minor Axis 3D
MNAXSP	Minor Axis
MXSUVSSP	Maximum SUV (1 cm Spot)
MXSUVVSP	Maximum SUV (Single Voxel)
PCCHBL	Percent Change From Baseline
PCCHNAD	Percent Change From Nadir
PREVIR	Lesion Previously Irradiated
PREVIRP	Lesion Progressing Since Irradiated
PRODUCT	Product
RADDESP	Radio Density
SAXIS	Short Axis
SUMAREA	Sum of Area
SUMAXTHK	Sum of Axial Thickness
SUMLDIAM	Sum of Longest Diameter
SUMLPERP	Sum of Longest Perpendicular
SUMPDIAM	Sum of the product of the diameters
SUMPROD	Sum of Product
SUMVOL	Sum of Volume
VOLPETSP	Total Tumor Volume
VOLUME	Volume
XPRO3SP	Cross Product 3D
XPRODSP	Cross Product

Note: The sponsor should not derive results for any test indicated in the list above (e.g. "Percent Change From Nadir") if the result was not collected. Tests would be included in the domain only if those data points have been collected on a CRF or have been supplied by an external assessor as part of an electronic data transfer. It is not intended that the sponsor would create derived records to supply those values.

3. The Acceptance Flag variable (TRACPTFL) identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.
4. The Evaluator Specified variable (TREVALID) is used in conjunction with TREVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the TREVAL variable. For example TREVAL="INDEPENDENT ASSESSOR" and TREVALID="RADIOLOGIST 1". The TREVALID variable is not subject to Controlled Terminology. TREVAL must also be populated when TREVALID is populated.

RESPONSE – RS

rs.xpt, Response - Findings, Version 3..x x One record per response assessment per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	RS	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App.C2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
RSSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
RSGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
RSREFID	Reference ID	Char		Identifier	Internal or external identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
RSSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4
RSLINKID	Link ID	Char		Identifier	Used to link the response assessment to the appropriate measurement records (in TR) used to determine the response result.	Perm	
RSTESTCD	Response Assessment Short Name	Char	*	Topic	Short name of the TEST in RSTEST. RSTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: TRGRESP, BESTRESP, SYMPTPD	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
RSTEST	Response Assessment Name	Char	*	Synonym Qualifier	Verbatim name of the response assessment. The value in RSTEST cannot be longer than 40 characters. Examples: Target Response, Best Overall Response, Symptomatic deterioration	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
RSCAT	Category for Response Assessment	Char		Grouping Qualifier	Used to categorize tumors.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
RSSCAT	Sub-Category for Response Assessment	Char		Grouping Qualifier	A further classification of the RSTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
RSORRES	Response Assessment Original Result	Char		Result Qualifier	Result of the Response assessment as originally received, collected, or calculated.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
RSSTRESC	Response Assessment Result in Std Format	Char		Record Qualifier	Contains the result value for the response assessment, copied or derived from RSORRES in a standard format or standard units. RSSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in RSSTRESN	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
RSSTAT	Response Assessment Status	Char	(ND)	Result Qualifier	Used to indicate the response assessment was not performed. Should be Null if a result exists in RSORRES.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
RSREASND	Reason Response Assessment Not Performed	Char		Record Qualifier	Describes why a response assessment was not performed. Examples: Subject does not have target lesions. Used in conjunction with TRSTAT when value is NOT DONE.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
RSNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the response assessment.	Perm	SDTM 2.2.3
RSEVAL	Evaluator	Char	(EVAL)	Record Qualifier	<p>Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST</p> <p>This column can be left <i>Null</i> when the Investigator provides the complete set of data in the domain. However the column should contain no <i>Null</i> values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR.</p>	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
RSEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with RSEVAL to provide an additional level of detail. When multiple assessors play the role identified in RSEVAL, values of RSEVALID will attribute a row of data to a particular assessor. RSEVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The RSEVALID variable would not be subject to CDISC Controlled Terminology. See Assumption 5	Perm	
RSACPTFL	Accepted Record Flag	Char		Record Qualifier	In cases where more than one independent assessor (e.g. independent Oncologist) provides an evaluation of response this flag identifies the record that is considered to be the accepted evaluation.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
RSDTC	Date/Time of Response Assessment	Char	ISO 8601	Timing	Date may be derived if based on multiple dates of scans Exception: derived data in RS needed for reviewer	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
RSDY	Study Day of Response Assessment	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. May be from rand date not first dose date 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.3. ASSUMPTIONS FOR THE TUMOR RESPONSE DOMAIN MODEL

RS Definition: The RS domain represents the response evaluation determined from the data in TR. Data from other sources (in other SDTM domains) might also be used in an assessment of response for example, MacDonald Response Criteria includes a neurological aspect.

1. The RSLINKID variable is used for values that support a relrec dataset to dataset relationship. RSLINKID would be required when a response evaluation relates back to an individual tumor.
2. RSTESTCD / RSTEST values for this domain (this is for illustration purposes these values will be published as Controlled Terminology):

RSTESTCD	RSTEST	Definition
TRGRESP	Target Response	
NTRGRESP	Non-target Response	
OVRLRESP	Overall Response	
BESTRESP	Best Response	
LESNRESP	Lesion Response	
SYMPTPD	Symptomatic Deterioration	

3. When an evaluation of Symptomatic Deterioration is recorded (which is symptomatic of progressive Disease) and additional description of the clinical symptoms is collected then that information would be recorded in the following Supplemental Qualifier:

QNAM	QLABEL	Definition
CLSYMP	Clinical Symptoms of PD	Textual description of clinical symptoms that led to the evaluation of Symptomatic deterioration

4. TS – TSPARM/TSVAL needed to represent the Response Criteria used in the clinical trial.

5. The Evaluator Specified variable (RSEVALID) is used in conjunction with RSEVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the RSEVAL variable. For example RSEVAL="INDEPENDENT ASSESSOR" and RSEVALID="RADIOLOGIST 1". The RSEVALID variable is not subject to Controlled Terminology. RSEVAL must also be populated when RSEVALID is populated.

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

/s/

GINA M DAVIS
03/16/2012



IND 113446

MEETING MINUTES

Exelixis, Inc.
Attention: Lisa Sauer
Director, Regulatory Affairs
210 East Grand Avenue
South San Francisco, CA 94083

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 the meeting between representatives of your firm and the FDA on December 20, 2011. The purpose of the meeting was to present the Division with results from the Phase 3 study of cabozantinib in medullary thyroid cancer and obtain agreement on a filing strategy for the planned NDA.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Gina M. Davis, M.T.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:

Meeting Minutes
OSI pre-NDA request document
Attendance Sheet

MEMORANDUM OF MEETING MINUTES

SPONSOR: Exelixis, Inc. [Exelixis]
MEETING DATE: December 20, 2011
TIME: 2:00 PM – 3:00 PM
LOCATION: CDER WO 22, Room 1313
APPLICATION: IND 113446
DRUG NAME: cabozantinib (XL184)
TYPE OF MEETING: pre-NDA
MEETING CHAIR: Suzanne Demko
MEETING RECORDER: Gina Davis

FDA ATTENDEES:

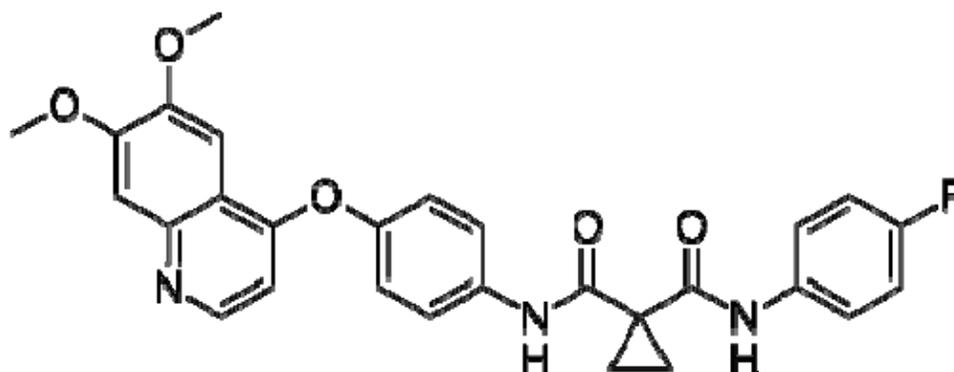
Patricia Keegan	Director, Division of Oncology Products 2
Suzanne Demko	Clinical Team Lead, Division of Oncology Products 2
Ruthann Giusti	Medical Officer, Division of Oncology Products 2
Lori Kotch	Toxicology Reviewer, Division of Hematology and Oncology Toxicology
Todd Palmby	Toxicology Supervisor, Division of Hematology and Oncology Toxicology
Hong Zhao	Team Lead, Division of Clinical Pharmacology V
Jun Yang	Reviewer, Division of Clinical Pharmacology V
Weishi Yuan	Statistics Reviewer, Office of Biostatistics
Debasis Ghosh	CMC Reviewer, Division on New Drug Quality Assessment
Janice Brown	Acting CMC Team Lead, Division on New Drug Quality Assessment
Zedong Dong	Biopharmaceutics Reviewer, Office of New Drug Quality Assessment
Erica McNeilly	Health Science Administrator, Office of Orphan Drug Development
Gina Davis	Regulatory Health Project Manager, Division of Oncology Products 2

EXELIXIS, Inc. ATTENDEES:

Gisela Schwab, MD	CMO and Executive Vice President, Development
Steve Sagar, MD	Executive Director, Clinical Research
Margaret Tonda, PharmD	Executive Director, Clinical Science
Yifah Yaron, MD, PhD	Senior Director, Clinical Research
Colin Hessel, MS	Executive Director, Biostatistics and Clinical Data Management
JoAnn Wilson, PhD	Vice President, Chemistry, Manufacturing and Controls
Steve Lacy, PhD	Vice President, Nonclinical Development
Kirk Rosemark, RAC	Vice President, Regulatory Affairs
Lisa Sauer	Director, Regulatory Affairs
Karen Hodsdon	Regulatory Affairs Manager

1.0 BACKGROUND:

Cabozantinib (XL 184) is a synthetically derived, inhibitor of the MET, VEGFR2, RET, and KIT tyrosine kinases. Cabozantinib's molecular formula is $C_{28}H_{24}FN_3O_5$.



Chemical Name:

N-(4-((6,7-Dimethoxyquinolin-4-yl)oxy)phenyl)-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide

Exelixis notes that cabozantinib is manufactured, tested, released, packaged in bulk and tested for stability by:



The drug substance (DS) validation began in August 2011, and is currently ongoing. Process validation protocols will be included in the submission, however, validation reports will not be available at the time of submission.

Exelixis will manufacture the drug product (DP) in the form of commercial capsules containing 20 mg or 80 mg (strengths expressed as the freebase weights) cabozantinib and inert excipients. These strengths are equivalent to the 25- and 100 mg (strengths expressed as the malate salt weights).

DP capsules will be packaged in blister card and bottle packaging systems. The blister card packaging systems contains three card configurations that provided 140-mg, 100-mg and 60-mg weekly dosage cards. Bottle packaging system contains sixty 20-mg capsules and is intended to provide for flexible dosing of a single capsule strength. DP validation is expected to begin in Q2/Q3 2012.

The initial IND for cabozantinib (XL 184) is IND (b) (4). Under this IND, cabozantinib was granted orphan drug status for medullary thyroid carcinoma (MTC) on November 29, 2010 and was granted fast tract designation on April 8, 2011. A request for proprietary name review for the proposed name 'Cometriq' was submitted to the Agency on June 20, 2011 and was found to be conditionally acceptable, as stated in FDA's letter dated on December 6, 2011.

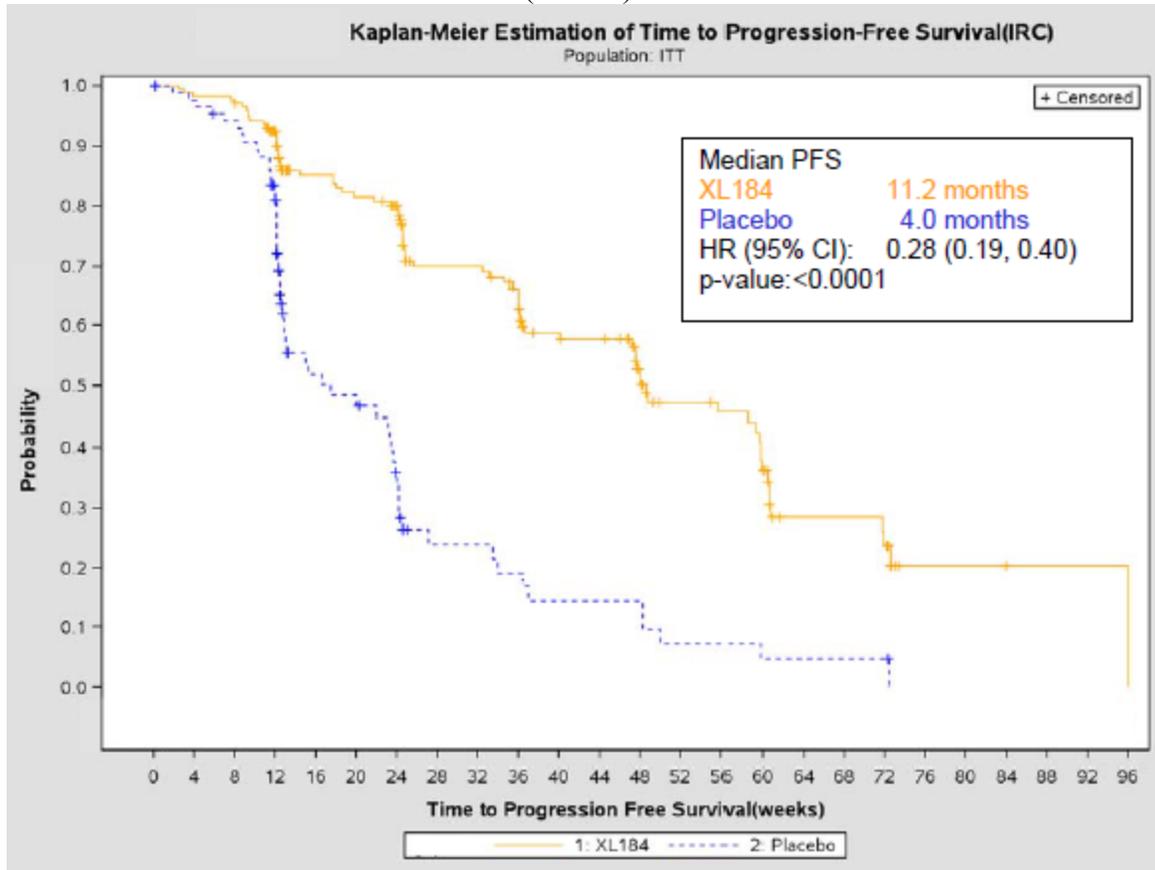
Exelixis met with FDA on March 6, 2008 to discuss the design of a registrational trial for the treatment of MTC (XL184-301), an international, double-blinded, randomized (2:1) trial of cabozantinib versus placebo in patients with unresectable, locally advanced, or metastatic MTC with progression documented within 14 months prior to enrollment. The study enrolled 330 patients (cabozantinib = 219; placebo = 111). Randomization was stratified by age (<65 years versus >65 years), and known prior receipt of a tyrosine kinase inhibitor (yes versus no). Patients in both arms received supportive care consistent with standard clinical practice. The primary endpoint for XL184-301 is progression free survival (PFS) as determined by blinded, independent radiology review. Secondary endpoints include overall response rate (ORR) and overall survival (OS). The primary analysis of PFS has 90% power to detect a 75% improvement in PFS, based on the assumptions of median PFS of 8 months in the control arm and 14 months in the experimental arm (HR=0.571) following a total of 138 PFS events. The primary analysis is a stratified log-rank test performed on the ITT population. If the null hypothesis is rejected, then the two key secondary endpoints, ORR and OS, will be tested in parallel while splitting the alpha between these two endpoints. The ORR will be tested at the 0.01 significance level while a total alpha of 0.04 will be allocated to the OS analyses. The final analysis of OS has 80% power to demonstrate a 50% improvement in OS with a total of 217 deaths, based on the assumptions of median OS of 22 months in the control arm and 33 months in the experimental arm (HR=0.667). One interim analysis for OS was planned at time of the PFS primary analysis (estimated to occur after 67 deaths) using the O'Brien-Fleming boundary. As overall survival in this patient population is highly variable and can be protracted, FDA agreed that a compelling improvement in PFS which is reliably assessed and consistent with other study endpoints was acceptable to support registration and XL184-301 was accepted under a Special Protocol Assessment (SPA).

Exelixis met with FDA on December 14, 2010 in a pre-NDA meeting to discuss the scope and presentation of clinical data in the planned submission. On March 4, 2011, a pre-NDA meeting was held to discuss the quality data to be provided in the application; discussion of non-clinical toxicology data needed to support the application was also noted.

(b) (4)
new IND (113, 446) for the MTC application was created. Exelixis was asked to schedule a PreIND/PreNDA meeting with the Division of Oncology Drug Products 2 (DOP2).

Exelixis presents high level summary data from the final analysis of PFS for Protocol XL184-301 in the premeeting package. The analysis was conducted on the first 138 PFS events in the trial. Exelixis states that median PFS, as determined by independent review, was 11.2 months in the cabozantinib arm versus 4.0 months in the placebo arm [HR=0.28; 95% CI: 0.19, 0.40; $p < 0.0001$] (Figure 1). The secondary endpoint of ORR as determined by independent review was 28% in the cabozantinib arm and 0% in the placebo arm ($p < 0.0001$).

Figure 1. Kaplan-Meier Curve: Progression-Free Survival in the ITT Population (N=330)



Exelixis further states that consistency of the effect on PFS was observed in three pre-specified sensitivity analyses and within demographic and prognostic subgroups. At the time of the final PFS analysis, 96 OS events have occurred (44% of the planned total OS events); the boundary was not crossed for this interim analysis. The final analysis of OS will be conducted when 217 events have occurred.

The most frequent Grade 3 and 4 adverse reactions of abozantinib (i.e., events occurring at a higher incidence in the cabozantinib-treated arm than in the placebo arm) were gastrointestinal disorders (diarrhea, dysphagia and stomatitis); asthenia and fatigue; mucosal inflammation; increased transaminases; decreased weight and appetite; hypocalcemia and hypokalemia; cutaneous (palmar-plantar erythrodysesthesia syndrome, other rashes); and hypertension. The most common serious adverse reactions of abozantinib (events occurring with greater frequency in the cabozantinib arm than in the placebo arm) are shown in Table 1 below.

Table 1. Serious Adverse Events in $\geq 2\%$ of Subjects Randomized to Cabozantinib with a Greater Frequency than Placebo

Preferred Term	Cabozantinib (N=214)	Placebo (N=109)
All	90 (42.1%)	25 (22.9%)
Mucosal Inflammation	6 (2.8%)	0
Pneumonia	7 (3.3%)	3 (2.8%)
Dehydration	5 (2.3%)	1 (0.9%)
Hypocalcemia	6 (2.8%)	0
Pulmonary embolism	5 (2.3%)	0
Hypertension	5 (2.3%)	0
Dysphagia	5 (2.3%)	2 (1.8%)

Adverse reactions common to the class of VEGF inhibitors [venous and arterial thrombosis, hemorrhage, gastrointestinal (GI) perforation GI fistula and intraabdominal abscess), and other fistula] occurred at a higher frequency in the cabozantinib-treated arm. The rate of serious adverse reactions due to infections was also increased in cabozantinib-treated patients (14% vs. 6%) than in the placebo arm. A higher frequency of deaths due to causes other than progressive disease (5.6% vs. 2.8% within 30 days of last dose of drug and 7.0% vs. 5.5% at any time during the trial) occurred in the cabozantinib arm as compared to the placebo arm (Table 2).

Table 2. Summary of Deaths (Safety Population)

	Cabozantinib n (%)		Placebo n (%)	
	Non-PD	PD	Non PD	PD
At any time ^a	15 (7.0)	50 (23)	6 (5.5)	24 (22)
≤ 30 days after last dose	12 ^b (5.6)	10 (4.7)	3 ^c (2.8)	5 (4.6)

^a The overall number of deaths observed in the ITT population was 96; this table excludes one subject who never received study drug

^b pneumonia (2), respiratory failure (2), fistulas (1 each: esophageal-cutaneous, tracheo-esophageal, pneumomediastinum), hemorrhage, cardiac arrest (2), septicemia, unknown

^c adult respiratory distress syndrome (ARDS), shock, general deterioration

Based on the outcome of Protocol XL 1840301, Exelixis plans to submit an NDA for cabozantinib for the treatment of patients with unresectable, locally advanced, or metastatic MTC. Findings from a single dose-escalation study (XL 184-001) in patients with advanced malignancies will be submitted in support of efficacy and safety. The results from a subset of patients with glioblastoma multiforme (XL 184-201) treated at the proposed MTC dose and schedule will be submitted in support of safety.

Study	Types of Study Reports	Primary Role of Study in NDA	
		Efficacy	Safety
XL184-301: An International, Randomized, Double-Blinded, Phase 3 Efficacy Study of XL184 Versus Placebo in Subjects with Unresectable, Locally Advanced or Metastatic Medullary Thyroid Cancer	Full	X	X
XL184-001: A Phase 1 Dose-Escalation Study of the Safety and pharmacokinetics of XL184 Administered Orally to Subjects With Advanced Malignancies	Full	X	X
XL184-201 ^a : A Phase 2 Study of XL184 in Subjects with Progressive or Recurrent Glioblastoma Multiforme in First or Second Relapse	Abbreviated		X

^a A subset of subjects will be included

Exelixis proposes to submit a “rolling NDA” with the Nonclinical sections of the NDA as the first portion to be submitted in December 2011; the Quality (CMC) sections of the NDA to be submitted in January 2012; and the Clinical sections of the NDA will be submitted in April 2012.

2.0 MEETING OBJECTIVES:

- To present the Division with results from the Phase 3 study of cabozantinib (XL184) in medullary thyroid cancer and obtain agreement on a filing strategy for the planned NDA for cabozantinib in medullary thyroid cancer (MTC).

Sponsor Submitted Questions and FDA Responses

- Cabozantinib received Fast Track Designation for MTC 08 April 2011. Exelixis requests acceptance of a “Submission of Portions” (or “rolling NDA”). The Nonclinical sections of the NDA (Modules 2.4, 2.6, and 4, and related information in Module 1) will be submitted in December 2011, the Quality (Chemistry, Manufacturing and Controls) sections of the NDA (Modules 2.3 and 3, and related information in Module 1) will be submitted in January 2012, and the entire Clinical section (Modules 2.5, 2.7, and 5) will be submitted by April 2012, along with remaining sections of Module 1. Exelixis wishes to send the first submission immediately after this meeting and presumes agreement to the plan at this meeting is sufficient to proceed.

Does the Agency agree with Exelixis’ proposal and timelines for a rolling NDA?

FDA Response: The proposed timeline is acceptable.

Exelixis' December 20, 2011, response via electronic (email) communication: Exelixis appreciates FDA's acceptance of the proposed timeline. However, Exelixis would like to update its proposal to: December 2011 for the Nonclinical submission, February 2012 for the Quality submission, and no later than May 2012 for the Clinical submission.

Does the Agency agree with Exelixis' updated proposal and timelines for the rolling NDA?

Discussion during the meeting: FDA stated that the modified proposal for the timeline was acceptable.

2. Cabozantinib Drug Product stability through 18 months and including one lot through 24 months will be provided in the January 2012 submission of the Quality information. Drug Product stability at the 24-month timepoint from three additional lots of capsules will not be available until after the submission of the Quality information. As this data is expected to further support the proposed expiry period, Exelixis proposes to provide updated stability data on these three lots (in Module 3.2.P.8.3) with the Clinical modules (April 2012).

Does the Agency agree with Exelixis' plan to provide additional stability data with the last submitted portion of the NDA?

FDA Response: The proposal is acceptable.

Please note as per GRMPs, all NDAs are to be complete in the original submission. This includes all stability data and corresponding data summaries necessary to establish a shelf life. Information submitted to an NDA subsequent to the original submission may or may not be reviewed as resources allow.

Exelixis' December 20, 2011, response via electronic (email) communication: Exelixis acknowledges the FDA's comments. Exelixis would also like to ask clarification regarding the "original submission," and whether this is intended to mean the sum of the submissions of portions.

Discussion during the meeting: FDA stated that the stability data and corresponding data summaries may be provided with the final submission to this rolling NDA.

3. The Phase 3 study XL184-301 evaluated an endpoint of PFS as determined by an Independent Radiology Facility (IRF). In accordance with the Guidance for Industry, Standards for Clinical Trial Imaging Endpoints (August 2011), Exelixis proposes that radiologic images will not be included in the submission (but will be available for review at the IRF).

Does the Agency agree with Exelixis' plans regarding radiologic images?

FDA Response: The proposal is acceptable; however, Exelixis should be prepared to submit images for specified patients to FDA in a timely manner, upon request, during the NDA review.

Exelixis' December 20, 2011, response via electronic (email) communication: Exelixis acknowledges the FDA's comments. However, Exelixis seeks clarification regarding the format, medium, and location in the CTD for images if they were to be requested. For the latter, would this be submitted as an amendment to the submission (with the files located under the appropriate clinical study report in Module 5)?

Discussion during the meeting: FDA stated that technical advice would be sought and a written response would be provided as an addendum to the meeting minutes.

FDA addendum to the December 20, 2011 minutes: During the conduct of FDA's review of the application, if submission of image files is requested, submit image files in PDF format in Module 5 within the file for the trial to which the images are related. Tag each file separately as "image" in the Study Tagging File. For additional information, please contact the CDER Electronic Submissions Coordinator at esub@fda.hhs.gov

4. The primary analysis of PFS in Study XL184-301 has been conducted, and no additional PFS analyses are planned. As such, Exelixis does not intend to have the IRF continue to collect and evaluate the radiologic images.

Does the Agency agree with Exelixis' plans to discontinue the IRF evaluation of radiologic images?

FDA Response: Yes; however, follow-up should continue on all study participants to assess overall survival.

Exelixis' December 20, 2011, response via electronic (email) communication: Exelixis acknowledges the FDA's comments and will continue to follow subjects for overall survival to conduct the final overall survival analysis (at 217 events).

Discussion during the meeting: No discussion occurred regarding question 4.

5. Electrocardiogram (ECG) monitoring was conducted in the Phase 3 study XL184-301 to characterize the effects of cabozantinib on the QTc interval. ECGs from Study XL184-301 will be uploaded to the FDA ECG warehouse by the vendor after completing submission of the NDA (April 2012).

Does the Agency agree with Exelixis' plans regarding ECGs?

FDA Response: Yes. Please provide the projected date of uploading the ECGs to the FDA ECG warehouse.

Exelixis' December 20, 2011, response via electronic (email) communication: Exelixis plans to have the ECGs uploaded to the FDA ECG warehouse near the time of the

submission of the Clinical modules of the NDA (no later than May 2012). Exelixis kindly requests the information for the FDA Contact that should be noted with the submission of ECGs.

Discussion during the meeting: FDA clarified that the project manager for the NDA is the appropriate contact.

6. Study XL184-301 required subjects to have progressive disease upon study entry in order to identify a symptomatic patient population requiring systemic intervention. Exelixis believes the observed treatment difference in PFS between the cabozantinib and placebo arms (11.2 vs. 4.0 months) is highly statistically significant and clinically meaningful for this patient population and requests the Agency consider review of the NDA under Priority Review.

Does the Agency agree that the NDA qualifies for Priority Review?

FDA Response: The review designation (priority or standard) will be determined at the time the application is filed.

Exelixis' December 20, 2011, response via electronic (email) communication: Exelixis acknowledges the FDA's comments.

Discussion during the meeting: No discussion occurred regarding question 6.

7. As discussed at the meeting with the Agency on 14 December 2010, the NDA submission for cabozantinib 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 subjects with MTC. Supportive safety data will come from Group A in the ongoing Phase 2 study XL184-201 (glioblastoma multiforme [GBM]). These three studies evaluated a dose of 140 mg qd cabozantinib (expressed as freebase weight, equivalent to 175 mg expressed as the malate salt). The Agency indicated that studies at lower doses of cabozantinib did not need to be included in the NDA. Clinical pharmacology studies, primarily in normal healthy volunteers, will also be included in the NDA.

Consistent with the Agency's request at the 14 December 2010 meeting, Exelixis wishes to provide in the NDA all significant safety information. Therefore, Exelixis proposes that, in addition to the safety data from the three clinical studies mentioned above, a summary of related serious adverse events from other ongoing single-agent studies will be descriptively summarized in Module 2.7.4. As these studies are still ongoing and the databases are not yet cleaned and locked, the information being provided is preliminary. As such, study reports and datasets will not be provided for these additional studies. A summary of the study status, number of subjects enrolled, incidence of related serious adverse events, and review of deaths within 30 days of last dose of cabozantinib will be provided as available from the Argus safety database.

Does the Agency agree with Exelixis' plan to provide additional safety data from other single-agent cabozantinib studies in the NDA?

FDA Response: At the time of the original NDA submission, it is acceptable to support the safety database from the three specified trials (XL184-301, XL184-001, and a data from a subset of patients with complete safety information enrolled in XL184-201) with safety information from additional ongoing single-agent trials in which the safety information from these additional trials will consist of a summary of the study status, number of subjects enrolled, incidence of related serious adverse events, a descriptive summary of the related serious adverse events and of deaths occurring within 30 days of last dose of cabozantinib. However, the safety information from all trials should be updated at the time of the 120 day safety update, using the proposed data cut-off date of Dec, 2011.

Exelixis' December 20, 2011, response via electronic (email) communication: Please see Exelixis' Response under Question 8 for clarifying questions regarding the 120-day safety update.

Discussion during the meeting: Discussion regarding question 7 is noted under question 8.

8. Three clinical studies (efficacy and/or safety) will be included in the NDA (XL184-001, XL184-201, and XL184-301). XL184-001 is a Phase 1 study that completed enrollment in 2008. At the time of database lock for the NDA (19 April 2010), 13 subjects were still on study, with a minimum follow-up of approximately 2 years. XL184-201 is a Phase 2 study in GBM. At the time of database lock for the NDA (01 September 2010), only 2 subjects from the cohort at 175 mg qd ("Cohort A") were still on study. Exelixis proposes that, for the 120-Day Safety Update, only data from the pivotal study XL184-301 will be included. A cut-off date of 31 December 2011 will be used for the data.

A written summary will be prepared, following the format of the safety section of the clinical study report (Section 13). The written summary will compare the updated cumulative data with the data originally included in the clinical study report, comparing the overall safety profile and noting any new signals (if any observed). Exelixis plans to include tables with cumulative summaries of the data from study start. Exelixis is not planning on providing listings or SAS datasets.

Does the Agency agree with Exelixis' plans for the content and format of the 120-Day Safety Update?

FDA Response: Exelixis should provide a descriptive summary of all new or previously unreported related serious adverse events and deaths within 30 days of the last dose of cabozantinib occurring in XL184-301 and in any of the other safety studies submitted as part of the application. In addition, Exelixis should provide update survival analyses and datasets which include all events through the proposed data cut-off date (Dec. 2011 or

date of submission of the first portion of the NDA, whichever is later). The proposed updated report for XL184-301 (cumulative summaries) can not be confirmed and therefore deemed reliable in the absence of the supporting data in updated datasets and analyses programs from which new analyses were derived. If a new safety signal is identified by Exelixis based on updated safety information, all information needed to fully assess this signal should be included in the 120-day safety update.

Exelixis' December 20, 2011, response via electronic (email) communication: Exelixis would like to clarify what the Agency is expecting to see in the 120-day safety update. Given the Agency's comments, Exelixis is planning to provide:

- A complete analysis of additional safety data from Study XL184-301 will be provided (in the format of Section 13 of the clinical study report). Exelixis will provide SAS datasets for this data.
- Related serious adverse events and a descriptive summary of the related serious adverse events and deaths occurring within 30 days of the last dose of cabozantinib will be provided from the additional safety studies included in the NDA (XL184-001 and XL184-201) as well as from any other ongoing Exelixis-initiated single-agent study.

The first portion of the NDA will be submitted in December 2011. It is therefore planned to use a cut-off date of December 2011 for the 120-day safety update.

Does the Agency agree with this proposed plan for the contents of the 120-day safety update?

Discussion during the meeting: FDA stated that Exelixis' proposal for the contents of the 120-day update is acceptable, provided that the datasets and programs needed to generate update survival curves (through the data cut-off date) are provided.

The final overall survival analysis is not planned until 217 events (deaths) have occurred; additional interim analyses are not planned. Safety-related information regarding deaths will be included in the 120-day safety update. Exelixis also notes that the study continues to be monitored by the IDMC.

Does the Agency agree with Exelixis' plan to only conduct the prospectively planned final overall survival (at 217 events)?

Discussion during the meeting: FDA requested that the 120-day safety update contain an additional unplanned analysis of overall survival as of the safety data cut-off date. FDA agreed that it was acceptable that Exelixis not conduct the additional analysis if they provide FDA with datasets containing updated survival information so that FDA may evaluate impact on survival with cabozantinib.

FDA noted that, because this analysis would be performed at FDA's request in order to assess product safety, an alpha adjustment would not be required.

9. Exelixis has provided a draft overall Table of Contents for the entire cabozantinib NDA (Modules 1-5).

Does the Agency agree with the proposed format and structure of the NDA in CTD format?

FDA Response: Consistent with applicable FDA and ICH guidance, FDA recommends that if the ISS and ISE summaries are included in Module 2, a cross-referenced hyperlink to these summaries should be included in Module 5 along with the complete study reports, supporting data sets and analysis programs Module 5. Refer to Guidances for Industry found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf>

Exelixis' December 20, 2011, response via electronic (email) communication: Exelixis acknowledges the FDA's comments and will include a link in Module 5 (5.3.5.3) to the efficacy and safety summaries. Supportive datasets and analysis programs will also be located in Module 5.

Discussion during the meeting: No discussion occurred regarding question 9.

Additional Comments

Clinical

10. For all adverse event data sets, provide verbatim terms as well as coding at all levels of the MedDRA hierarchy.

Exelixis' December 20, 2011, response via electronic (email) communication: Exelixis acknowledges the FDA's comments and plans to include all levels of the MedDRA coding hierarchy.

Does FDA require the numeric coding fields? Or are the plain-text fields for the coding hierarchy adequate?

Discussion during the meeting: Exelixis will provide the coding hierarchy as plain text fields. FDA stated that this is sufficient.

Statistical

11. In the NDA please include the SAS programs used to create the derived datasets for the efficacy endpoints and the SAS programs used for efficacy data analysis. If the SAS programs use any SAS macro, please provide all necessary macro programs.

Exelixis' December 20, 2011, response via electronic (email) communication: Exelixis requests clarification on the following:

- a. Are SAS programs required at the time the clinical sections of the NDA are submitted, or can SAS programs be provided during the course of FDA review?

Discussion during the meeting: FDA clarified that SAS program are required at the time of submission of the clinical module.

- b. Exelixis proposes to provide SAS programs for Study XL184-301 derived efficacy datasets and efficacy analyses.

Does the Agency agree with this proposal?

Discussion during the meeting: FDA stated that this is acceptable. FDA further stated that all the analyses programs that are necessary to confirm efficacy in the pivotal trial and safety analyses in the three trials contained in the ISS should be submitted. Exelixis confirmed their intent to provide these programs and stated that the name of analyses program will be captured in the legend for each table displaying summary information.

- c. Exelixis planned to provide raw data as SAS XPT Case Report Tabulations that are “decoded” and “unformatted” and therefore do not require association with SAS format libraries. However, analysis data sets and TLFs for submission studies including XL184-301 are generally derived from raw data with coded variables that require SAS format libraries. To facilitate the Agency request for SAS programs and macros, Exelixis proposes the following:

Provide two sets of raw data: one with decoded/unformatted values to serve the purpose of Case Report Tabulations, and a second set that includes coded/formatted variables, SAS formats and an associated SAS format catalog, to be used as the basis to run the SAS programs for derived data sets and summary tables.

Does the Agency agree with this proposal?

Discussion during the meeting: Exelixis stated that the intent is to provide two programs containing raw datasets in decoded and in coded/formatted variables. Exelixis will also provide a case report form that is annotated for each variable field name corresponding to the case report entry. Exelixis confirmed that the datasets are generally harmonized across studies at the level of the analysis data sets for the ISS, but that raw data are not harmonized across studies. FDA stated that the proposal is acceptable.

FDA requested that Exelixis provide analysis of the incidence of laboratory toxicities based on NCI CTCAE severity grade in addition to shift tables. Exelixis agreed to consider this request.

12. In the NDA please provide SAS programs for derived datasets and the analyses which are associated with the results presented in the proposed package insert.

Exelixis' December 20, 2011, response via electronic (email) communication: Exelixis seeks clarification as to whether SAS programs for derived data sets and analyses for the efficacy results presented in the proposed package insert are adequate, or if these are required for safety analyses and other summaries presented in the package insert?

Discussion during the meeting: FDA stated that analysis programs and derived datasets should be provided for safety analyses. Exelixis acknowledged FDA's request.

13. In the NDA provide a mock-up define file to show the variables which will be included in the derived datasets for the primary and key secondary efficacy analyses including, but not limited to, the variables for reasons of censoring, dates of IRC determined PFS (or investigator assessed PFS) event or censoring and variables for subgroup analyses, etc. Variables used for sensitivity Analysis of the SAP should be included as well.

Exelixis' December 20, 2011, response via electronic (email) communication: Exelixis intends to provide final define files with the NDA, not mock-up define files, to describe the primary, key secondary, and sensitivity analysis efficacy variables for Study XL184-301.

Discussion during the meeting: FDA stated that this is acceptable as long as the required information is included in this final define file.

Biopharmaceutics

14. FDA recommends that Exelixis provide the dissolution method development report in Module 3 of the NDA submission. The report should include data to justify the selected dissolution method and instrumental parameters (i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.) and to demonstrate the discriminating capability of the selected dissolution method. Validation data for the dissolution method should also be submitted.

Exelixis' December 20, 2011, response via electronic (email) communication: Exelixis acknowledges the FDA's comments and plans to include the requested information regarding the dissolution method in Module 3.

Discussion during the meeting: No discussion occurred regarding additional comment 14.

15. FDA recommends that Exelixis collect complete dissolution profile data from the bio-batches (PK and clinical) and primary (registration) stability batches of the drug product. These data should be used to set the dissolution acceptance criteria of your proposed product.

Exelixis' December 20, 2011, response via electronic (email) communication: Exelixis acknowledges the FDA's comments. Dissolution data will be presented in a tabular format for the PK, clinical, and registration stability batches.

Discussion during the meeting: No discussion occurred regarding additional comment 15

16. If a biowaiver is requested for the lower strength of the DP, supporting information/data should be submitted per CFR 320.22.

Exelixis' December 20, 2011, response via electronic (email) communication: No biowaiver is planned. The same capsule formulation, strengths, and dosing configurations have been used in the clinical studies (including Study XL184-301) as will be used commercially. Dissolution data for both capsule strengths will be included in Module 3.

Discussion during the meeting: No discussion occurred regarding additional comment 16.

Clinical Pharmacology

17. Exelixis' proposal to provide a summary of the results of the exposure-response (E-R) analyses from protocol XL184-301 in module 2.7.3 and 2.7.4 is acceptable; however, the full study report of the E-R analyses for both effectiveness and toxicity should be provided in Modules 5.

For the E-R analyses, refer to Guidances for Industry found at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf> and

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf> for more information.

Exelixis' December 20, 2011, response via electronic (email) communication:

Exelixis plans to include the complete details of the exposure-response analyses in a report that will be provided in Module 5.3.3.5.

Discussion during the meeting: No discussion occurred regarding additional comment 17.

18. In the NDA submission, please provide datasets from all clinical pharmacology studies in SAS transport format.

Exelixis' December 20, 2011, response via electronic (email) communication: Exelixis plans to submit SAS transport datasets for the clinical pharmacology studies.

Discussion during the meeting: No discussion occurred regarding additional comment 18.

19. FDA acknowledges that a [REDACTED] (b) (4), but would not be completed by the time of the NDA submission. Please provide the projected date for submitting the final study report.

Exelixis' December 20, 2011, response via electronic (email) communication: Exelixis anticipates having a complete study report available by [REDACTED] (b) (4)

Discussion during the meeting: No discussion occurred regarding additional comment 19.

Nonclinical

20. The nonclinical development of XL184 for the proposed population of unresectable, locally advanced or metastatic medullary thyroid cancer is subject to the Guidance for Industry ICH M3(R2): Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals. A pre-postnatal developmental toxicity study and a carcinogenicity assessment will be needed as per ICH M3(R2). At the time of the NDA submission a complete description of any known postmarketing requirements or commitments including but not limited to carcinogenicity assessments should be provided in module one.

Exelixis' December 20, 2011, response via electronic (email) communication: Exelixis acknowledges the FDA's comments. Exelixis has conducted nonclinical toxicity studies on the effects of XL184 on embryo-fetal development and on fertility and early embryonic development. A toxicity study in juvenile animals (rats) is planned. No other pre-postnatal developmental toxicity studies are planned, consistent with guidance in ICH S(9) ("Nonclinical Evaluation for Anticancer Pharmaceuticals").

Immature, interim overall survival data in Study XL184-301 indicate a median overall survival of approximately 21 months in the placebo arm (which may be considered the natural course of disease for this patient population). Median PFS in the cabozantinib arm (approximately the median time of drug exposure) was 11.2 months. These data support the relatively short prognosis of this advanced patient population with progressive disease at study entry. In accordance with ICH S(9) and ICH S1A ("The Need for Long-term Rodent Carcinogenicity Studies of Pharmaceuticals"), which indicate carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with late stage or advanced cancer, Exelixis believes that carcinogenicity studies of XL184 are not warranted, and thus has not initiated such studies to date. Once mature data are available for the final overall survival analysis, Exelixis will re-evaluate the plans for a carcinogenicity study, if indicated.

Discussion during the meeting: FDA stated that the acceptability of the nonclinical program with regard to the need for a pre/post developmental toxicity study and a carcinogenicity study would be a review issue upon submission of the NDA. Exelixis stated that based on projected overall survival for patients enrolled on these studies, such as a nonclinical study will not be required. FDA advised Exelixis to submit plans for the conduct of these studies as postmarketing commitments in module one and to request release of the commitments if the mature survival data support this approach.

Any Postmarketing Requirements (PMR) or Commitments (PMC) that you would like to propose should be filed in Module 1, section 1.2 as a separate leaf under the cover letters section. However, if you intend to propose a postmarketing study under SPA, the SPA request should be filed under the appropriate sub-file in Module 1, section 1.8 (1.8.1 Clinical study, 1.8.2 Carcinogenicity study, 1.8.3 Stability study, 1.8.4 Animal efficacy study for approval under the animal rule). Please also be advised that in the future, proposed PMR and PMC documents will have a dedicated section within the eCTD; and any additional information you may require with regard to this matter can be addressed to the CDER Electronic Submissions Coordinator at esub@fda.hhs.gov.

Comments from Exelixis

21. Exelixis would like to ask where in Module 1 should postmarketing requirements or commitments be listed.

Discussion during the meeting: See comments under question #20.

22. Exelixis acknowledges that conditional approval was granted for the proposed propriety name for cabozantinib, Cometriq, and a submission for review under the NDA is required. Exelixis plans to submit the request in January 2012, and requests clarification from the Agency as to the section in Module 1 this information should be located.

Discussion during the meeting: FDA stated that this should be provided with other documents relating to regulatory history.

Action Items:

Exelixis will submit the first section of the rolling NDA in December 2011.

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

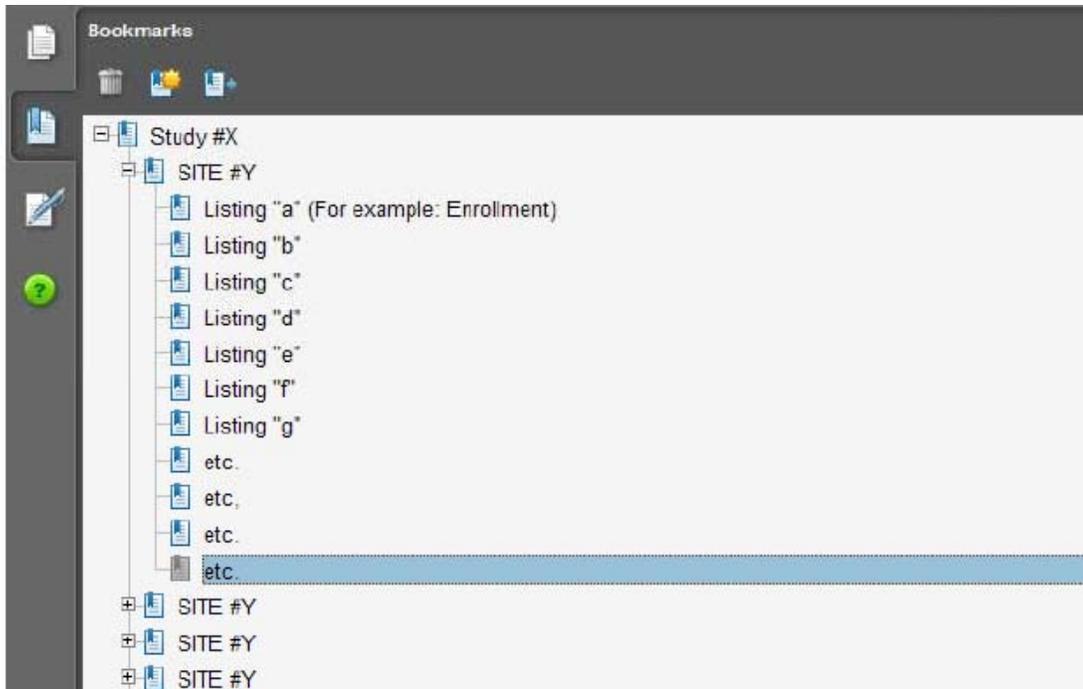
I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3/Pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3/Pivotal clinical trials:
 - a. Number of subjects screened for each site by site
 - b. Number of subjects randomized for each site by site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3/Pivotal clinical trials:
 - a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
 - b. Name, address and contact information of all CROs used in the conduct of the clinical trials
 - c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
 - d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)

4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).
5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data (“line”) listings. For each site provide line listings for:
 - a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
 - b. Subject listing for treatment assignment (randomization)
 - c. Subject listing of drop-outs and subjects that discontinued with date and reason
 - d. Evaluable subjects/non-evaluable subjects and reason not evaluable
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of laboratory tests performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application review process. Please refer to [Attachment 1](#), “Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions” for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

Attachment 1

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

1.1 Introduction

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

1.2 Description of the Summary level clinical site dataset

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

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

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

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

Site-Specific Efficacy Results

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

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)
- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.

- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

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

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

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

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

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

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

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

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt).

Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to descr be the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., <u>not limited to</u> only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount (\$USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount (\$USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parties. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	INITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

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

Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

MINITAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

Attachment 2

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

OSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

2 Page(s) has been Withheld in Full as B6 immediately following this page

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

/s/

GINA M DAVIS
01/06/2012



NDA 203756

NDA PRESUBMISSION ACKNOWLEDGEMENT

Exelixis, Inc.
Attention: Lisa Sauer
Director, Regulatory Affairs
210 East Grand Avenue
South San Francisco, CA 94083

Dear Ms. Sauer:

We have received the first section of your New Drug Application (NDA) under the program for step-wise submission of sections of an NDA (section 506 of the Federal Food, Drug, and Cosmetic Act) for the following:

Name of Drug Product: cabozantinib

Date of Submission: December 20, 2011

Date of Receipt: December 21, 2011

Our Reference Number: NDA 203756

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Please cite the NDA number listed above at the top of the first page of any communications concerning 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 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Gina Davis, Regulatory Project Manager at (301) 796-0704.

Sincerely,

{See appended electronic signature page}

Sharon Sickafuse, M.S.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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

/s/

SHARON K SICKAFUSE
12/30/2011

MEETING MINUTES

MEETING DATE: March 6, 2008 **TIME:** 1pm **LOCATION:** room 1311

Drug Name: XL184

IND: (b) (4)

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,
BiometricsV**

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

Colin Hessel, MS, Senior Director, Biostatistics and
Clinical Data Management

Gisela Schwab, MD, Chief Medical Officer and
Executive Vice President, Development

Steven Sherman, MD, Professor and Chair, Endocrine
Neoplasia and HD, University of Texas MD Anderson
Cancer Center

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) (b) (4) will evaluate the 175-mg dose of XL184 in subjects with glioblastoma multiforme (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 μ 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.

FINANCIAL DISCLOSURE FINAL RULE:

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

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

PEDIATRIC RESEARCH EQUITY ACT (PREA):

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

PEDIATRIC EXCLUSIVITY:

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

DEMOGRAPHICS:

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

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

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

Linked Applications

Sponsor Name

Drug Name

IND (b) (4)

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.

/s/

RAMZI N DAGHER

03/18/2008