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APPLICATION NUMBER:

203756Orig1s000

OTHER REVIEW(S)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 203,756
Product Name: COMETRIQ

PMR/PMC Description: Carcinogenicity Study in Rats

PMR/PMC Schedule Milestones: SPA (Final Protocol Submission): 04/15/2013
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: 10/15/2016
Other: _____ MM/DD/YYYY

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

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

1. Expected extended survival (5 years or longer after first exposure to cabozantinib)
 2. Extended dosing duration of the medullary thyroid cancer patient population
 3. Carcinogenicity is a safety concern with chronic drug exposure
 4. Cabozantinib is a kinase inhibitor, and other kinase inhibitors have demonstrated carcinogenicity in nonclinical carcinogenicity studies

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Long-term (2-year) rat carcinogenicity study

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
Nonclinical study, safety-related
-

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

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

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

MARGARET E BROWER
11/28/2012

WHITNEY S HELMS
11/28/2012

JEFFERY L SUMMERS
11/28/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 203,756
Product Name: COMETRIQ

PMR/PMC Description: Carcinogenicity Study in Mice

PMR/PMC Schedule Milestones: SPA (Final Protocol Submission): 06/15/2013
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: MM/DD/YYYY
Other: _____ 10/15/2015

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

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

- | |
|---|
| <ol style="list-style-type: none">1. Expected extended survival (5 years or longer after first exposure to cabozantinib)2. Extended dosing duration of the medullary thyroid cancer patient population3. Carcinogenicity is a safety concern with chronic drug exposure4. Cabozantinib is a kinase inhibitor, and other kinase inhibitors have demonstrated carcinogenicity in nonclinical carcinogenicity studies |
|---|

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Mouse carcinogenicity study (Long term [2-year] or alternative)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
Nonclinical study, safety-related
-

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

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

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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/s/

MARGARET E BROWER
11/28/2012

WHITNEY S HELMS
11/28/2012

JEFFERY L SUMMERS
11/28/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 203,756
Product Name: COMETRIQ

PMR/PMC Description: Pre-natal/post-natal reproductive toxicology study

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: MM/DD/YYYY
Other: _____ 10/15/2014

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

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

1. Expected extended survival (5 years or longer after first exposure to cabozantinib)
 2. Extended dosing duration of the medullary thyroid cancer patient population
 3. The pharmacological mechanism of action of cabozantinib (e.g. inhibition of MET and VEGF pathways) may result in altered bone development in neonates

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

Pre-natal/post-natal reproductive toxicology study

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
Nonclinical study, safety-related
-

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

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

PMR/PMC Development Coordinator:

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PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 203,756
Product Name: COMETRIQ

PMR/PMC Description: *In vitro* mutagenicity assay of the M4 metabolite (monohydroxy sulfate)

PMR/PMC Schedule Milestones: Final Protocol Submission: MM/DD/YYYY
Study/Trial Completion: MM/DD/YYYY
Final Report Submission: 12/15/2013
Other: _____

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

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

1. Clinical level of the M4 metabolite (monohydroxy sulfate) significantly exceeds the level of exposure of this metabolite in animal models
 2. Expected extended survival (5 years or longer after first exposure to cabozantinib)
 3. Extended dosing duration of the medullary thyroid cancer patient population

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

In vitro mutagenicity assay of the M4 metabolite (monohydroxy sulfate)

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
Nonclinical study, safety-related
-

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

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

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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JEFFERY L SUMMERS
11/28/2012

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # NDA 203,756, COMETRIQ® (Cabozantinib)
Product Name: _____

PMR/PMC Description: Impaired Hepatic Function

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>05/31/2013</u>
	Study/Trial Completion:	<u>05/31/2014</u>
	Final Report Submission:	<u>11/30/2014</u>
	Other: _____	<u>MM/DD/YYYY</u>

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

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

The mass balance study suggested that hepatic elimination is the major elimination pathway of cabozantinib. Patients with hepatic impairment may have higher exposure of cabozantinib than that of normal patients, which could cause more toxicities.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the clinical trial is to assess the need for a dose reduction or recommend avoidance of cabozantinib for patients with hepatic impairment.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
-

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

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

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs)

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # NDA 203,756, COMETRIQ® (Cabozantinib)
Product Name: _____

PMR/PMC Description: Drug Interaction

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>05/31/2013</u>
	Study/Trial Completion:	<u>05/31/2014</u>
	Final Report Submission:	<u>11/30/2014</u>
	Other: _____	<u>MM/DD/YYYY</u>

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

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

The solubility of cabozantinib is pH-dependent with the solubility at normal gastric pH the highest and practically insoluble when pH is greater than 4. The gastric pH elevating drugs can significantly decrease the solubility of cabozantinib by increase the stomach pH, and therefore would change the PK profile of cabozantinib. The effect of gastric pH modifying drugs (proton pump inhibitors, H2 blockers, antacids) on PK of cabozantinib based on a population PK analysis (sparse PK samples) was inconclusive.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the clinical trial is to determine how to co-administer gastric pH elevating agents with cabozantinib.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

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 of 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.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial

Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

Pharmacokinetic studies or clinical trials

Drug interaction or bioavailability studies or clinical trials

Dosing trials

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

Other

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

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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/s/

JUN YANG
11/16/2012

HONG ZHAO
11/19/2012
I concur.

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Consumer Drug Promotion**

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

Memorandum

Date: November 13, 2012

To: Gina M. Davis
Regulatory Health Project Manager
Division of Oncology Products 2 (DOP-2)
Office of Hematology and Oncology Drug Products

From: Karen Munoz-Nero, BSN, RN, Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP)
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 203756
COMETRIQ (cabozantinib) capsules
OPDP Comments on proposed PPI

In response to the Division of Oncology Products 2 (DOP 2) June 4, 2012, consult request, OPDP has reviewed the proposed patient labeling (PPI) for COMETRIQ (cabozantinib) capsules (Cometriq).

This review is based on the following documents:

- The substantially complete prescribing information (PI) sent by Gina Davis to OPDP via e-mail on October 26, 2012, entitled "2012-OCT-25-NDA 203756 - Cometriq Active Label.doc."
- The revised Cometriq PPI posted in DARRTS on November 9, 2012 by Karen Dowdy, RN, BSN, Patient Labeling Reviewer, Division of Medical Policy Programs (DMPP).

OPDP has no comments on the proposed PPI at this time.

Thank you for the opportunity to comment on this proposed labeling. If you have any questions regarding this consult review, please contact Karen Munoz-Nero at 301-796-3274 or Karen.Munoz@fda.hhs.gov.

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/s/

KAREN MUNOZ-NERO
11/13/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: November 9, 2012

To: Patricia Keegan, M.D.
Director
Division of Oncology Products 2 (DOP2)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Karen Dowdy, RN, BSN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: DMPP Review of Patient Labeling: Patient Package Insert
(PPI)

Drug Name (established name): COMETRIQ (cabozantinib)

Dosage Form and Route: capsules

Application Type/Number: NDA 203-756

Applicant: EXELIXIS, Inc.

1 INTRODUCTION

On May 29, 2012 EXELIXIS, Inc. submitted for the Agency's review a New Drug Application (NDA) 203-756, for COMETRIQ (cabozantinib) capsules. The proposed indication for COMETRIQ (cabozantinib) capsules is for the treatment of patients with progressive metastatic medullary thyroid cancer (MTC).

On June 6, 2012, the Division of Oncology Products 2 (DOP2) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI). The Applicant originally included a Medication Guide (MG) as part of the labeling submitted on May 29, 2012. In a Filing Communication letter dated July 27, 2012, FDA provided comments to EXELIXIS, Inc. regarding potential review issues, and requested responses to various labeling format issues, including that the labeling should contain a PPI rather than a MG. The Applicant submitted revised labeling on August 7, 2012 in response to the Agency's request for information, including a PPI in place of the previously submitted MG.

This review is written in response to a request by DOP2 for DMPP to review the Applicant's proposed PPI for COMETRIQ (cabozantinib) capsules.

2 MATERIAL REVIEWED

- Draft COMETRIQ (cabozantinib) capsules Patient Package Insert (PPI) received on August 7, 2012, and received by DMPP on October 29, 2012.
- Draft COMETRIQ (cabozantinib) capsules Prescribing Information (PI) received on May 29, 2012, revised by the Review Division throughout the review cycle, and received by DMPP on October 29, 2012.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the PPI the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 11.

In our review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)

- removed unnecessary or redundant information
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our review of the PPI is appended to this memorandum. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

KAREN M DOWDY
11/09/2012

SHARON R MILLS
11/09/2012

LASHAWN M GRIFFITHS
11/09/2012

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
Division of Professional Drug Promotion**

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

Memorandum

Date: November 8, 2012

To: Gina Davis, Regulatory Project Manager
Division of Oncology Products 2 (DOP-2)
Office of Hematology Oncology Drug Products

From: Carole Broadnax, PharmD, Regulatory Review Officer
Division of Professional Drug Promotion (DPDP)
Office of Prescription Drug Promotion (OPDP)

Cc: Karen Munoz, Regulatory Review Officer
Division of Consumer Drug Promotion (DCDP), OPDP

Subject: NDA 203756
Cometriq (cabozantinib) capsules
OPDP Labeling Comments

OPDP/DPDP has reviewed the proposed labeling (Package Insert (PI) and carton/container) as requested in your consult dated June 4, 2012. OPDP/DPDP comments for the proposed Dear Healthcare Provider Letter will be provided in a separate consult response. OPDP/DCDP comments for the proposed Medication Guide will be provided in a separate consult response.

DPDP's comments are based on the substantially complete version of the proposed PI titled, "2012-OCT-25-NDA 203756 – Cometriq Active Label.doc," sent via electronic mail to OPDP (Carole Broadnax) from DOP 2 (Gina Davis) on October 26, 2012. OPDP's comments are provided directly in the attached document. Please note that for the PI, OPDP hid DOP 2's deletions and formatting changes so that OPDP comments are easier to read.

DPDP reviewed the proposed revised carton and container labeling sent via electronic mail to OPDP (Carole Broadnax) from DOP 2 (Gina Davis) on November 8, 2012. OPDP does not have comments on the carton and container labeling at this time.

Thank you for your consult. If you have any questions, please contact Carole Broadnax at (301) 796-0575 or Carole.Broadnax@fda.hhs.gov.

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/s/

CAROLE C BROADNAX
11/08/2012

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

IND or NDA	NDA 203756
Brand Name	COMETRIQ
Generic Name	Cabozantinib (XL184)
Sponsor	Exelixis Inc.
Indication	Unresectable, locally advanced, or metastatic medullary thyroid cancer
Dosage Form	Capsules
Drug Class	Tyrosine kinase inhibitor
Therapeutic Dosing Regimen	140 mg once daily taken without food (175 mg as L-malate salt)
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	175 mg QD
Submission Number and Date	SDN004_29 May 2012
Review Division	DOP2

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No large changes in mean QT interval (>20 ms) was detected in the trial following the treatment of cabozantinib 175 mg once daily. The largest upper bounds of the 2-sided 90% confidence interval (CI) for the mean change from baseline was 13.95 ms, observed at 0 hours (pre-dose) on Day 1 of Cycle 2, following continuous dosing of 28 days. Since the trial did not incorporate a positive-control (moxifloxacin arm), assay sensitivity was not assessed. Therefore, a small increase in mean QT interval (i.e., <10 ms) cannot be ruled out.

In this randomized, double-blinded, placebo controlled phase 3 study, 315 patients with unresectable, locally advanced, or metastatic medullary thyroid cancer, received cabozantinib 175 mg once daily for two cycles in which ECGs were taken at Cycle 1 Day 1 and Cycle 2 Day 1 (Day 29) of treatment. An overall summary of findings is presented in Table 1.

Table 1: The Point Estimate and the 90% CIs Corresponding to the Largest Upper Bounds for Cabozantinib maleate (175 mg) for Cycle 2 (Day 1) (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
Cabozantinib maleate (Cycle 2 Day 1)	0	11.3	(8.7, 13.95)

The therapeutic dose (175 mg orally administered cabozantinib maleate) produces mean C_{\max} values 1640 ng/ml (average C_{\max} obtained in Cycle 2 after uninterrupted dosing for 28 days). A supratherapeutic dose was not used in the study. As the half-life of cabozantinib is 55 h, continuous daily dosing is expected to yield accumulation of exposures (~5.1 fold) and steady state concentrations are achieved by approximately 15 days. Therefore the evaluation of QT was conducted at day 1 of treatment and at steady-state PK of cabozantinib during the second cycle (Day 29).

Cabozantinib is a substrate of CYP3A4, and is primarily cleared via the hepatic route. Administration of the strong CYP3A4 inhibitor ketoconazole (400 mg daily for 27 days) to healthy volunteers decreased cabozantinib clearance (by 29%) and increased single-dose plasma cabozantinib exposure (AUC range: 34-38% higher, but no effect on C_{\max}). It is expected from drug interaction studies that co-administration with CYP450 3A4 inhibitors or inducers will have an effect on the exposures. A high-fat meal moderately increased C_{\max} and AUC values (41% and 57%, respectively) relative to fasted conditions in healthy volunteers administered a single 175 mg oral cabozantinib maleate dose.

Exposure data in patients with hepatic or renal impairment is not available. Other intrinsic factors (e.g., age, gender or race) and extrinsic factors (e.g., drug interactions, food effect), have been explored as potential factors of PK variability in population PK analysis of the Phase 3 data. Cabozantinib PK was not affected by age and the apparent clearance of cabozantinib was 22% lower in female than males.

2 PROPOSED LABEL

2.1 THE SPONSOR PROPOSED LABEL:



2.2 QT-IRT PROPOSED LABEL:

QT-IRT recommends that following language in the label. Our recommendations are suggestions only. We defer final labeling decisions to the review division.

5.7 QT Prolongation

QT prolongation has been observed with COMETRIQ. COMETRIQ should be used with caution in patients with a history of QT interval prolongation or who are taking drugs known to prolong the QT interval. When using COMETRIQ, periodic monitoring with on-treatment ECGs and electrolytes (serum calcium, potassium, and magnesium) should be considered.

12.6 Cardiac Electrophysiology

The effect of orally administered COMETRIQ 140 mg on QTc interval was evaluated in a randomized, double-blinded, placebo-controlled, two-treatment-arm parallel study in medullary thyroid cancer patients. An increase from baseline in QTcF of 10 - 15 ms within the first 4 weeks of initiating COMETRIQ treatment was observed (b) (4)

(b) (4) A pharmacokinetic/pharmacodynamic analysis suggested a concentration-dependent QTc interval prolongation. This effect was not associated with a change in cardiac wave form morphology or new rhythms. No COMETRIQ-treated subjects had a QTcF >500 ms.

3 BACKGROUND

3.1 PRODUCT INFORMATION

XL184 (cabozantinib; EXEL-7184, EXEL-02977184) is a multi-targeted inhibitor of receptor tyrosine kinases (RTKs). Primary targets of XL184 include several RTKs known to play important roles in tumor cell proliferation and/or tumor neovascularization (ie, MET, VEGFR2 and RET).

3.2 MARKET APPROVAL STATUS

Cabozantinib is not approved for marketing in any country

3.3 PRECLINICAL INFORMATION

From eCTD 2.4

XL184 did not inhibit hERG channel activity when tested at 1, 10, and 30 μ M as determined by patch-clamp electrophysiology. No biologically significant effects on systolic blood pressure, heart rate, or left ventricular pressure were apparent at doses of 150 mg/kg or 1000 mg/kg in male Beagle dogs. The 1000-mg/kg dose produced a transient increase in diastolic pressure (approximately 22%) that resulted in an increased mean arterial pressure (approximately 12%). XL184 administration at either 150 or 1000 mg/kg had no effect on electrocardiographic parameters (including QT and QTc intervals). The 1000-mg/kg dose was associated with emesis. The NOAEL for effects on cardiovascular parameters in conscious dogs administered a single oral dose of XL184 was considered to be 150 mg/kg. However, estimated plasma exposure in these dogs dosed at 150 mg/kg would be approximately 5-fold higher than measured at steady-state in patients with solid tumors administered 175 mg XL184 capsule form daily.

3.4 PREVIOUS CLINICAL EXPERIENCE

From eCTD 2.7.4

ECG Data from Studies XL184-001 and XL184-201. In Study XL184-001, clinically significant changes on ECGs were to be reported as AEs. There were abnormal ECG findings compared to baseline ECGs on actual ECG results reported; none were considered to be clinically significant (XL184-001 CSR Section 12.5.3). In Study XL184-201, one subject had a QTc of 486 msec in a hospital setting of elevated troponin and myocarditis as possibly related to study drug; study drug was held until resolution of the AEs (XL184-201 CSR Section 12.6.3). The prolonged QTc decreased to 466 msec approximately 2 hours after the initial finding and was normal (447 msec) 8 days later.

As shown in Table 60, one subject from the cabozantinib arm in Study XL184-301 experienced an AE of Grade 3 ECG QT prolonged (XL184-301 CSR Section 12.4.2.7.2). This subject experienced a QTcB value >500 ms on Cycle 2 Day 1 post-dose (XL184-301 CSR Listing 16.2.7.1). Per Table 60, four additional subjects from the cabozantinib arm in Study XL184-301 experienced AEs of ECG QT prolonged. One subject (11203005) experienced a Grade 2 event on an unscheduled ECG, the other three subjects experienced Grade 1 AE events per investigator assessment. Analysis of ECG data is presented in Section 2.7.4.4.2.1. For Study XL184-301, the ECG data was analyzed in an external report by an independent cardiologist (XL184-301.ECG.001 Appendix A).

Table 2: ECG QT Prolonged Reported as Adverse Events (Safety Analysis Set)

Preferred Term	XL184-001 Cabozantinib (175 mg) (N = 35)	XL184-301 Cabozantinib (175 mg) (N = 214)	XL184-301 Placebo (N = 109)	XL184-201 Cabozantinib (175 mg) (N = 46)
Electrocardiogram QT prolonged ^a	0	5 (2.3%)	1 (0.9%)	0
Grade 3 or higher	—	1 (0.5%)	0	—

—, not applicable; AE, adverse event; ECG, electrocardiogram.

At each level of summarization, a subject was counted once for the most severe event if the subject reported one or more events.

^a Events of electrocardiogram QT prolonged reported as AEs based on investigator assessment of ECG abnormalities.

Source: [SCS Table 2.8](#), [SCS Table 2.14](#).

Source: eCTD 2.7.4, Table 60

A summary of selected cardiac-related AEs that could potentially be related to increased QTc interval is provided in Table 61. Results from ECGs are discussed in Section 2.7.4.4.2.

Table 3: Incidence of Cardiac Disorder-Related Adverse Events (Safety Analysis Set)

Subjects with a TEAE Preferred Term ^a	XL184-001 Cabozantinib (175 mg) (N = 35)	XL184-301 Cabozantinib (175 mg) (N = 214)	XL184-301 Placebo (N = 109)	XL184-201 Cabozantinib (175 mg) (N = 46)
Cardiac arrest	1 (2.9%)	1 (0.5%)	0	0
Grade 3 or higher	1 (2.9%)	1 (0.5%)	0	0
SAE	1 (2.9%)	1 (0.5%)	0	0
Cardiopulmonary failure	0	1 (0.5%)	1 (0.9%)	0
Grade 3 or higher	0	1 (0.5%)	1 (0.9%)	0
SAE	0	1 (0.5%)	1 (0.9%)	0
Cardio-respiratory arrest	1 (2.9%)	0	0	0
Grade 3 or higher	1 (2.9%)	0	0	0
SAE	1 (2.9%)	0	0	0

SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Adverse events were graded per NCI-CTCAE V3.0. Reported adverse events were coded using MedDRA V14.0.

At each level of summarization, a subject was counted once for the most severe event if the subject reported one or more events.

^a The preferred terms are selected events within the cardiac disorders system organ class.

Source: [SCS Table 2.2](#), [SCS Table 2.4](#), [SCS Table 2.8](#), [SCS Table 2.14](#).

Source: eCTD 2.7.4, Table 61

Reviewer's comments: There were reports of QTc prolongation and sudden death in cabozantinib clinical program. No cases of Torsade de pointes were reported.

3.5 CLINICAL PHARMACOLOGY

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

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND (b)(4). The sponsor submitted the Cardiac ECG Safety Report for study XL184-301-ECG-001 and other related materials for cabozantinib, including electronic datasets and waveforms, to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

An international, randomized, double-blinded, phase 3 efficacy study of XL184 versus placebo in subjects with unresectable, locally advanced, or metastatic medullary thyroid cancer.

4.2.2 Protocol Number

XL184-301

4.2.3 Study Dates

10 September 2008 – 15 June 2011

4.2.4 Objectives

The primary objective of the clinical trial was to evaluate progression-free survival (PFS) with XL184 treatment as compared with placebo in subjects with unresectable, locally advanced, or metastatic medullary thyroid cancer (MTC).

The secondary objectives of this study were to assess the pharmacokinetics and pharmacodynamic effects of XL184 and to evaluate the safety and tolerability of XL184 treatment. Electrocardiogram assessments were performed pre-dose and up to 6 hours post-dose on Day 1 of Cycles 1 and 2.

4.2.5 Study Description

4.2.5.1 Design

This was an international, randomized, double-blinded, multi-center, placebo-controlled Phase 3 study of unresectable, locally advanced, or metastatic MTC. Three hundred fifteen eligible subjects were to be enrolled (actual enrollment of 330) in two parallel treatment arms to receive either an oral daily dose of XL184 or placebo comparator.

4.2.5.2 Controls

The Sponsor used only a negative control (placebo).

4.2.5.3 Blinding

All treatment arms were administered blinded. Placebo was administered in the same manner as the active agent, and was packaged and color-, size-, and shape- matched to be indistinguishable from XL184.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

There were two treatment arms. Subjects were randomized in a 2:1 ratio to receive XL184 (175 mg QD) or placebo in a double-blinded fashion. Randomization was stratified by age (≤ 65 years, >65 years) and prior use of a TKI (yes, no) as determined at study entry. The randomization scheme employed a permuted block design to help ensure a 2:1 ratio of assignment to the XL184 and placebo treatment groups for the overall population as well as within each level of stratification factors.

4.2.6.2 Sponsor's Justification for Doses

In a Phase 1 dose escalation study in subjects with advanced solid tumors (Study XL184-001) the maximum tolerated dose (MTD) for XL184 was determined to be 175 mg (L-malate salt weight basis) administered once daily. This was confirmed to be a highly

active dose: 7 of 25 MTC subjects treated at the MTD had a confirmed PR in that study. The median duration of treatment at the time of data cut-off for those subjects was 429 days (range: 159-708). *Source: Clinical Study Report XL184-301, pg 43*

Reviewer's Comments: The dose selected for the study is acceptable based on the risk for GI, skin and other toxicities. Based on the currently proposed label, this dose represents the maximum therapeutic dose.

4.2.6.3 Instructions with Regard to Meals

Subjects were instructed to fast for two hours before taking study treatment every morning and continued to fast for one hour after their dose. Subjects were instructed to take one dose of study treatment each day and not to make up missed doses unless the missed dose could be taken within 12 hours of the normal dosing time. Subjects were instructed not to administer another dose after vomiting. *Source: Clinical Study Report XL184-301, pg 44*

Reviewer's Comments: Administration of XL184, under fasted conditions, is appropriate. Based on a dedicated food-effect study, C_{max} and AUC were moderately increased by 41% and 57%, respectively, when XL184 was administered with a high-fat, high calorie meal. In the clinical studies, subjects have been instructed to take cabozantinib in a fasted-state (i.e., fast at least 2 hours before and at least 1 hour after each dose) to avoid possible effects on XL184 exposure. The proposed label stipulates XL184 should be taken under fasting conditions. Patients who take XL184 with food may be at greater risk of QT prolongation.

4.2.6.4 ECG and PK Assessments

Twelve-lead ECGs were recorded in triplicate (recording repeated three times consecutively within 30 minutes with an interval of at least 2 minutes between ECG). All ECG assessments (except for screening) were time matched with PK samples such that the ECG assessments were performed just prior to the PK blood sample collection. XL184 concentration was measured in plasma samples taken at selected intervals throughout the study.

Study Day(s)	-1 (for Cycles 1 and 2)	1 (for Cycles 1 and 2)
Intervention	No treatment	One (1) 175-mg oral capsule of XL184
12-Lead ECGs	Pre-dose, 2, 4, and 6 hours post dose.	Pre-dose, 2, 4, and 6 hours post dose.
PK Samples for drug	None collected	Pre-dose, 2, 4, and 6 hours post dose.

Reviewer's Comment: The PK and ECG assessments are adequate to capture QT at peak concentrations of XL184 (median T_{max} ~ 4 hours). This T_{max} is within the expected range of 1.5 to 4 hours upon oral dosing of XL184 capsules. The assessments of ECGs and PK were conducted after the first and second cycle (29 days, after continuous administration). As the half-life of XL184 is 55 h, the evaluation of QT was conducted at steady-state PK of XL184 during the second cycle.

4.2.6.5 Baseline

The sponsor used a time-matched baseline.

4.2.7 ECG Collection

The ECGs were recorded at the sites using 12-lead ECG recorders (Mortara, Milwaukee, WI, USA). Digital ECGs were to be transmitted from the sites via modem to a central laboratory, (b) (4), for a treatment-blinded measurement of the cardiac intervals and morphological assessment by a central cardiologist blinded to the study treatment.

The ECG analysis was conducted in Lead II and when Lead II was not analyzable, then in Lead V5. If Lead V5 was not analyzable, the Lead V2 was used, followed by the most appropriate lead if necessary. ECG readers were blinded to subject identifiers, treatment and visit.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

Subjects were required to be at least 18 years old with an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 , to have adequate organ and marrow function, and to have recovered from recent chemotherapy, immunotherapy, and radiotherapy.

Subjects were stratified by age and by prior TKI use. A total of 330 subjects (219 cabozantinib, 111 placebo) were randomized to receive study drug; 214 subjects in the cabozantinib arm and 109 subjects in the placebo arm received study drug.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

The central tendency analysis was performed on data in the Electrocardiographic Analysis Population. Visit and time-point averaged analyses of the ECG population were performed for data collected on the Day 1 (C1D1) and Day 29 (C2D1) visits. Data from subjects with and without dose modifications prior to ECG collection were combined in this analysis.

The baseline ECG interval value was defined as the mean of all evaluable ECGs prior to dosing on C1D1 (i.e., 3 screen and 3 predose C1D1). This mean was used as the baseline for each additional time point: C1D1 at hours 2, 4 and 6 and on C2D1 at hours 0 (i.e., predose), 2, 4 and 6. Descriptive statistics were used to summarize the ECG variables and the corresponding changes from the mean baseline to each time point for

placebo and the 175 mg XL184 dose groups. The Δ ECG intervals were also presented with 2-sided data-based 90% confidence intervals.

For all subjects, the change from the mean baseline to the mean of all on-treatment ECG values (traditional time-averaged analysis) for each ECG interval for placebo and XL184 at 175 mg per day was calculated for C1D1 and again separately for C2D1.

The Frederica formula (QTcF) was chosen over Bazett's (QTcB) as the more accurate QTc-correction method. QTcB values were also provided to facilitate comparisons with historical data.

The sponsor's results are shown in Table 4 and Figure 1. The sponsor concludes that there was no increase in QTcF change from baseline for cabozantinib-treated subjects on Day 1 (Cycle 1), but a significant increase on Day 29 for the cabozantinib arm versus placebo.

Table 4: Sponsor’s Comparisons of Change from Time-matched Baseline in QTcF between Cabozantinib 175 mg and Placebo

Time Point	Visit			
	Day 1 (C1D1)		Day 29 (C2D1)	
	Cabozantinib ^a	Placebo	Cabozantinib ^a	Placebo
Pre-dose	NA	NA	12.0 (14.1) N = 153	0.7 (2.3) N = 90
2 hours post-dose	0.0 (1.3) N = 209	3.4 (4.9) N = 106	11.5 (13.4) N = 162	1.7 (3.5) N = 95
4 hours post-dose	-3.0 (-1.8) N = 208	-2.0 (-0.5) N = 106	8.4 (10.3) N = 163	-0.8 (1.1) N = 96
6 hours post-dose	-3.1 (-1.8) N = 205	-1.9 (-0.2) N = 107	7.9 (9.8) N = 158	-2.3 (-0.6) N = 96

CI, confidence interval; CnDn, Cycle n, Day n; ms, milliseconds; N, number of subjects; NA, not applicable; QTcF, Fridericia correction.

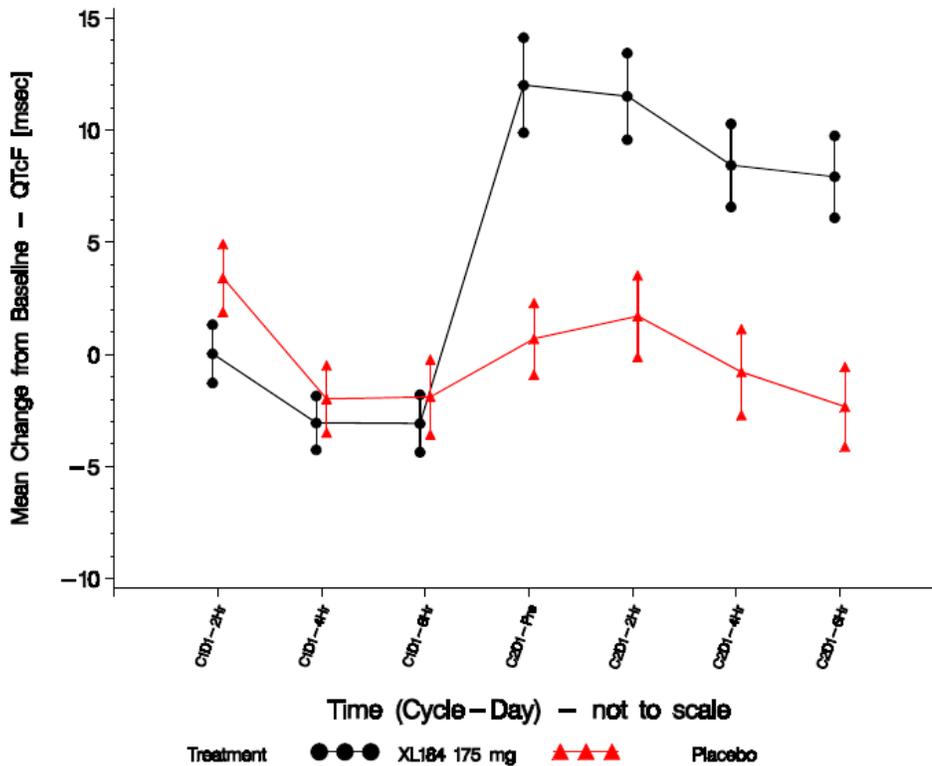
Note: The upper bound of the 1-sided 95% CI is equivalent to the upper bound of the 2-sided 90% CI. Values represent the mean [upper bound of the 1-sided 95% CI] in milliseconds.

^a Planned cabozantinib dose: 175 mg/day administered once-daily.

Source: [XL184-301.ECG.001 Table ECG-14.2.3.5](#).

Source: Sponsor’s Summary of Clinical Safety, page 119, In Text Table 59.

Figure 1: Sponsor’s Mean and 90% CI ΔQTcF for All Treatments



Source: Sponsor’s report, page 19, In Text Figure 3-4.

Reviewer’s Comments: Our independent analysis agrees with the sponsor’s conclusion. See section 5.

4.2.8.2.2 Assay Sensitivity

A positive control was not used in this study. Therefore, no formal assessment of assay sensitivity was performed for this study.

4.2.8.2.3 Categorical Analysis

Categorical analysis for maximum QT, QTcB, and QTcF intervals were classified by the sponsor using the following thresholds: >30 to ≤60 ms, > 60 ms, > 480 ms, and > 500 ms. The sponsor's categorical analysis for QT/QTc intervals and changes, as a mean change from baseline and new outliers from baseline for placebo and the XL184 dose group for Cycle 1 Day 1 (C1D1) and Cycle 2 Day 1 (C2D1) are shown in Table 5.

Table 5: Sponsor's Categorical Analysis

Treatment	XL184 ^a	Placebo	XL184 ^a	Placebo
Visit	Day 1 (C1D1)	Day 1 (C1D1)	Day 29 (C2D1)	Day 29 (C2D1)
Sample Size	209	107	166	97
Heart Rate Bradycardic Outliers N (%)	0	0	1 (1%)	0
Heart Rate Tachycardic Outliers N (%)	0	0	1 (1%)	2 (2%)
PR Outliers N (%)	0	0	2 (1%)	0
QRS Outliers N (%)	1 (<1%)	1 (1%)	0	0
QT new >500 ms N (%)	0	0	0	0
QTcF new >500 ms N (%)	0	1 (1%)	0	1 (1%)
QTcF new >480 ms N (%)	1 (<1%)	0	1 (1%)	0
QTcF changes from baseline >30 to ≤60 ms N (%)	4 (2%)	0	25 (15%)	0
QTcF changes from baseline >60 ms N (%)	0	0	1 (1%)	0
QTcB new >500 ms N (%)	2 (1%)	0	2 (1%)	0
QTcB new >480 ms N (%)	2 (1%)	1 (1%)	8 (5%)	1 (1%)
QTcB changes from baseline >30 to ≤60 ms N (%)	3 (1%)	1 (1%)	24 (14%)	3 (3%)
QTcB changes from baseline >60 ms N (%)	0	0	2 (1%)	0
New abnormal U wave N (%)	0	0	0	0
New ST segment depression N (%)	1 (<1%)	1 (1%)	5 (3%)	3 (3%)
New T wave inversion N (%)	4 (2%)	2 (2%)	9 (5%)	2 (2%)
New Second or Third Degree Heart Block N (%)	0	0	0	0
New RBBB or LBBB N (%)	0	0	0	0
New AF N (%)	0	0	0	0
New MI N (%)	0	0	0	0

Source: Sponsor's Report XL184-301, page 208, In Text Table 78.

4.2.8.3 Safety Analysis

In Study XL184-301, the incidence of deaths in the cabozantinib and placebo arms was 65 (30.4%) and 30 (27.5%), respectively. There was a slightly higher incidence of deaths in the cabozantinib arm through 30 days of last dose (22 [10.3%] vs 8 [7.3%]; Section 2.7.4.2.1.2.1); the incidence of deaths after 30 days of last dose was similar in each treatment arm (43 [20.1%] vs 22 [20.2%]; Section 2.7.4.2.1.2.2).

In Study XL184-301, the incidence of death through 30 days of last dose due to disease progression was similar between the cabozantinib arm and the placebo arm (10 [4.7%] vs 5 [4.6%]) but higher in the cabozantinib arm for other causes (12 [5.6%] vs 3 [2.8%]).

Reviewer's comments: One case of sudden death at day 17 of treatment was possibly related to study drug.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

The PK results of the therapeutic dose of XL184 (175 mg PO) were not reported in the QT report by the sponsor. As reported from the primary clinical study report, two hundred subjects had reportable values of C_{max} and AUC(0-6) on C1D1, where corresponding mean values were 541 ng/mL and 2110 h•ng/mL, respectively. On C2D1 (dose day ≥27), C_{max} and AUC (0-6), were 1510 ng/mL and 7190 h•ng/mL, respectively, based on reportable values from 150 subjects.

4.2.8.4.2 Exposure-Response Analysis

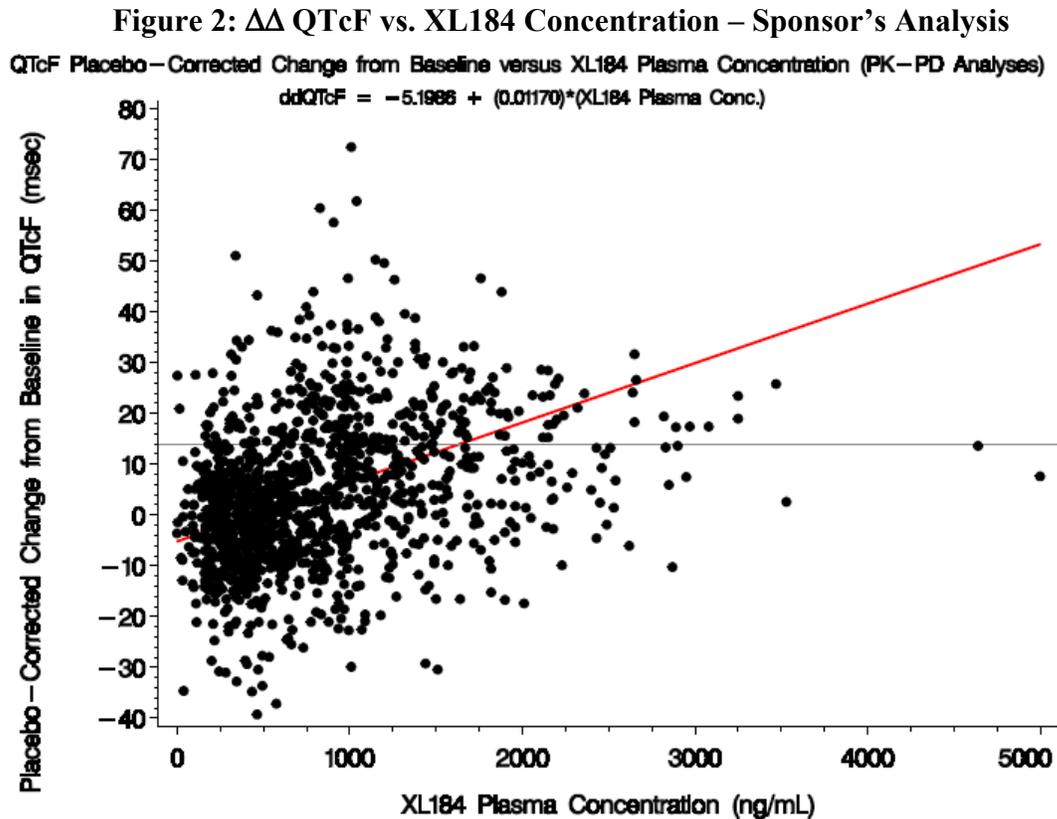
Table 6 details the pharmacokinetic-pharmacodynamic model results showing that the slopes of the relationships for plasma concentration of XL184 and the predicted QTc change at C_{max}.

Table 6: Placebo-corrected change from baseline QTc vs. XL184 Plasma Concentration – Estimates from the Linear Mixed Effects Model

QT Parameter	Slope of Plasma Conc. Effect on ΔΔ QTc	Standard Error of Slope of Plasma Conc. Effect on ΔΔ QTc	p-value	Overall Model Fit
QTcF	0.01170	0.00132	<.0001	<.0001
QTcB	0.00954	0.00149	<.0001	<.0001
QT Parameter	Predicted ΔΔ QTc at Average C _{max} 1640 ng/ml	One-sided Upper 95% Confidence Bound of Predicted ΔΔ QTc [2]		
QTcF	13.9846	16.7978		
QTcB	7.8707	11.0349		

Source: Sponsor's ECG Report, page 21, In Text Table 3-2

Figure 2 shows the relationship between baseline/placebo corrected QTcF and XL184 plasma concentrations for time-matched ECG-concentration measurements.



Reviewer’s Analysis: The relationship between $\Delta\Delta\text{QTcF}$ and XL184 concentrations is visualized in Figure 2 and an evident exposure-response relationship is seen. The sponsor reports a slope for linear regression of plasma XL184 concentrations versus ΔQTcF to be 0.0117 ms/ng/mL (95%CI: 0.009-0.0142), and concludes there was an association (p -value<0.0001). Moreover, the sponsor reports the predicted change in QTcF at the plasma Cmax (i.e., 1640 ng/mL) was 14 ms with an upper 1-sided upper 95% confidence interval bound of 16.8 ms. Despite these findings the sponsor suggest that model predictions of the concentration-QTc effect should be viewed with caution, and may be particularly unreliable at concentrations > 1500 ng/mL due to a lack of high concentration data. Ultimately, the sponsor concludes the PKPD analysis was inconclusive due to the difference in the concentration-effect relationship between ECG evaluation visits after single vs. steady state dosing.

Based on the provided plot, the linearity assumption for the relationship seems to be invalid. At concentrations above 2500 ng/mL, the linear model over predicts all of the observations, suggesting model misspecification. An independent review was conducted to assess this discrepancy and is presented in Figure 6. Independent review yielded a

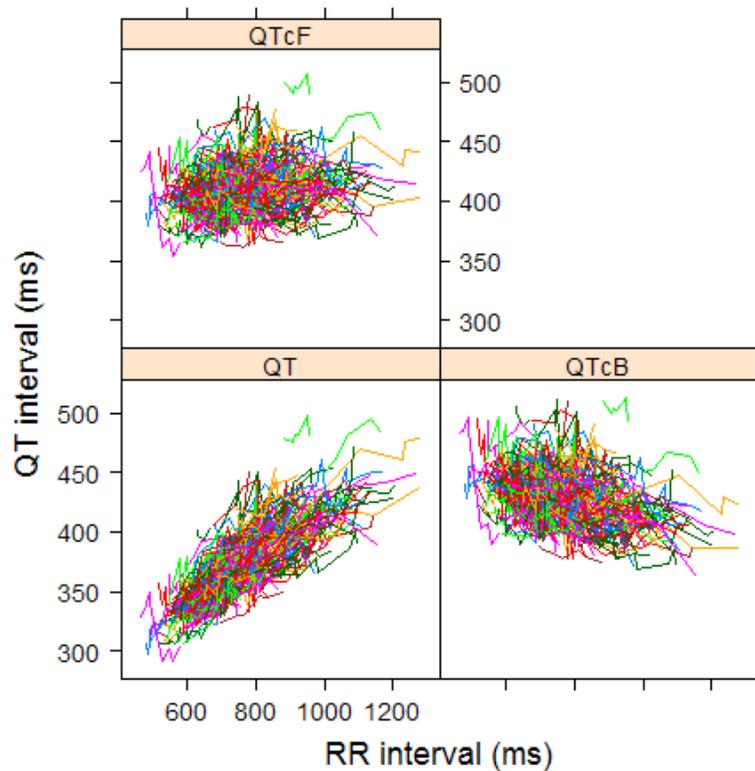
significant positive relationship between XL184 plasma concentrations and $\Delta\Delta QTcF$ with a slope of 7.54 ms per log ng/mL (95%CI: 6.13 – 8.96, p-value = <0.0001). The reviewer's analysis is presented in Figure 8.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods (QTcF and QTcB). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals. The relationship between different correction methods and RR is presented in Figure 3. QTcF was chosen as the correction method for the study.

Figure 3: QT, QTcB, and QTcF, vs. RR (Each Subject's Data Points are Connected with a Line)



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

5.2.1.1 The Primary Analysis for XL184

The reviewer used mixed model to analyze the QTcF change from baseline ($\Delta\Delta\text{QTcF}$) effect on both Day 1 Cycle 1 and Day 1 Cycle 2. The analysis results are listed in the following tables.

Table 7: Analysis Results of $\Delta\Delta\text{QTcF}$ for XL184 175 mg

Cycle and Time (hr)	$\Delta\Delta\text{QTcF}$		
	Mean	StdErr	90% CI
Cycle 1, 2hr	-3.38	1.20	(-5.37, -1.39)
Cycle 1, 4hr	-1.06	1.16	(-2.97, 0.85)
Cycle 1, 6hr	-1.18	1.27	(-3.27, 0.92)
Cycle 2, 0hr	11.31	1.60	(8.67, 13.95)
Cycle 2, 2hr	9.81	1.60	(7.17, 12.44)
Cycle 2, 4hr	9.22	1.61	(6.57, 11.88)
Cycle 2, 6hr	10.26	1.54	(7.72, 12.80)

The largest upper bound of the 2-sided 90% CI for the mean difference between XL184 175 mg and placebo was 13.4 ms.

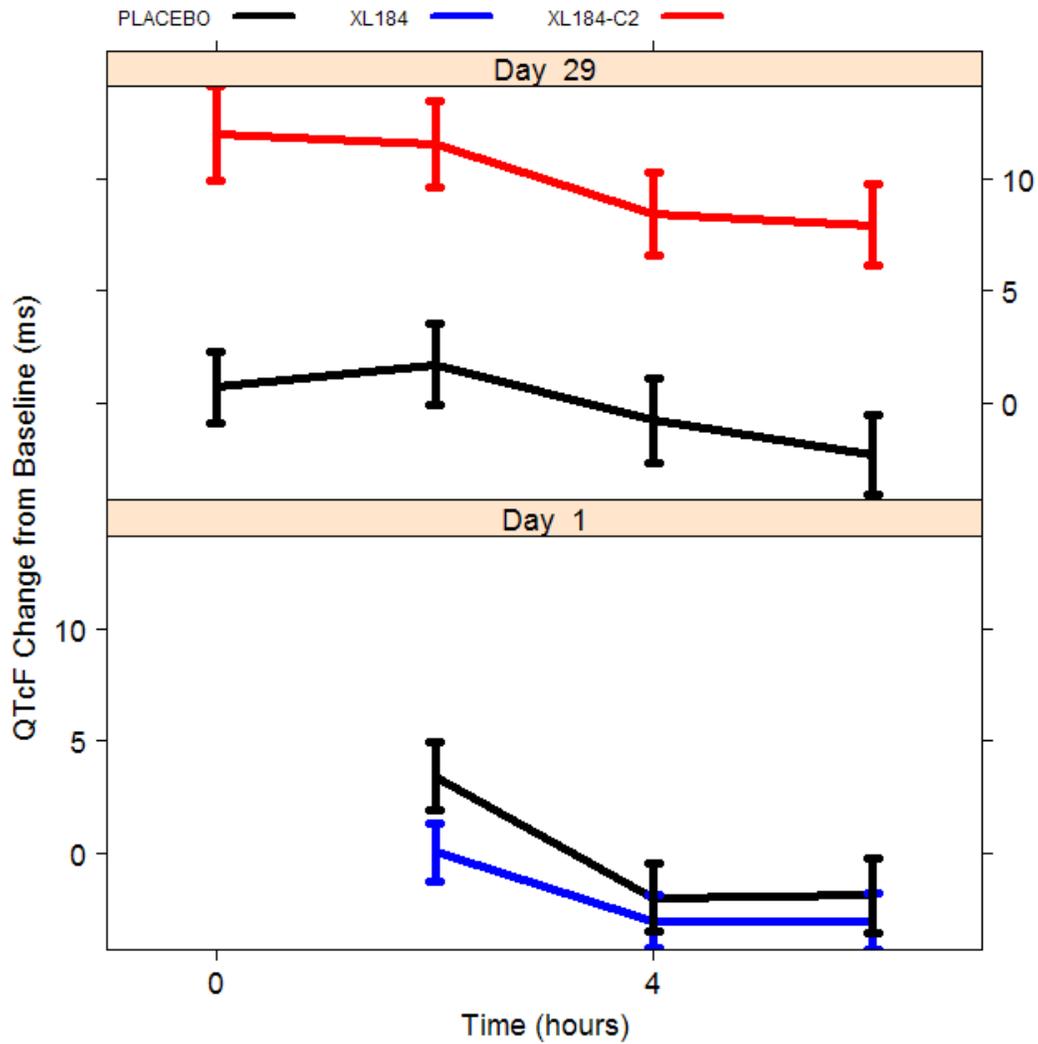
5.2.1.2 Assay Sensitivity Analysis

A moxifloxacin arm was not used in this study, therefore assay sensitivity was not assessed by the reviewer.

5.2.1.3 Graph of ΔQTcF Over Time

Figure 4 displays the time profile of ΔQTcF for different treatment groups for both Cycle 1 (Day 1) and Cycle 2 (Day 29).

Figure 4: Mean and 90% CI Δ QTcF Time Course – Cycle 1 (Day 1, bottom) and Cycle 2 (Day 29, top)



Note: all CIs are unadjusted.

Reviewer's comments: The QTcF difference from placebo was more pronounced during Cycle 2 where XL184 had larger change from baseline in QTcF compared to placebo at all time points evaluated. The largest single delta change from the baseline for XL184 was at pre-dose of Cycle 2 (Day 29) and 2 hours post-dose, both being on average greater than 10 ms.

5.2.1.4 Categorical Analysis

Table 8 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 and 480 ms, and >480 ms for placebo and XL184 arms (Cycles 1 and 2). A total of 3 subjects had a QTcF above 480 ms.

Table 8: Categorical Analysis for QTcF

Treatment Group	Total N	Total N	Value \leq 450 ms	Value \leq 450 ms	450<Value \leq 480 ms	450<Value \leq 480 ms	Value $>$ 480 ms	Value $>$ 480 ms
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
PLACEBO	109	805	102 (93.6%)	778 (96.6%)	6 (5.5%)	19 (2.4%)	1 (0.9%)	8 (1%)
XL184	213	835	202 (94.8%)	815 (97.6%)	10 (4.7%)	19 (2.3%)	1 (0.5%)	1 (0.1%)
XL184-C2	166	636	148 (89.2%)	600 (94.3%)	17 (10.2%)	34 (5.3%)	1 (0.6%)	2 (0.3%)

Table 9 lists the number of subjects as well as the number of observations whose Δ QTcF values are ≤ 30 ms, between 30 and 60 ms, and >60 ms for placebo and XL184 arms (Cycles 1 and 2). A total of 1 subject had a Δ QTcF above 60 ms (during Cycle 2 of XL184 treatment).

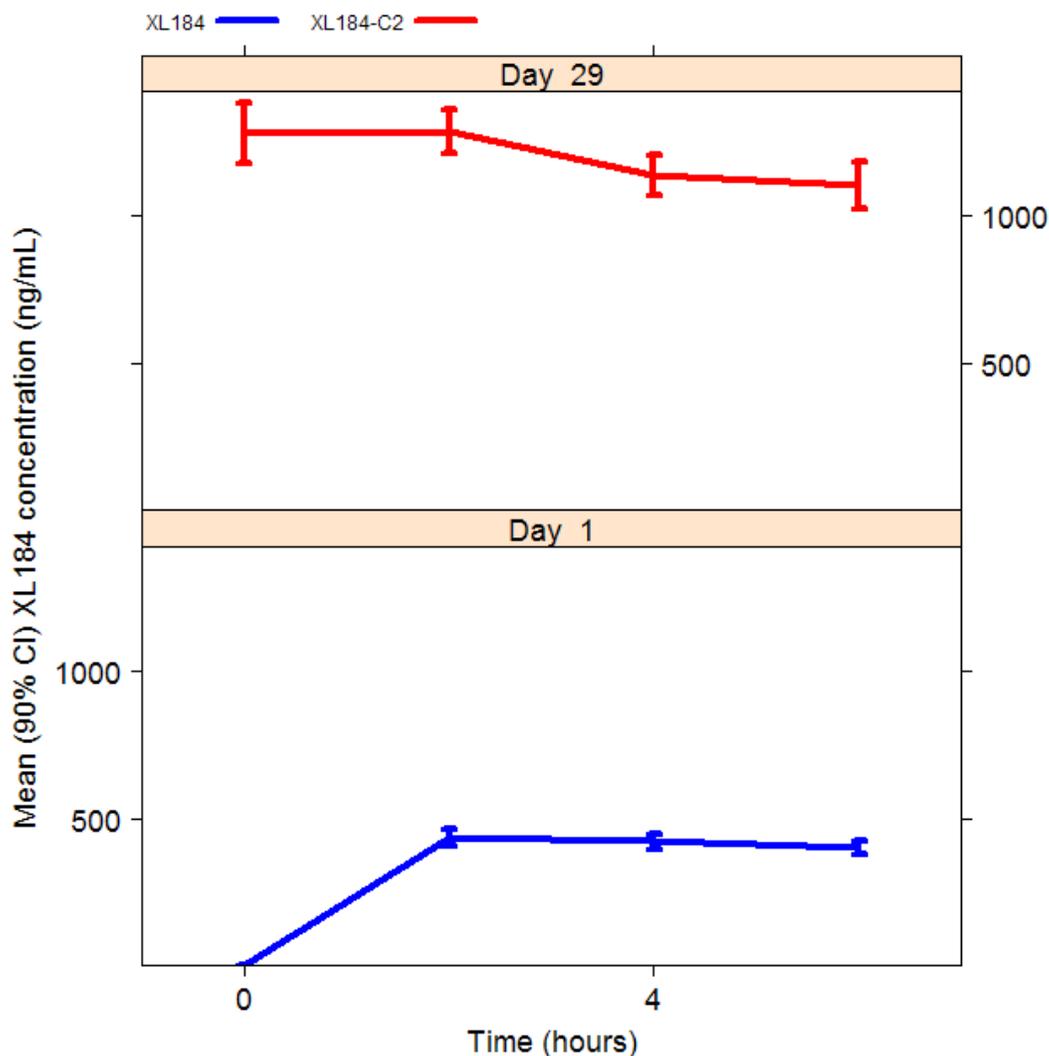
Table 9: Categorical Analysis for QTcF

Treatment Group	Total N	Total N	Value \leq 30 ms	Value \leq 30ms	30<Value \leq 60ms	30<Value \leq 60ms	Value $>$ 60 ms	Value $>$ 60 ms
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
PLACEBO	109	696	109 (100%)	696 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
XL184	213	622	205 (98.1%)	618 (99.4%)	4 (1.9%)	4 (0.6%)	0 (0%)	0 (0%)
XL184-C2	166	636	140 (84.3%)	589 (92.6%)	25 (15.1%)	45 (7.1%)	1 (0.6%)	2 (0.3%)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

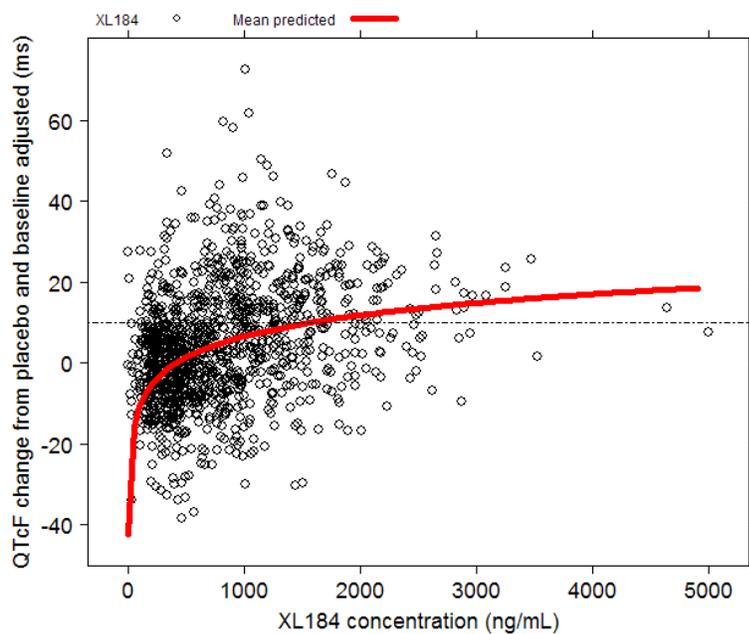
The mean drug concentration-time profile is illustrated in Figure 5.

Figure 5: Mean XL184 Concentration-Time Profiles for 175 mg during Cycle 2 (Day 29) (Red Line) and Cycle 1 Day 1 (Blue Line).



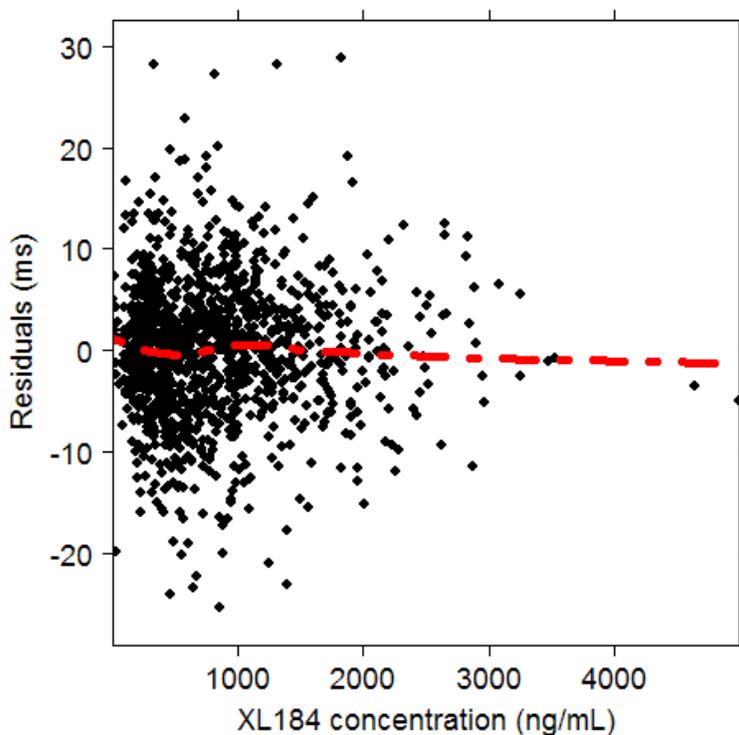
In order to address the concern of model misspecification, an independent review was conducted to ascertain the relationship between $\Delta\Delta\text{QTcF}$ and XL184 concentrations. Based on graphical method and mixed effects linear modeling, a linear model with log-transformed concentrations was chosen as a superior model compared to the Sponsor's model. The exposure-response relationship is depicted in Figure 6. Independent review yielded a positive and significant relationship between log XL184 plasma concentrations and $\Delta\Delta\text{QTcF}$ with a positive slope of 7.54 ms per log ng/mL (95%CI: 6.13 – 8.96, p-value = <0.0001).

Figure 6: $\Delta\Delta$ QTcF vs. log XL184 Concentration – Reviewer’s Analysis



Residuals analysis for the log-linear model yielded an adequate fit (Figure 7).

Figure 7: $\Delta\Delta\text{QTcF}$ vs. log XL184 Concentration (residuals vs. XL184 concentration) – Reviewer’s Analysis



The relationship between $\Delta\Delta\text{QTcF}$ and log XL184 concentrations was investigated by linear mixed-effects modeling.

The following three linear models were considered:

Model 1 is a linear model with an intercept

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

Model 3 is a linear model with no intercept

Table 10 summarizes the results of the XL184 concentration- $\Delta\Delta\text{QTcF}$ analyses. Model 1 was used for further analysis since the model with an intercept was found to fit the data best.

Table 10: Exposure-response Analysis of XL184 Associated $\Delta\Delta\text{QTcF}$ Prolongation

Parameter	Estimate	p-value	Interindividual Variability (CV%)
<i>Model 1: $\Delta\Delta\text{QTcF} = \text{Intercept} + \text{slope} * \log \text{XL184 Concentration}$</i>			

Intercept (ms)	-45.51 (-54.24; -33.77)	<.0001	62.43
Slope (ms per log ng/mL)	7.54 (6.13; 8.96)	<.0001	10.19
Residual Variability (ms)	7.87		

Model 2: $\Delta\Delta QTcF = \text{Intercept} + \text{slope} * \log \text{XL184 Concentration (Fixed Intercept)}$

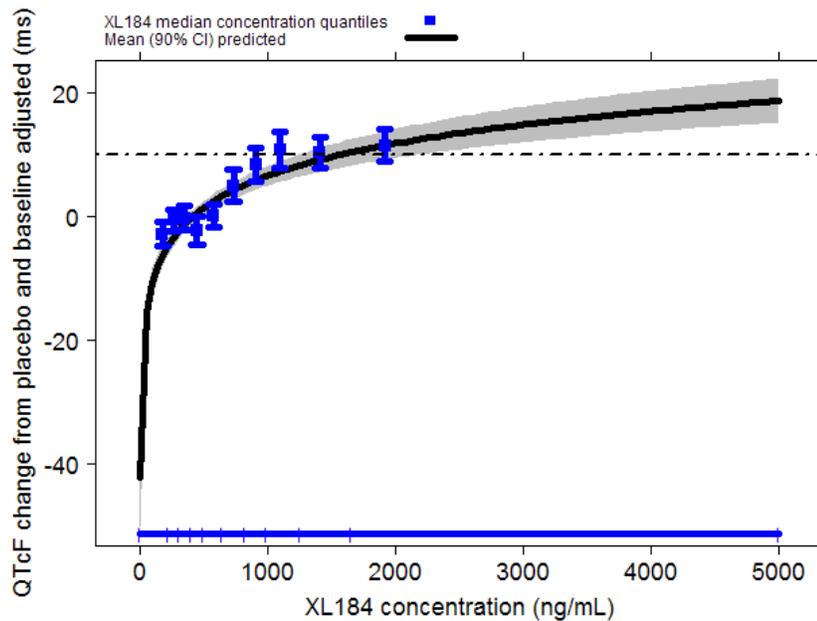
Intercept (ms)	0		11.56
Slope (ms per log ng/mL)	0.196 (0.0067; 0.385)	0.0886	12.76
Residual Variability (ms)	8.09		

Model 3: $\Delta\Delta QTcF = \text{slope} * \log \text{XL184 Concentration (No Intercept)}$

Slope (ms per log ng/mL)	0.598 (0.41; 0.785)	<.0001	1.47
Residual Variability (ms)	10.84		

The goodness-of-fit plot in Figure 8 shows the observed median-quantile XL184 concentrations and associated mean (90% CI) $\Delta\Delta QTcF$ (90% CI) together with the mean (90% CI) predicted $\Delta\Delta QTcF$.

Figure 8: $\Delta\Delta QTcF$ vs. XL184 Concentration, log linear model prediction - Reviewer's Analysis

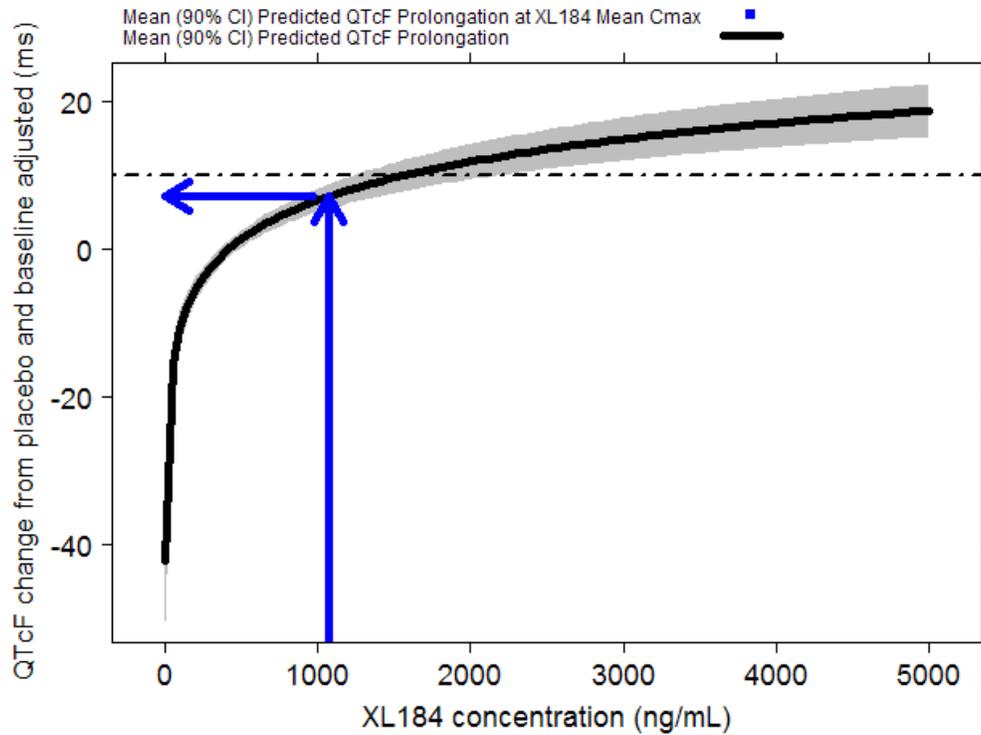


The predicted $\Delta\Delta\text{QTcF}$ at the geometric mean peak XL184 concentrations can be found in Table 11.

Table 11: Predicted $\Delta\Delta\text{QTcF}$ Interval at Geometric Mean Peak XL184 Concentration Using Model 1

Treatment	Geometric C_{max} (ng/mL)	Predicted ΔQTcF (ms)	90% Confidence Interval
175 mg XL184	1070	7.13	(5.5, 8.8)

Figure 9: $\Delta\Delta\text{QTcF}$ vs. XL184 Concentration, log linear model prediction - Reviewer's Analysis



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

There were significant ventricular arrhythmias reported in the study. One sudden death occurred in this study ruled as possibly related to study drug.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 77% of the ECGs were annotated in the primary lead V5, with less than 1% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

(Note: Table below is from the IND (b) (4) submission, and no updated Highlights of Clinical Pharmacology table was provided. Therefore, additional clinical pharmacology information was obtained from the Summary of Clinical Pharmacology document from the current submission NDA 203756)

Therapeutic dose	Include maximum proposed clinical dosing regimen. 175 mg qd	
Maximum tolerated dose	Include if studied or NOAEL dose: MTD = 175 mg qd	
Principal adverse events	<p>Include most common adverse events; dose limiting adverse events most common AEs: gastrointestinal (eg, nausea, vomiting, diarrhea), fatigue; palmar plantar erythrodysesthesia (PPE), skin rash, elevated liver function tests, thrombotic events, hypertension and increased amylase and lipase.</p> <p>Dose-limiting AEs were alanine aminotransferase elevation, aspartate aminotransferase elevation, mucositis, PPE, and increased lipase (based on XL184-001 data)</p>	
Maximum dose tested	Single Dose	Specify dose: Not Available (only multiple doses testing in clinical studies)
	Multiple Dose	Specify dosing interval and duration: 250 mg qd
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC Cmax: 570 ng/mL (36.4%); AUC _{0-24h} on Day 1 after daily dosing: 9560 ng*h/mL (33%). Note: AUC _{0-24h} on Day 1 for XL184 is lower than AUC _{0-inf} for single dosing.
	Multiple Dose	Mean (%CV) Cmax and AUC 2040 (23.9%) ng/mL for Cmax and 38300 (33.4%) ng*hr/mL for AUC
Range of linear PK	Specify dosing regimen: 0.08 mg/kg qd to at least 11.52 mg/kg qd, Powder in Bottle formulation, 5&9 regimen (approximately equivalent to 1 mg to at least 145 mg, capsule qd)	
Accumulation at steady state	Mean (%CV); specify dosing regimen: 5.1 fold (72%), daily dosing	
Metabolites	Include listing of all metabolites and activity: Three metabolites (M1, M4, and M6) were detected in human liver microsomes.	
Absorption	Absolute/Relative Bioavailability	Mean (%CV): 59% (26%) in dogs
	Tmax	<ul style="list-style-type: none"> • Median (range) for parent: 2 hours (2-24 hours) • Median (range) for metabolites: NA
Distribution	Vd/F or Vd	Mean (%CV): 431L (25%)
	% bound	Mean (%CV): 99.7 (0.05%) in human plasma
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated: Not available at this time • Other routes: Not available
	Terminal t _{1/2}	• Mean (%CV) for parent: 91 hours (36%)

		<ul style="list-style-type: none"> • Mean (%CV) for metabolites: Not available
	CL/F or CL	Mean (%CV): 4.6 L/hr (34%)
Intrinsic Factors	Age	Specify mean changes in C _{max} and AUC Not Available
	Sex	Specify mean changes in C _{max} and AUC Not Available
	Race	Specify mean changes in C _{max} and AUC Not Available
	Hepatic & Renal Impairment	Specify mean changes in C _{max} and AUC Not Available
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in C _{max} and AUC: Not Available (DDI studies planned)
	Food Effects	Specify mean changes in C _{max} and AUC and meal type (i.e., high-fat, standard, low-fat) Not available (food effect study planned)
Expected High Clinical Exposure Scenario	Describe worst case scenario and expected fold-change in C _{max} and AUC. The increase in exposure should be covered by the supra-therapeutic dose. Expected exposure is close to that from 175 mg.	

Additional Clinical Pharmacology Information from Summary of Clinical Pharmacology

Study Report No.	Study Objective	Study Design	Treatments (oral dose, dosage form)	Study Population	PK Parameters for 100 or 175 mg XL184 L-malate for Daily dosing mean (%CV) [No. of Subjects]		
					C _{max} (ng/mL)	AUC _{0-24h} (ng h/mL)	Accumulation Factor
XL184-001	Evaluate safety, tolerability, MTD, and PK	Phase 1 Dose Escalation	175 mg XL184 L-malate caps	Cancer subjects (Advanced malignancies including MTC)	570 (43) ^b [N=35] 2220 (37) ^c [N=29]	8228 (34) ^b [N=34] 37850 (43) ^c [N=26]	4.6 (52) ^a [N=29] 5.4 (64) ^d [N=25]
XL184-201	Evaluate objective response rate, safety and tolerability	Phase 2, Group A	175 mg XL184 L-malate caps	Cancer subjects (GB)	566 (47) ^b [N=40] 1660 (40) ^d [N=11]	ND ^b ND ^d	3.2 (39) ^a [N=10]
XL184-301	Evaluate PFS for XL184 treatment vs. placebo	Phase 3, Pivotal Study	175 mg XL184 L-malate caps	Cancer subjects (MTC)	541 (42) ^b [N= 200] 1640 (43) ^d [N= 90]	ND ^b ND ^d	3.6 (66) ^a [N= 86]
XL184-012	Metabolism, excretion, and PK of XL184	Phase 1, Mass Balance	175 mg XL184 L-malate (100 µCi ¹⁴ C-XL184), solution	Healthy male volunteers	1250 (19) ^b [N=8]	14300 (18) ^b [N=8]	NA
XL184-016 ^a	Bioequivalence (b) (4)	Phase 1, Bioequivalence	100 mg XL184 L-malate caps	Healthy volunteers	294 (61) [N=43]	3980 (55) [N=43]	NA

^a Studies described in detail in Section 2.7.1 (Summary of Biopharmaceutics); ^b Day 1; ^c Day 19; ^d Day 29; ^e C_{max} ratio (Day 19 or 29/Day1); ^f AUC ratio (Day 19/Day1); MTC = medullary thyroid cancer; GB = glioblastoma multiforme; ND (not determined); NA (not applicable)

Source: Summary of Clin Pharm, In text Table 2, page 20

Study Report No.	Study Objective	Study Design	Treatments (oral dose, dosage form)	No. Subjects* (M/F) Population Median Age (range)	Pharmacokinetic Parameters ^b					
					gMean C _{max} (ng/mL)	Ratio % gMean C _{max} (Test/Ref) [90% CI]	gMean AUC _{0-t} (h·ng/mL)	Ratio % gMean AUC _{0-t} (Test/Ref) [90% CI]	gMean AUC _{0-inf} (h·ng/mL)	Ratio % gMean AUC _{0-inf} (Test/Ref) [90% CI]
XL184-004 ^c	Comparative BA study of XL184 L-malate capsule under fasted and fed conditions.	Randomized, single-dose, two-period, two-sequence crossover Study	Test ^d : 175 mg XL184 L-malate caps (1x100mg + 3x25mg), [Fed] Reference ^d : 175 mg XL184 L-malate caps (1x100mg + 3x25mg), [Fasted]	56 (26/30) Healthy volunteer 38 yr (18-55)	709 505	140.51% [117.93-167.41%]	89,800 57,000	157.37% [135.75-182.44%]	95,200 60,700	156.95% [135.13-182.31%]
XL184-006	Effect of CYP3A4 inducer rifampin on XL184 PK	Two treatment, single sequence, crossover	Test ^d : 175 mg XL184 L-malate caps single dose + rifampin (600 mg qd x 31) Reference ^d : 175 mg XL184 L-malate caps single dose	28 (16/12) Healthy volunteer 34 yr (22-49)	574 532	107.84% [94.38-123.23%]	13,000 53,500	24.25% [22.11-26.59%]	13,000 56,500	23.03% [20.89-25.40%]

Study Report No.	Study Objective	Study Design	Treatments (oral dose, dosage form)	No. Subjects* (M/F) Population Median Age (range)	Pharmacokinetic Parameters ^b					
					gMean C _{max} (ng/mL)	Ratio % gMean C _{max} (Test/Ref) [90% CI]	gMean AUC _{0-t} (h·ng/mL)	Ratio % gMean AUC _{0-t} (Test/Ref) [90% CI]	gMean AUC _{0-inf} (h·ng/mL)	Ratio % gMean AUC _{0-inf} (Test/Ref) [90% CI]
XL184-007	Effect of CYP3A4 inhibitor ketoconazole on XL184 PK	Two treatment, single sequence, crossover	Test ^d : 175 mg XL184 L-malate caps single dose + keto (400 mg qd x 27) Reference ^d : 175 mg XL184 L-malate caps single dose	28 (19/9) Healthy volunteers 37 yr (22-54)	438 449	97.37% [83.07-114.11%]	61,400 45,700	134.30% [122.45-147.30%]	66,200 48,000	138.05% [124.51-153.07%]
XL184-008.PK.001	Effect of XL184 on PK of CYP2C8 substrate rosiglitazone	Two treatment, single sequence, crossover	Test ^e : rosi (4 mg) single dose + 175 mg XL184 L-malate caps (≥125 mg qd x ≥21) Reference ^e : rosi (4 mg) single dose	40 (27/13) Cancer subjects 60 yr (41-79)	305 294	103.96% [92.61-116.71%]	1622 1550	104.64% [99.06-110.53%]	1714 1609	106.56% [100.80-112.65%]

^a Table shows enrolled subjects. PK analysis population =47/47 [test/reference XL184-004 except AUC_{0-inf}=46/46]; =25/28 [test/reference XL184-006]; = 27/28 [test/reference XL184-007, except AUC_{0-inf} = 25/26] , = 32/32 [test/reference XL184-008.PK.001]; ^b gMean (geometric mean); ^c detailed study description provided in Section 2.7.1.3.2; ^d Lot numbers L0209927 (25 mg XL184 L-malate), L0301013 (100 mg XL184 L-malate); ^e Rosiglitazone PK data presented; Lot numbers L0205272 and L0301013 (100 mg XL184 L-malate), and L0209383, L0209927, and L0303838 (25 mg L-malate)

Source: Summary of Clin Pharm, In text Table 3, pages 21-22

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/s/

SATJIT S BRAR
10/31/2012

KEVIN M KRUDYS
10/31/2012

MONICA L FISZMAN
10/31/2012

NORMAN L STOCKBRIDGE
10/31/2012

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: October 19, 2012

TO: Gina Davis, M.T., Regulatory Project Manager
Ruthann Giusti, M.D., Medical Officer
Division of Oncology Products II

FROM: Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 203756

APPLICANT: Exelixis

DRUG: Cometriq[®] (cabozantinib)

NME: Yes

THERAPEUTIC
CLASSIFICATION: Priority Review

INDICATION: Treatment of medullary thyroid cancer

CONSULTATION REQUEST DATE: June 20, 2012
CLINICAL INSPECTION SUMMARY DATE: October 19, 2012
DIVISION ACTION GOAL DATE: November 29, 2012
PDUFA DATE: November 29, 2012

I. BACKGROUND:

The Applicant submitted this NDA to support the use of Cometriq® (cabozantinib) for the indication of treatment of medullary thyroid cancer.

The pivotal study Protocol XL 184-301, entitled “An International, Randomized, Double-Blinded, Phase 3 Efficacy Study of XL184 versus Placebo in Subjects with Unresectable, Locally Advanced, or Metastatic Medullary Thyroid Cancer” was submitted and inspected in support of the indication.

Dr. Shah’s site below was selected because it was one of the few sites to enroll 3% or more of the total number of subjects in the trial. This site also had a hazard ratio well below that of the overall estimates. The foreign sites were selected for inspection because there is insufficient domestic data.

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ Site #/ # of Subjects	Inspection Dates	Final Classification
Shah, Manisha, MD The Ohio State University James Cancer Hospital 320 West 10th Avenue Columbus, OH 43210	XL 184-301/ Site 1315/ 10 (randomized)	30 Jul-15 Aug 2012	VAI. Pending final classification.
Elisei, Rossella, MD U.O.Endocrinologia 1 Univ.- Dipartimento di Endocrinologia e Metabolismo Ortopedia e Traumatologia Medicina del Lavoro Ospedale Cisanello – Azienda Ospedaliero Universitaria Pisana Via Paradisa 2 56124 Pisa, Italy	XL 184-301/ Site 3908/ 20 (randomized)	7-14 Sep 2012	NAI. Pending final classification.
Bockisch, Andreas, MD Universitätsklinikum Essen Klinik für Nuklearmedizin Hufelandstr. 55 45122 Essen, Germany	XL 184-301/ Site 4902/ 12 (randomized)	14-21 Sep 2012	NAI. Pending final classification.
Exelixis (sponsor) 210 East Grand Avenue, P.O. Box 511 South San Francisco, CA 94083-0511	XL 184-301	10- 27 Sep 2012	VAI. Pending final classification.

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

1. Manisha Shah, M.D.
The Ohio State University
James Cancer Hospital
320 West 10th Avenue
Columbus, OH 43210

- a. What was inspected:** At this site, 14 subjects were screened and 10 subjects were randomized to the study. Records reviewed included, but were not necessarily limited to, informed consent forms, case report forms, progress charts, laboratory reports, ECGs, drug accountability records, IRB, sponsor, and CRO correspondence, primary efficacy endpoints, and subject randomization and discontinuation.
- b. General observations/commentary:** A Form FDA 483 was issued at the conclusion of the inspection for not reporting SAEs within 24 hours of awareness of the event. The observation noted that Subject 3002 experienced tachycardia, agitation, and confusion in September and October of 2009. The site was informed of these events on October 16, 2009, but did not report these SAEs until October 20, 2009. This same subject expired on [REDACTED] ^{(b) (6)}, with the site being informed on the same day. The sponsor was not notified of this SAE until November 25, 2009.
- c. Assessment of data integrity:** These observations of delayed reporting of SAEs do not significantly affect the evaluation of safety and/or efficacy. Other than these delayed SAE reports, the study appears to have been conducted adequately, and the data submitted by this site may be used in support of the respective indication.

Note: The observations noted above for Dr. Shah's site are based on a review of preliminary communications. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

2. Rossella Elisei, M.D.
U.O.Endocrinologia 1 Univ.-
Dipartimento di Endocrinologia e Metabolismo
Ortopedia e Traumatologia
Medicina del Lavoro Ospedale
Cisanello – Azienda Ospedaliero
Universitaria Pisana
Via Paradisa 2
56124 Pisa, Italy

- a. What was inspected:** At this site, 31 subjects were screened and 20 subjects were enrolled. An audit of the records of six subjects was conducted. Signed informed consent forms were present for all subjects. Records reviewed included, but were not limited to, source documents, CRO and site correspondence, primary efficacy data, adverse events, and concomitant medications.

- b. General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records indicated the presence of a significant number of queries by the CRO, (b) (4), related to inadequate source documentation. The sponsor's written response of October 5, 2012, related to findings during the sponsor inspection, stated that CRFs were sometimes used as source documents at this site. In such cases, data verification between the CRF and supporting source documentation would not be possible. These instances of lack of data verification at this site were addressed by the monitor in a series of interim monitoring visit reports. The monitor noted that this lack of data verification was "not resolvable" and that "Notes to File" would be prepared documenting this issue. There is no regulation forbidding the use of CRFs as source documentation although the sponsor did agree that such data entry practices should have been clearly identified prior to implementation. Dr. Elisei's written response of October 18, 2012, notes her site's intent to create a query database to ensure that queries are appropriately addressed. No significant discrepancies or regulatory violations were noted.
- c. Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

Note: The observations noted above for Dr. Elisei's site are based on a review of preliminary communications. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

3. Andreas Bockisch, M.D.
Universitätsklinikum Essen
Klinik für Nuklearmedizin
Hufelandstr. 55
45122 Essen, Germany

- a. What was inspected:** At this site, 14 subjects were screened, 12 subjects were enrolled, and 10 subjects completed the study. The study records of two subjects who failed screening and five subjects who were randomized were audited. Signed informed consent forms were present for all screened subjects, although Subject 3006 did not sign the most current version of the form. Records reviewed included, but were not limited to, source documents, physical examinations, EKGs, SAE reports, and laboratory results.
- b. General observations/commentary:** A Form FDA 483 was not issued at the conclusion of the inspection. Several minor discrepancies between source documents and CRFs and/or line listings were noted for Subjects 3002 and 3003. Subject 3005 experienced an SAE of back pain that was reported four days later. Subject 3010 had documented disease progression on August 16, 2011, with a report signed on August 23rd, but the subject was not informed to stop study medication until September 6, 2011. Subject 3003 had several low hemoglobin results not reported in the listings of abnormal laboratory results. Similarly, Subject 3004 had an elevated WBC count not reflected in the data listings. ECGs for six of 12 subjects were conducted without

documented two-minute intervals between ECGs. Review of the records noted above revealed no significant discrepancies or regulatory violations.

- c. Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

Note: The observations noted above for Dr. Bockisch's site are based on a review of preliminary communications. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

4. Exelixis

210 East Grand Avenue, P.O. Box 511
South San Francisco, CA 94083-0511

- a. What was inspected:** This sponsor inspection focused on the following clinical investigators: Dr. Manisha Shah (Site #1315), Dr. Rosella Elisei (Site #3908), and Dr. Andreas Bockisch (Site #4902). Records reviewed during the inspection included, but were not necessarily limited to, monitoring visit reports (MVRs), CRO (b) (4) and sponsor correspondence and meeting minutes, monitoring plans, informed consent process documentation, SOPs, SAE reporting, and, as an assessment of the sponsor's actions in dealing with a lot of investigational drug product that failed dissolution testing, the records documenting the withdrawal of Lot #303614.

- b. General observations/commentary:** A Form FDA 483 was issued at the conclusion of the inspection. The observations included several instances of inadequate source documentation and a lack of oversight resulting in two subjects (3908-3010 and 3908-3012) not having the study drug available for a period of time and one subject (3908-3004) being overdosed by the site (i.e., the subject was dosed twice on Cycle 10 Day 1 having taken the drug at home and then again at the study visit of the same day). A lack of documentation of the informed consent process was also noted at Dr. Elisei's site; i.e., whether subjects were given a copy of the consent form, given time to review the material, asked if they had any questions, etc. Dr. Elisei's written response of October 18, 2012, states her site's commitment to capturing all due data at the time of the signature on the consent form.

Subject 1315-3002 died on (b) (6). The CRO's monitoring visit report noted that multiple laboratory reports were not reviewed and signed in a timely manner.

The sponsor did not adequately document its reviews of MVRs between September 30, 2008, and September 1, 2010, despite its monitoring plan indicating that a certain percentage of the trip reports would be reviewed.

The protocol stated that all SAEs must be reported to the sponsor within 24 hours of the investigator's awareness of the event. The SAE Reporting Form did not contain or collect the information necessary to determine whether SAEs were reported within 24 hours of knowledge of the event.

The sponsor addressed the observations on the Form FDA 483 in written correspondence dated October 5, 2012. The sponsor acknowledged that CRFs were sometimes used as source documents and that investigator assessments were sometimes entered directly on these forms. The sponsor stated that the use of CRFs as source documents should have been documented. The lack of such documentation and the inconsistent nature of source data entry resulted in the observation of inadequate source data.

With respect to the follow up of MVRs, the sponsor provided an updated, revised SOP dated October 5, 2012, outlining the responsibilities for such review, the process by which findings would be escalated, and the actions required for the resolution of such findings.

The sponsor acknowledged the lack of documentation regarding the informed consent process and referred to the development of its SOP for addressing MVRs. Though documentation of the consent process was lacking, informed consent was obtained from study subjects and documented.

With regards to the expired subject, the sponsor acknowledged the lapse in time for the review of laboratory reports noting that there were multiple phone calls and meetings with the involved site and the CRO ((b) (4)) to address this issue. The sponsor stated that it did not discuss this matter directly with the clinical investigator but noted that there were improvements in the timeliness of the review process as the study progressed, particularly with the addition of a new study coordinator.

The sponsor revised and submitted its SOP on SAE reporting. The SOP was revised to capture the timeline of events related to the reporting of SAEs by clinical investigators.

According to the biopharmaceutics (Product Quality) reviewer, the dissolution specifications for Lot #303614 were determined using an older, defunct dissolution method. This dissolution specification issue for Lot #303614 did not raise any safety concerns.

- c. Assessment of data integrity:** While the observations on the Form FDA 483 appear problematic, particularly with regards to appropriate documentation of what constitutes source documentation, of the timely review of MVRs and laboratory findings, and of the timeliness of SAE reporting, the sponsor has developed SOPs and committed to their implementation to assure the identification of source documentation and the timely review of study reports. Despite such lapses in documentation, the studies appear to have been conducted at the site level in such a manner that the data may be relied upon for assessments of safety and efficacy. OSI finds the sponsor's written response acceptable, the studies appear to have been conducted adequately, and the data submitted by the sponsor appear acceptable in support of the respective indication.

The review division may wish to consider excluding data from Subjects 3908-3904, 3908-3010, and 3908-3012 due to study drug administration irregularities noted in (b.) above.

Note: The observations noted above for the inspection of Exelixis are based on a review of a draft EIR and/or preliminary communications. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Shah's, Elisei's and Bockisch's clinical investigator sites were inspected in support of this NDA. Drs. Elisei and Bockisch were not issued Form FDA 483s. Dr. Shah was issued a Form FDA 483 based on the delayed reporting of SAEs. The sponsor, Exelixis was also issued a Form FDA 483, primarily for observations regarding a lack of adequate source and monitoring documentation and delayed SAE reporting. The sponsor's written response noting that CRFs were sometimes used as source documents is adequate if not optimal. The sponsor has implemented SOPs to address source documentation needs and expediting SAE reporting. Overall, the data generated by the clinical sites and submitted by the sponsor appear adequate in support of the respective indication.

The review division may wish to consider excluding data from Subjects 3908-3904, 3908-3010, and 3908-3012 due to study drug administration irregularities noted in 4(b.) above.

Note: The observations noted above for Drs. Shah, Elisei and Bockisch and the sponsor, Exelixis, are based on reviews of draft Establishment Inspection Reports (EIRs) and/or preliminary communications. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIRs.

{See appended electronic signature page}

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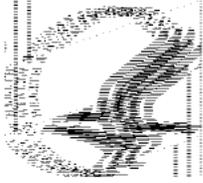
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/s/

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Pediatric and Maternal Health Staff Labeling Review

Date: October 9, 2012 **Date Consulted:** June 6, 2012

From: Jeanine Best, MSN, RN, PNP,
Senior Clinical Analyst
Pediatric and Maternal Health Staff

Through: Melissa Tassinari, PhD, DABT,
Acting Team Leader, Maternal Health
Pediatric and Maternal Health Staff

Lynn Yao, MD,
Acting OND Associate Director
Pediatric and Maternal Health Staff

To: Division of Drug Oncology Products II (DDOP 2)

Drug: COMETRIQ (Cabozantinib Capsules), NDA 203756

Applicant: Exelixis

Subject: Pregnancy and Nursing Mothers Labeling

Materials Reviewed:

- Applicant proposed labeling

Consult Question: DDOP 2 requests that The Pediatric and Maternal Health Staff (PMHS) – Maternal Health Team review and comment on the proposed Pregnancy and Nursing Mothers subsections of cabozantinib capsules labeling.

INTRODUCTION

On May 29, 2012, Exelixis submitted the final portion of a rolling submission NDA for cabozantinib capsules, NDA 203756. Cabozantinib is proposed for the treatment of progressive, unresectable, locally advanced, or metastatic medullary thyroid cancer (MTC)

On June 6, 2012, the Division of Drug Oncology Products II (DDOP 2) consulted the Pediatric and Maternal Health Staff (PMHS) – Maternal Health Team (MHT) - to review the Pregnancy and Nursing Mothers subsections of cabozantinib labeling.

BACKGROUND

Cabozantinib

Is a multi-targeted inhibitor of receptor tyrosine kinases (RTKs) that are implicated in tumor growth and angiogenesis, pathologic bone remodeling, and metastatic progression of cancer.

Cytokine receptors, including RTKs are critical control components for embryonic development with c-kit and PDGFR α (platelet derived growth factor receptor) having a major role in placental development and angiogenesis.¹ Human embryofetal toxicity is expected based on cabozantinib's mechanism of action. Animal reproduction studies with cabozantinib at exposures much lower than the human exposure at the recommended daily dose resulted in embryolethality and teratogenicity

DISCUSSION and CONCLUSIONS

Pregnancy and Nursing Mothers Labeling

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule while still complying with current regulations. The first paragraph in the pregnancy subsection of labeling summarizes available data from published literature, outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy and lactation. A further goal of this restructuring is to make the pregnancy and lactation section of labeling a more effective tool for communication to clinicians.

¹ Ali R, Ozkalemkas F, Kimya Y, Koksall N, Ozkocaman V, Gulten T, Yorulmaz H, Tunali A: Imatinib use during pregnancy and breast feeding: a case report and review of the literature. Archives of Gynecologiacl Obstetrics; 2009; 280: 169-175

PMHS RECOMMENDATIONS

The following labeling recommendations were discussed at a DDOP 2 labeling meeting held on October 1, 2012.

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----WARNINGS AND PRECAUTIONS-----

- Embryofetal toxicity: Can cause fetal harm. Advise women of potential risk to a fetus (5.13, 8.1).

5 WARNINGS AND PRECAUTIONS

5.13 Embryofetal Toxicity

COMETRIQ can cause fetal harm when administered to a pregnant woman. Cabozantinib was embryolethal in rats at exposures below the recommended human dose, with increased incidences of cardiovascular and skeletal malformations in rats, and visceral variations and malformations in rabbits. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving taking this drug, the patient should be apprised of the potential hazard to the fetus [*see Use in Specific Populations (8.1)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

Risk Summary

Based on its mechanism of action, COMETRIQ can cause fetal harm when administered to a pregnant woman. Cabozantinib was embryolethal in rats at exposures below the recommended human dose, with increased incidences of cardiovascular and skeletal malformations in rats, and visceral variations and malformations in rabbits. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Animal Data

In an embryo-fetal development study in rats, increased loss of pregnancy compared to controls was observed at doses as low as 0.03mg/kg (<1% of the clinical plasma exposure at the recommended human dose).

(b) (4)

In pregnant rabbits administered cabozantinib daily during organogenesis there were findings of visceral malformations and variations including splenic size reduction and missing lung lobe at 3mg/kg (b) (4)

8.3 Nursing Mothers

It is unknown whether cabozantinib or its metabolites are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Cometriq, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.6 Females and Males of Reproductive Potential

Contraception

Use effective contraception during treatment and up to 4 months after completion of therapy.

Infertility

There are no data on the effect of COMETRIQ on human fertility. Results from animal studies indicate that cabozantinib can impair male and female fertility [*see Nonclinical Toxicology (13.1)*]

17 PATIENT COUNSELING INFORMATION

- Advise females of reproductive potential to use effective contraception during therapy and for at least four months following their last dose of COMETRIQ.
- Advise breast-feeding mothers to discontinue nursing while receiving COMETRIQ therapy.

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/s/

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10/09/2012

MELISSA S TASSINARI
10/11/2012

LYNNE P YAO
10/15/2012

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Label, Labeling and Packaging Review

Date: September 11, 2012

Reviewer: James Schlick, RPh, MBA
Division of Medication Error Prevention and Analysis

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

Deputy Director: Kellie Taylor, Pharm.D., MPH
Division of Medication Error Prevention and Analysis

Drug Name and Strengths: Cometriq (Cabozantinib) Capsules
20 mg and 80 mg

Application Type/Number: NDA 203756

Applicant: Exelixis, Inc.

OSE RCM #: 2012-1232

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

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1 INTRODUCTION

This review evaluates the proposed container label, carton, and insert labeling for Cometriq (Cabozantinib), NDA 203756, for areas of vulnerability that could lead to medication errors.

1.1 PRODUCT INFORMATION

The following product information is provided in the May 31, 2012 proprietary name submission.

- Active Ingredient: Cabozantinib (S) - malate
- Indication of Use: Indicated for the treatment of patients with progressive, unresectable locally advanced or metastatic medullary thyroid cancer (MTC).
- Route of Administration: Oral
- Dosage Form: Capsules
- Strength: 20 mg and 80 mg
- Dose and Frequency: 140 mg once daily. If dose reductions occur due to toxicity, Cometriq can be given at 100 mg and 60 mg once daily
- How Supplied:
 - 20-mg gelatin capsules are grey with “XL184 20mg” printed in black on the body of the capsule.
 - 80-mg gelatin capsules are Swedish orange with “XL184 80mg” printed in black on the body of the capsule.
- Storage: Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (between 59°F and 86°F).
- Container and Closure Systems:
 - One blister card containing a 7-day supply of capsules for a 140 mg daily dose (one 80-mg and three 20-mg capsules per dose)
 - One blister card containing a 7-day supply of capsules for a 100 mg daily dose (one 80-mg and one 20-mg capsule per dose)
 - One blister card containing a 7-day supply of capsules for a 60 mg daily dose (three 20-mg capsules per dose)
 - Bottle containing sixty 20-mg capsules

2 METHODS AND MATERIALS REVIEWED

DMEPA searched the FDA AERS database for cabozantinib medication error reports. We also reviewed the Cometriq labels and labeling submitted by the Applicant.

2.1 SELECTION OF MEDICATION ERROR CASES

We searched the FDA Adverse Event Reporting System (AERS) database using the strategy listed in Table 1.

Table 1: AERS Search Strategy	
Date	No Date Range
Drug Names	Active ingredient: Cabozantinib Verbatim term: Cabozanti%
MedDRA Search Strategy	Medication Errors (HLGT) Product Packaging Issues HLT Product Label Issues HLT Product Quality Issues (NEC) HLT

The AERS database search yielded zero cases.

2.2 LITERATURE SEARCH

We searched PubMed and the ISMP publications listed below on July 6, 2012, for additional cases and actions concerning Cometriq. The PubMed search consisted of the search terms “cabozantinib” and “medication error”. The ISMP search consisted of the search term “cabozantinib”. The following ISMP newsletters were searched:

- ISMP Acute Care Newsletter
- ISMP Community Edition
- ISMP Nursing Edition
- ISMP Canada Safety Bulletin

The searches yielded zero cases.

2.3 LABELS AND LABELING

Using the principals of human factors and Failure Mode and Effects Analysis¹ along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted May 21, 2012 (Appendix B)

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

- Carton Labeling submitted May 21, 2012 (Appendix C)
- Insert Labeling submitted May 21, 2012
- Sample of Blister card obtained via email communication dated June 7, 2012

2.4 PREVIOUSLY COMPLETED REVIEWS

DMEPA had previously reviewed the name Cometriq in OSE review 2011-2394 and provided comments to the Applicant about strength selection (80 mg and 20 mg) and the proposed doses (60 mg, 100 mg, 140 mg).

3 INTEGRATED SUMMARY OF MEDICATION ERROR RISK ASSESSMENT

DMEPA notes that the strengths (20 mg and 80 mg) proposed by the Applicant in their NDA submission require the administration of multiple capsules to achieve the doses of 60 mg, 100 mg and 140 mg, and therefore does not provide the patient with the simplest and most convenient dosing. The conditionally acceptable proprietary name letter for Cometriq (IND (b) (4) OSE 2011-2394) dated December 6, 2011 provided the following comments to the applicant to explain their rationale for the 20 mg and 80 mg strengths.

We note that the proposed capsule strengths (20 mg and 80 mg) are inconsistent with the proposed dosing regimen of 140 mg daily. It is not possible to achieve the proposed daily dose when using the 80 mg capsules without the concomitant use of 20 mg capsules, or without taking seven of the 20 mg capsules. The use of two strengths will be prone to medication error since one cannot achieve a daily dose using only the 80 mg capsules, and seven capsules per day places a large pill burden on patients and may lead to non-compliance. Please consider revising your capsule strengths to better reflect your proposed daily dose and to decrease pill burden for the patient.

Because the Applicant submitted the same product strengths with the NDA submission and did not provide a rationale, DMEPA requested that they explain their rationale in an email dated June 25, 2012. The Applicant provided their response below:

The 20- and 80-mg capsule strengths were used in the Phase 3 pivotal study XL184-301 (where the strengths were expressed as the malate salt weight equivalents, 25 mg and 100 mg, respectively) and also are the proposed commercial strengths. At the time DMEPA comments were received in December 2011, the NDA application was being submitted and the formulation and process had been finalized and locked. No changes to strengths or formulation could be made at that time, as a bioequivalence study would have been necessary.

The Sponsor acknowledges the required combination of two capsule strengths, particularly for the 140- and 100-mg doses. Experience from the Phase 3 study suggest that subject compliance regarding the administered dose was not an issue, as few subjects took non-protocol-specified doses (and for short durations). Regardless, the proposed commercial packaging was designed to help facilitate patient dosing and potentially reduce the incidence of dosing errors. A blister card contains 7 days of doses and will be available for all three doses. The daily dose is presented in a horizontal line, with instructions to take all capsules across a row. Alternatively, a bottle will be available for the 20-mg capsules, to provide a simpler presentation of single-strength dosing (60 mg daily dose) for patient convenience. It is not intended that the 140-mg dose will be administered as seven 20-mg capsules.

(b) (4)

Therefore, DMEPA will provide comments to the Division of Oncology Products 2 (DOP2) and the Applicant to help minimize medication error risk with the current proposed packaging configurations given the constraints of formulating a dose-specific capsule for this product.

DMEPA also obtained sample blister cards to determine if the capsules inside the blister foil would be prone to breakage when attempting to remove them from the foil. Also, we attempted to determine how difficult it is to remove the capsule from the foil. The directions were followed to remove the capsule from the foil. On 12 separate attempts, the capsule could be removed without breaking or cracking. DMEPA also found that the backing could be removed easily exposing the blister foil. Thus, the capsules could be removed easily from the foil.

4 CONCLUSIONS

DMEPA concludes that the proposed labels and labeling can be improved to promote the safe use of the product. Specifically, recommendations include changes to the blister cards and cartons to minimize the risk of taking the dose incorrectly. Additionally, labeling changes are recommended in the package insert to change the negative statement “do not take with food” to a positive statement “take on an empty stomach”.

The Sponsor has proposed a unique packaging configuration with the daily dose blister cards. DMEPA has limited experience with these packaging configurations. However, we are providing recommendations based on our experience of medication errors.

5 RECOMMENDATIONS

We forwarded our recommendations to ONDQA. However, we have not had an opportunity to review and discuss the comments with them. We look forward to discussing our comments at the upcoming labeling meetings. Based on this review, DMEPA recommends the following be implemented prior to approval of this NDA:

A. 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).

B. Carton Labeling and Container Label for 140 mg Dose

1. 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.

C. Container Label for 20 mg Bottle

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

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

1. 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.

140 mg Daily Dose Pack

Each row contains a 140 mg daily dose comprised of:

- one 80 mg orange capsule and
- three 20 mg grey capsules

2. Remove the statements (b) (4) located below the dose presentation on the principal display panel.
3. 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.”
4. 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.
5. 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.
6. 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.
7. 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.**”
8. 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:

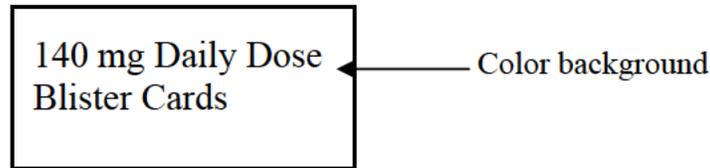
Seven 80 mg capsules

Twenty-one 20 mg capsules

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

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

1. 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:



2. 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.
3. For each place it occurs on the carton, remove the asterisks at the beginning of the statement (b) (4)
4. Revise to include National Drug Code (NDC) numbers on each carton.

F. Insert Labeling

1. Highlights of Prescribing Information – Dosage and Administration
 - a. Revise the statement (b) (4) to read “Take Cometriq on an empty stomach at least 1 hour before or 2 hours after eating.”
 - b. Add the following statement: “Capsules should be swallowed whole”
2. Dosage and Administration, Section 2
 - a. Revise the statement “ (b) (4) to read “The recommended daily dose of COMETRIQ is 140 mg daily, taken on an empty stomach at least 1 hour before or 2 hours after eating.”

- b. Revise the statement [REDACTED] (b) (4) [REDACTED] to read “COMETRIQ capsules should be swallowed whole. Do not open capsules.”
3. How Supplied/Storage and Handling, Section 16.
- a. Add the NDC numbers to this section.
 - b. Revise the statement “Cometriq capsules are supplied as follows:” to read “Cometriq capsules are supplied in cartons containing 4 blister cards in each carton.”
 - c. Revise each of the three statements [REDACTED] (b) (4) [REDACTED] to read “Each blister card contains a 7-day supply of capsules...”
4. Patient Counseling Information, Section 17
- a. Revise the following statement [REDACTED] (b) (4) [REDACTED] to read “Cometriq capsules should be swallowed whole. Do not open capsules.”
 - b. Revise the following statement [REDACTED] (b) (4) [REDACTED] [REDACTED] to read “Take Cometriq on an empty stomach with a full glass of water. Take Cometriq at least 1 hour before or 2 hours after eating.”
5. Patient Information Sheet– How should I take COMETRIQ?
- a. Revise the following statement [REDACTED] (b) (4) [REDACTED] [REDACTED] to read “Take Cometriq on an empty stomach at least 1 hour before or 2 hours after eating.”

If you have further questions or need clarifications, please contact Sue Kang, OSE project manager, at 301-796-4216.

APPENDICES

APPENDIX A. DATABASE DESCRIPTIONS

Adverse Event Reporting System (AERS)

The Adverse Event Reporting System (AERS) is a computerized information database designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The FDA uses AERS to monitor adverse events and medication errors that might occur with these marketed products. The structure of AERS complies with the international safety reporting guidance ([ICH E2B](#)) issued by the International Conference on Harmonisation. Adverse events in AERS are coded to terms in the Medical Dictionary for Regulatory Activities terminology (MedDRA).

AERS data do have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive all adverse event reports that occur with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, AERS cannot be used to calculate the incidence of an adverse event in the U.S. population.

APPENDIX B: CONTAINER LABELS



(b) (4)

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

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

/s/

JAMES H SCHLICK
09/11/2012

KELLIE A TAYLOR on behalf of TODD D BRIDGES
09/11/2012

KELLIE A TAYLOR
09/11/2012

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: [REDACTED] (b) (4)</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review</u></p> <p>Comments: No comments.</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>REGULATORY PROJECT MANAGEMENT</p>	
<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

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
08/31/2012

KAREN D JONES
09/04/2012

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Application: NDA 203756
Application Type: New NDA
Name of Drug: Cometriq (cabozantinib)
Applicant: Exelixis, Inc.
Submission Date: May 21, 2012
Receipt Date: May 29, 2012

1.0 Regulatory History

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) the medullary thyroid cancer indication was assigned IND 113446 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 for the treatment of progressive, unresectable, locally advanced, or metastatic medullary thyroid cancer. During the December 20, 2011, pre-NDA meeting, FDA informed Exelixis that their proposed order of submissions for the rolling NDA was acceptable. The last portion containing the clinical module and CMC stability data was received on May 29, 2012.

2.0 Review of the Prescribing Information (PI)

This review is based on the applicant's submitted Microsoft Word format of the PI. The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (attached).

3.0 Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI.

All SRPI format deficiencies will be conveyed to the applicant in the filing or 74-day letter. The applicant will be asked to correct said deficiencies and resubmit the PI in Word format by August 10, 2012.

Selected Requirements of Prescribing Information (SRPI)

The Selected Requirements of Prescribing Information (SRPI) version 2 is 48-item, drop-down checklist of critical format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and labeling guidances.

Highlights (HL)

GENERAL FORMAT

- YES** 1. Highlights (HL) must be in two-column format, with ½ inch margins on all sides and in a minimum of 8-point font.

Comment:

- YES** 2. The length of HL must be less than or equal to one-half page (the HL Boxed Warning does not count against the one-half page requirement) unless a waiver has been granted in a previous submission (i.e., the application being reviewed is an efficacy supplement).

Instructions to complete this item: If the length of the HL is less than or equal to one-half page then select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page:

➤ **For the Filing Period (for RPMs)**

- *For efficacy supplements:* If a waiver was previously granted, select “YES” in the drop-down menu because this item meets the requirement.
- *For NDAs/BLAs and PLR conversions:* Select “NO” in the drop-down menu because this item does not meet the requirement (deficiency). The RPM notifies the Cross-Discipline Team Leader (CDTL) of the excessive HL length and the CDTL determines if this deficiency is included in the 74-day or advice letter to the applicant.

➤ **For the End-of Cycle Period (for SEALD reviewers)**

- The SEALD reviewer documents (based on information received from the RPM) that a waiver has been previously granted or will be granted by the review division in the approval letter.

Comment:

- YES** 3. All headings in HL must be presented in the center of a horizontal line, in UPPER-CASE letters and **bolded**.

Comment:

- YES** 4. White space must be present before each major heading in HL.

Comment:

- NO** 5. Each summarized statement in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The preferred format is

Selected Requirements of Prescribing Information (SRPI)

the numerical identifier in parenthesis [e.g., (1.1)] at the end of each information summary (e.g. end of each bullet).

Comment: *The sponsor failed to reference sections under Indication and Usage, Dosage and Administration and Adverse Reactions.*

YES

6. Section headings are presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a Boxed Warning is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions sections.

Comment:

YES

7. A horizontal line must separate HL and Table of Contents (TOC).

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

YES

8. At the beginning of HL, the following heading must be **bolded** and appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment: *N/A*

Highlights Limitation Statement

NO

9. The **bolded** HL Limitation Statement must be on the line immediately beneath the HL heading and must state: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”

Comment: *The HL Limitation statement does not appear in bold.*

Product Title

NO

10. Product title in HL must be **bolded**.

Comment: *Product title is not bolded.*

Selected Requirements of Prescribing Information (SRPI)

Initial U.S. Approval

- NO** 11. Initial U.S. Approval in HL must be placed immediately beneath the product title, **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment: *The four digit year does not appear in the proposed label.*

Boxed Warning

- N/A** 12. All text must be **bolded**.

Comment: *The Review team has determined a Boxed Warning is needed - to be requested in the filing letter.*

N/A

13. 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 (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 14. Must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” centered immediately beneath the heading.

Comment:

N/A

15. Must be limited in length to 20 lines (this does not include the heading and statement “*See full prescribing information for complete boxed warning.*”)

Comment:

N/A

16. Use sentence case for summary (combination of uppercase and lowercase letters typical of that used in a sentence).

Comment:

Recent Major Changes (RMC)

- N/A** 17. Pertains to only the following five sections of the FPI: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.

Comment:

N/A

18. Must be listed in the same order in HL as they appear in FPI.

Comment:

N/A

19. Includes heading(s) and, if appropriate, subheading(s) of labeling section(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Dosage and Administration, Coronary Stenting (2.2) --- 3/2012”.

Comment:

N/A

20. Must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Selected Requirements of Prescribing Information (SRPI)

Indications and Usage

- YES** 21. If a product belongs to an established pharmacologic class, the following statement is required in the Indications and Usage section of HL: [(Product) is a (name of class) indicated for (indication)].”

Comment:

Dosage Forms and Strengths

- N/A** 22. For a product that has several dosage forms, bulleted subheadings (e.g., capsules, tablets, injection, suspension) or tabular presentations of information is used.

Comment:

Contraindications

- YES** 23. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known.

Comment:

- N/A** 24. Each contraindication is bulleted when there is more than one contraindication.

Comment:

Adverse Reactions

- YES** 25. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement

- YES** 26. Must include one of the following three **bolded** verbatim statements (without quotation marks):

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.**”

Comment: *Label incorrectly identifies a Medication Guide. The following statement should be used, "PATIENT COUNSELING INFORMATION and FDA-approved patient labeling".*

Revision Date

- YES** 27. **Bolded** revision date (i.e., “**Revised: MM/YYYY or Month Year**”) must be at the end of HL.

Comment:

Contents: Table of Contents (TOC)

Selected Requirements of Prescribing Information (SRPI)

GENERAL FORMAT

- NO** 28. A horizontal line must separate TOC from the FPI.
Comment: There is no horizontal line between the TOC and FPI.
- YES** 29. The following **bolded** heading in all UPPER CASE letters must appear at the beginning of TOC: **“FULL PRESCRIBING INFORMATION: CONTENTS”**.
Comment:
- YES** 30. The section headings and subheadings (including title of the Boxed Warning) in the TOC must match the headings and subheadings in the FPI.
Comment:
- N/A** 31. The same title for the Boxed Warning that appears in the HL and FPI must also appear at the beginning of the TOC in UPPER-CASE letters and **bolded**.
Comment:
- YES** 32. All section headings must be **bolded** and in UPPER CASE.
Comment:
- YES** 33. All subsection headings must be indented, not bolded, and in title case.
Comment:
- YES** 34. When a section or subsection is omitted, the numbering does not change.
Comment:
- YES** 35. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading **“FULL PRESCRIBING INFORMATION: CONTENTS”** must be followed by an asterisk and the following statement must appear at the end of TOC: **“*Sections or subsections omitted from the Full Prescribing Information are not listed.”**
Comment:

Full Prescribing Information (FPI)

GENERAL FORMAT

- YES** 36. The following heading must appear at the beginning of the FPI in UPPER CASE and **bolded**: **“FULL PRESCRIBING INFORMATION”**.
Comment:
- YES** 37. All section and subsection headings and numbers must be **bolded**.
Comment:
- YES** 38. The **bolded** section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below. If a section/subsection is omitted, the numbering does not change.

Boxed Warning
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION

Selected Requirements of Prescribing Information (SRPI)

3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 39. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under Section 17 (Patient Counseling Information). All patient labeling must appear at the end of the PI upon approval.

Comment:

- YES** 40. The preferred presentation for cross-references in the FPI is the section heading (not subsection heading) followed by the numerical identifier in italics. For example, [*see Warnings and Precautions (5.2)*].

Comment:

- N/A** 41. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

Boxed Warning

- N/A** 42. All text is **bolded**.

Comment:

Selected Requirements of Prescribing Information (SRPI)

- N/A** 43. Must have a 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 (e.g., “**WARNING: SERIOUS INFECTIONS**”).

Comment:

- N/A** 44. Use sentence case (combination of uppercase and lowercase letters typical of that used in a sentence) for the information in the Boxed Warning.

Comment:

Contraindications

- N/A** 45. If no Contraindications are known, this section must state “None”.

Comment: *The sponsor will be requested to document cases of hypersensitivity in the filing letter.*

Adverse Reactions

- YES** 46. When clinical trials adverse reactions data is included (typically in the “Clinical Trials Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.”

Comment:

- N/A** 47. When postmarketing adverse reaction data is included (typically in the “Postmarketing Experience” subsection of Adverse Reactions), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

Patient Counseling Information

- NO** 48. Must reference any FDA-approved patient labeling, include the type of patient labeling, and use one of the following statements at the beginning of Section 17:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

Comment: *Incorrect statement - There is no medication guide.*

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
08/31/2012

KAREN D JONES
09/04/2012