

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206192Orig1s000**

**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.

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NDA/BLA # 206192/New Molecular Entity  
Product Name: COTELLIC (cobimetinib)

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PMR/PMC Description: Submit the clinical report at the time of the final analysis of Trial GO28141, A Phase III, Double-Blind, Placebo-Controlled Study of Vemurafenib Versus Vemurafenib Plus Cobimetinib (GDC-0973) in Previously Untreated BRAFV600-Mutation Positive Patients with Unresectable Locally Advanced or Metastatic Melanoma (coBRIM) to update the label with mature overall survival data.

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PMR/PMC Schedule Milestones:

Final Report Submission:

June 30, 2016

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

COTELLIC is being approved for use in combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with the BRAF V600E and V600K mutations who have not received prior treatment with a BRAF inhibitor. Data for the secondary endpoint of overall survival is not mature at the time of the approval. Once mature, information on effects on overall survival will provide important information on the extent of the clinical benefit of cobimetinib in this setting.

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 PMC is recommended for submission of the final OS data of Trial GO28141 to provide long-term data on the efficacy of cobimetinib used in combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with the BRAF V600E and V600K mutations who have not received prior treatment with a BRAF inhibitor. The OS data will be used to better describe the treatment effects of COTELLIC.

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.

Submit the clinical report at the time of the final analysis of Trial GO28141, A Phase III, Double-Blind, Placebo-Controlled Study of Vemurafenib Versus Vemurafenib Plus Cobimetinib (GDC-0973) in Previously Untreated BRAFV600-Mutation Positive Patients with Unresectable Locally Advanced or Metastatic Melanoma (coBRIM) to update the label with mature overall survival data.

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)
- 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

Continuation of Question 4

- 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?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

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**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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(signature line for BLAs)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RUTHANN M GIUSTI  
12/03/2015

MARC R THEORET  
12/03/2015

JEFFERY L SUMMERS  
12/03/2015

## 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 # 206192	NDA Supplement #: S- # N/A	Efficacy Supplement Category: <input checked="" type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Animal Rule Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Pediatric
Proprietary Name: Cotellic ( <i>Proposed</i> ) Established/Proper Name: cobimetinib Dosage Form: tablets Strengths: 20 mg		
Applicant: Genentech, Inc. Agent for Applicant (if applicable): N/A		
Date of Application: December 11, 2014 Date of Receipt: December 11, 2014 Date clock started after UN: N/A		
PDUFA/BsUFA Goal Date: August 11, 2015		Action Goal Date (if different):
Filing Date: February 9, 2015		Date of Filing Meeting: January 29, 2015
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s):  for use in combination with Zelboraf® (vemurafenib) for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation.		
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)
<b><i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i></b> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a>		

Type of BLA		<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)		
<b><i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i></b>				
Review Classification:		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority		
<b><i>The application will be a priority review if:</i></b> <ul style="list-style-type: none"> <li><b><i>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</i></b></li> <li><b><i>The product is a Qualified Infectious Disease Product (QIDP)</i></b></li> <li><b><i>A Tropical Disease Priority Review Voucher was submitted</i></b></li> <li><b><i>A Pediatric Rare Disease Priority Review Voucher was submitted</i></b></li> </ul>		<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher		
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)			
<b><i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i></b>				
<input checked="" type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input checked="" type="checkbox"/> Rolling Review <input 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 (FDCA Section 505B) <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): As listed on the FDA FORM 356h: IND 76798, IND 109307, IND 114068, IND 118126, IND 118555, IND 118753				
<b>Goal Dates/Product Names/Classification Properties</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
PDUFA/BsUFA and Action Goal dates correct in tracking system?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Verified on 1/2/15
<b><i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i></b>				

Are the 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>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Verified on 1/2/15 (Asked to be corrected)
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Verified on 1/2/15
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Verified on 1/2/15
<b>If yes, explain in comment column.</b>				N/A
<b>If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:</b>	<input type="checkbox"/>	<input type="checkbox"/>		N/A
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Verified on 1/2/15 (Included in first piece of the rolling review)
<u>User Fee Status</u>  <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>	Payment for this application ( <i>check daily email from <a href="mailto:UserFeeAR@fda.hhs.gov">UserFeeAR@fda.hhs.gov</a></i> ):  <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			
<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>	Payment of other user fees:  <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			

<b>User Fee Bundling Policy</b>  <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</a>		Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i>  <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>		<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application a 505(b)(2) NDA? <i>(Check the 356h form, cover letter, and annotated labeling). If yes, answer the bulleted questions below:</i>		<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<ul style="list-style-type: none"> <li>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> </ul>		<input type="checkbox"/>	<input type="checkbox"/>		N/A (NME)
<ul style="list-style-type: none"> <li>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)].</li> </ul>		<input type="checkbox"/>	<input type="checkbox"/>		N/A (NME)
<ul style="list-style-type: none"> <li>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)]?</li> </ul> <p><i>If you answered yes to any of the above bulleted 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 for advice.</i></p>		<input type="checkbox"/>	<input type="checkbox"/>		N/A (NME)
<ul style="list-style-type: none"> <li>Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</li> </ul> <p><i>Check the Electronic Orange Book at:</i>  <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a></p>		<input type="checkbox"/>	<input type="checkbox"/>		N/A (NME)
<b>If yes, please list below:</b>					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<p><i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, 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 may block the approval but not the submission of a 505(b)(2) application.</i></p>					
<b>Exclusivity</b>		<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at:</i> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/opd/index.cfm</a>		<input type="checkbox"/>	<input checked="" type="checkbox"/>		Verified on 1/2/15

<p><b>If another product has orphan exclusivity</b>, 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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p><b>NDAs/NDA efficacy supplements only:</b> Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?</p> <p><b>If yes, # years requested:</b> 5 years</p> <p><i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Verified on 1/2/15 (Included in last piece of the rolling review)
<p><b>NDAs only:</b> Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?</p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<p><b>If yes</b>, 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 the Orange Book Staff (CDER-Orange Book Staff).</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<p><b>BLAs only:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?</p> <p><i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i></p> <p><i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Format and Content</b>				
<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><b>If mixed (paper/electronic) submission</b>, which parts of the application are submitted in electronic format?</p>				

Overall Format/Content	YES	NO	NA	Comment
<b>If electronic submission</b> , does it follow the eCTD guidance? <sup>1</sup> <b>If not</b> , explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Verified on 1/2/15
<b>Index</b> : Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:  <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)  <b>If no</b> , explain.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Verified on 1/2/15
<b>BLAs only</b> : Companion application received if a shared or divided manufacturing arrangement?  <b>If yes</b> , BLA #	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Forms and Certifications</b>				
<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 (3397/3792), 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>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Verified on 1/2/15
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Verified on 1/2/15 (Included in last piece of the rolling review)
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Verified on 1/2/15 (Included in last piece of the rolling review)
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>

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

Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?  <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>  <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Verified on 1/2/15 (Included in last piece of the rolling review)
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?  <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>  <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Verified on 1/2/15 (Included in last piece of the rolling review)
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?  <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>  <i>Note: Debarment Certification should use wording in FD&amp;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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Verified on 1/2/15 (Included in last pieces of the rolling review)
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?  <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>  <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Electric submission; however, sponsor elected to include in the first pieces of the rolling review

<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<p><b><u>PREA</u></b></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify <a href="mailto:PeRC@fda.hhs.gov">PeRC@fda.hhs.gov</a> to schedule required PeRC meeting<sup>2</sup></i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Verified on 1/2/15
<p><b>If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?</b></p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Exempt
<p><b>If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?</b></p> <p><i>If no, may be an RTF issue - contact DPMH for advice.</i></p>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Exempt
<p><b><u>BPCA:</u></b></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)<sup>3</sup></i></p>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Verified on 1/8/15

2

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

3

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

REMS	YES	NO	NA	Comment
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
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) <input checked="" type="checkbox"/> Carton labels <input checked="" 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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Verified on 1/2/15
Is the PI submitted in PLR format? <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		Verified on 1/2/15
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , 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>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? <i>(send WORD version if available)</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
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)			

4

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

	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		N/A
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
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>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	QT-IRT
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? <b>Date(s):</b> CMC only: 11/27/12 Multidiscipline: 6/27/12 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> Multidiscipline: 10/8/14 CMC only: 3/5/14 <i>If yes, distribute minutes before filing meeting</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b> <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** February 3, 2015

**BACKGROUND:** This New Drug Application (NDA) is for regular approval of Cotellic [Proposed] (cobimetinib) for the “for use in combination with Zelboraf® (vemurafenib) for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation.” The NDA will be supported by efficacy and safety data from the following pivotal study and supportive study:

- Study GO28141 (A Phase III double-blind, placebo controlled study of vemurafenib versus vemurafenib plus GDC-0973 in previously untreated BRAF600-mutation positive patients with unresectable locally advanced or metastatic melanoma.”
- Study NO25395 entitled, “A Phase Ib, open label, dose-escalation study evaluating the safety, tolerability and pharmacokinetics of vemurafenib in combination with GDC-0973 (cobimetinib) when administered in BRAFV600E mutation–positive patients previously treated (but without prior exposure to BRAF or MEK inhibitor therapy) or previously untreated for locally advanced/unresectable or metastatic melanoma or those who have progressed after treatment with vemurafenib”

Regulatory History:

The regulatory history in the US includes the following: initial development program for the cobimetinib began under IND (b)(4) in 2006 in solid tumor and expanded to use of in combination with vemurafenib with the allowance of new IND 109307 to proceed in September 2010; an EOP1/Pre-Phase 3 multidiscipline meeting was held on June 27, 2012; an EOP2 CMC only meeting was held on November 27, 2012; two Type C Written request only meetings were held on April 22, 2013 and November 29, 2013; a Pre-NDA CMC only meeting scheduled for March 5, 2014; and a Pre-NDA multidiscipline meeting was held October 8, 2014, to discuss the content and format of the NDA and obtain agreement on any late components of an application.

Finally, Genentech was granted Fast Track Designation for their program investigating cobimetinib and vemurafenib for the treatment of patients with BRAF V600E-mutation positive, unresectable or metastatic melanoma to demonstrate improved progression-free survival and overall survival on August 15, 2014, and orphan designation for treatment of stage IIb, IIc, III, and IV melanoma with BRAFV600 mutation” on January 31, 2014.

REVIEW TEAM:

<b>Discipline/Organization</b>	<b>Names</b>		<b>Present at filing meeting? (Y or N)</b>
Regulatory Project Management	RPM:	Meredith Libeg	Y

	CPMS/TL:	Monica Hughes (CPMS)	Y
Cross-Discipline Team Leader (CDTL)		Marc Theoret	Y
Division Director/Deputy		Patricia Keegan (Director) Joseph Gootenberg (Deputy Director)	Y N
Office Director/Deputy		Richard Pazdur (Director)	N
Clinical	Reviewer:	Ruthann Giusti	Y
	TL:	Marc Theoret	Y
Clinical Pharmacology	Reviewer:	Ruby Leong	Y
	TL:	Hong Zhao	Y
Biostatistics	Reviewer:	Xiaoping (Janet) Jiang	Y
	TL:	Kun He	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Anwar Goheer	N
	TL:	Whitney Helms	Y
Product Quality (CMC)	Reviewer:	Gaetan Ladoucer Donghao Lu Zengfang Ge Liang Zhou	Y Y
	TL:	Olen Stephens	Y
OSE/DMEPA (proprietary name, carton/container labels))	Reviewer:	Otto Townsend	Y
	TL:		
OSE/DRISK (REMS)	Reviewer:	Latonia Ford Tracy Salaam Shaily Arora	Y Y Y
	TL:	Naomi Redd	Y

Other attendees	Erik Laughner	
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**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>• 505 b)(2) filing issues: <ul style="list-style-type: none"> <li>○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> </li> </ul> <p>Describe the scientific bridge (e.g., BA/BE studies):</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no</b>, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> No comments
<p><b>CLINICAL</b></p> <p><b>Comments:</b> Labeling comments</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"> <li>• Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no</b>, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></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"> <li>○ <i>this drug/biologic is not the first in its class</i></li> <li>○ <i>the clinical study design was acceptable</i></li> <li>○ <i>the application did not raise significant safety</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined  Reason: <ul style="list-style-type: none"> <li>○ <b>the application did not raise significant safety or efficacy issues</b></li> <li>○ <b>the application did not raise</b></li> </ul>

<ul style="list-style-type: none"> <li>○ <i>or efficacy issues</i></li> <li>○ <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></li> </ul>	<p><b>significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</b></p> <ul style="list-style-type: none"> <li>○ <b>this drug/biologic is not the first in its class</b></li> </ul>
<ul style="list-style-type: none"> <li>• 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?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CONTROLLED SUBSTANCE STAFF</b></p> <ul style="list-style-type: none"> <li>• Abuse Liability/Potential</li> </ul> <p><b>Comments:</b> Consult may be needed. Determination still under review</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><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></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><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b> Information request will be sent on PK modeling.</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"> <li>• Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b></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><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b></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

<b>IMMUNOGENICITY</b> (protein/peptide products only)  <b>Comments:</b>	<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
<b>PRODUCT QUALITY (CMC)</b>  <b>Comments:</b>	<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
<b>New Molecular Entity (NDAs only)</b>  <ul style="list-style-type: none"> <li>• Is the product an NME?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<u><b>Environmental Assessment</b></u>  <ul style="list-style-type: none"> <li>• Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p style="margin-left: 40px;"><b>If no</b>, was a complete EA submitted?</p> <p style="margin-left: 40px;"><b>If EA submitted</b>, consulted to EA officer (OPS)?</p> <b>Comments:</b>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<u><b>Quality Microbiology</b></u>  <ul style="list-style-type: none"> <li>• Was the Microbiology Team consulted for validation of sterilization?</li> </ul> <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<u><b>Facility Inspection</b></u>  <ul style="list-style-type: none"> <li>• Establishment(s) ready for inspection?</li> <li>▪ Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ?</li> </ul> <b>Comments:</b>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO

<p><b>Facility/Microbiology Review (BLAs only)</b></p> <p><b>Comments:</b></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><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• Were there agreements made at the application’s pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<input type="checkbox"/> N/A  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	<p>CMC stability update</p>
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>REGULATORY PROJECT MANAGEMENT</b></p>	
<p><b>Signatory Authority:</b> Richard Pazdur, M.D.</p> <p><b>Date of Mid-Cycle Meeting</b> (for NME NDAs/BLAs in “the Program” PDUFA V): March 23, 2015 (proposed)</p> <p><b>21<sup>st</sup> Century Review Milestones (see attached)</b> (listing review milestones in this document is optional):</p>	

**Comments:**

<b>Filing Meeting Summary Notes</b>
The review team confirmed the application is sufficiently complete to permit a substantive review; therefore, is acceptable to be considered filed 60 days after the date we received the application.
The review team reconfirmed that the application will be priority review.
The review team determined to include initial potential review issues (high level labeling comments) in the Day 74 letter to the sponsor
The review team determined that a consult for SGE(s) will be obtained, as appropriate. If SGE(s) are not able to be obtained, this will be documented in the clinical review
Application Orientation Presentation was held on Monday January 12, 2015
The review team determined ODAC was not required for this application.

**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.</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, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone 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"/>	351(k) BLA/supplement: If filed, send filing notification letter on day 60
<input checked="" type="checkbox"/>	<p>If priority review:</p> <ul style="list-style-type: none"><li>• notify sponsor in writing by day 60 (see CST for choices)</li><li>• notify OMPQ (so facility inspections can be scheduled earlier)</li></ul>

<input type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MEREDITH LIBEG

12/02/2015

Review completed on Feb 3, 2015

## 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 #                      206192, COTELLIC (cobimetinib)  
Product Name: \_\_\_\_\_

PMR/PMC Description: Hepatic Impairment Pharmacokinetic Study

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>Submitted</u>
	Study/Trial Completion:	<u>Completed</u>
	Final Report Submission:	<u>06/30/2016</u>
	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

The mass balance study suggests that hepatic elimination is the major route of elimination. Patients with hepatic impairment may have higher cobimetinib systemic exposures than patients with normal hepatic function, which may lead to 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 pharmacokinetic trial is to determine appropriate cobimetinib doses in patients with moderate to severe 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.

Complete a pharmacokinetic study to determine the appropriate dose of cobimetinib in patients with hepatic impairment in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”

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 NDAs)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RUBY LEONG  
11/13/2015

HONG ZHAO  
11/13/2015  
I concur.

JEFFERY L SUMMERS  
11/13/2015



**MEMORANDUM**  
**Department of Health and Human Services**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

**Date:** November 3, 2015

**To:** Patricia Keegan, M.D., Director  
Division of Oncology Products (DOP2)  
Office of Hematology and Oncology Products

**Through:** Michael Klein, Ph.D., Director  
Controlled Substance Staff (CSS)

**From:** Katherine Bonson, Ph.D., Pharmacologist  
Joshua Hunt, Pharm.D., Pharmacist  
Controlled Substance Staff

**Subject:** Cobimetinib  
NDA 206,192  
Indication: Treatment of patients with unresectable or  
metastatic melanoma with BRAF V600 mutation  
Sponsor: Genentech, Inc.

**Materials reviewed:** Abuse-related preclinical and clinical data in NDA  
(submission #000, 12/11/14)

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## **1. Background**

This memorandum responds to a consult request to CSS by the Division of Oncology Products (DOP) to assess the abuse potential of cobimetinib (NDA 206,192). The drug is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation, sponsored by Genentech, Inc. CSS was consulted on this NDA after it had been filed and we were not consulted when the drug was being developed under (b)(4) IND 109,307.

According to the Sponsor, “Cobimetinib is a potent and highly selective, non-competitive small molecule inhibitor of mitogen-activated protein kinase (MEK), which is a central component of the RAS/RAF/MEK/ERK pathway. Cobimetinib is being developed for use in the treatment of cancers, including in combination with vemurafenib (Zelboraf) for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation. Zelboraf is approved in many countries worldwide including in the United States for the treatment of patients with unresectable or metastatic melanoma with the BRAF V600E mutation.”

## **2. Conclusions**

After reviewing the NDA submission, CSS has concluded that:

- Cobimetinib has moderate affinity at mu opioid receptors in the brain (600 nM).
- The Sponsor did not conduct any dedicated abuse-related studies in animals or humans.
- There are no abuse-related adverse events (including euphoria) produced by cobimetinib in Phase 1 or Phase 2/3 clinical studies.
- Based on the information submitted in the NDA, cobimetinib does not appear to have any abuse potential, despite having activity at the mu opioid receptor.
- In the absence of abuse-related signals in humans, it is not necessary to conduct a full abuse potential assessment for a drug indicated for the treatment of patients with cancer under serious medical supervision.

## **3. Recommendations**

- Although cobimetinib does not appear to have abuse potential, its moderate affinity at mu opioid receptors suggests there may be a safety issue of interactions with opioid analgesics in terms of an increased risk of respiratory depression.
- CSS recommends that the Division consider whether the Sponsor should be encouraged to evaluate incidents of respiratory depression post-marketing.

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KATHERINE R BONSON  
11/03/2015

JOSHUA S HUNT  
11/03/2015

MICHAEL KLEIN  
11/03/2015

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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**Date of This Memorandum:** November 2, 2015  
**Requesting Office or Division:** Division of Oncology Products 2 (DOP2)  
**Application Type and Number:** NDA 206192  
**Product Name and Strength:** Cotellic (cobimetinib) Tablets, 20 mg  
**Submission Date:** October 29, 2015  
**Applicant/Sponsor Name:** Genentech, Inc.  
**OSE RCM #:** 2014-2484-1  
**DMEPA Primary Reviewer:** Otto L. Townsend , PharmD  
**DMEPA Team Leader:** Chi-Ming (Alice) Tu, PharmD

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#### 1 PURPOSE OF MEMORANDUM

The Division of Oncology Products 2 (DOP2) requested that we review the revised container label and carton labeling for Cotellic (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>1</sup>

#### 2 CONCLUSIONS/RECOMMENDATIONS:

The Agency provided labeling recommendations to Genentech via electronic mail on October 26, 2015.

In their October 29, 2015 response, Genentech noted that the Agency changed the storage statement in the Package Insert (PI) to read, "Store at room temperature below 30°C (86°F)", but the storage statement "(b) (4)" on the container label and carton labeling was not changed to reflect this change. Genentech agreed with the storage statement change

<sup>1</sup> Townsend, O. Label and Labeling Review for Cotellic (NDA 206192). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 MAY 20. 6 p. OSE RCM No.: 2014-2484.

in the PI and have proposed the same statement be printed on the container label and carton labeling. We find this proposal acceptable, but defer to the Office of Pharmaceutical Quality on the acceptability of this proposal.

We recommended removal [REDACTED] (b) (4)

In response to our request to increase the font size of the container label text, they have increased the font size by 23%. In addition, they state that the label is too small to increase the font size more. To further address the font size issue, their proposal is moving the content statement to the opposite side panel to increase white space. In addition, Genentech changed the previous Usual Dosage statement from, [REDACTED] (b) (4)

[REDACTED] .” Genentech is proposing the statement be changed to read, [REDACTED] (b) (4)

” Their rationale is the dosage regimen for Cotellic is unique and this statement ensures clarity of the dosing regimen. This dosage regimen may be unique to the Genentech product line, but is not unique to health care professionals who provide services to oncology patients. We feel that a more general Usual Dosage statement should be included, but defer to the Clinical team for further recommendations to Genentech on this issue. If the clinical team agrees, we recommend a more general statement such as, “Usual Dosage: See prescribing information.” The proposed statement requires less space on the side panel of the container label.

In addition to the proposed changes above, Genentech proposed two additional labeling changes:

- The first was a change of artwork color scheme for the container label and carton labeling. This change is acceptable.
- The second change is the addition of a Global Trade Identification Number (GTIN) to the bottom panel of the carton labeling to support serialization. We find the addition of this identifier acceptable because it does not compete in prominence with safety information and is clearly labeled as the GTIN and should not be confused with lot or expiry information.

**APPENDIX A. LABEL AND LABELING SUBMITTED ON OCTOBER 29, 2015**

Container Label (400%)

(b) (4)



Carton Labeling

(b) (4)



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/s/  
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OTTO L TOWNSEND  
11/02/2015

CHI-MING TU  
11/02/2015



Division of Pediatric and Maternal Health  
Office of New Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Silver Spring, MD 20993  
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### Division of Pediatric and Maternal Health Memorandum

**Date:** July 7, 2015      **Date consulted:** February 27, 2015

**From:** Miriam Dinatale, D.O., Medical Officer, Maternal Health  
Division of Pediatric and Maternal Health

**Through:** Tamara Johnson, MD, MS, Acting Team Leader, Maternal Health  
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, OND, Acting Division Director  
Division of Pediatric and Maternal Health

**To:** Office of Hematology and Oncology Products (OHOP)/  
Division of Oncology Products 2 (DOP2)

**Drug:** Cotellic (cobimetinib), 20mg tablets

**Indication:** for use in combination with Zelboraf (vemurafenib) for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations

**NDA:** 206192

**Applicant:** Genentech, Inc.

**Subject:** Pregnancy and Lactation Labeling

**Materials**

**Reviewed:**

- DPMH consult request dated February 27, 2015, DARRTS Reference ID 3709616
- Sponsor's submitted background package for NDA 206192, cobimetinib
- Nonclinical Team Primary Review, Cotellic (cobimetinib), NDA 206192. Shawna Weis, PhD, Anwar Goheer, PhD. May 29, 2015. DARRTS Reference ID 3768701

- Nonclinical Team Secondary Review, Cotellic (cobimetinib), NDA 206192. Whitney Helms, PhD. May 29, 2015. DARRTS Reference ID 3769107

**Consult Question:**

DOP2 requests DPMH assistance with pregnancy and nursing mothers labeling for a new molecular entity.

**INTRODUCTION**

On October 30, 2014, Genentech, Inc. submitted a 505(b)(1) new molecular entity (NME) new drug application (NDA) for Cotellic (cobimetinib), which is a kinase inhibitor of mitogen-activated protein kinase (MEK) 1 and 2. Cobimetinib has the proposed indication of treatment of unresectable or metastatic melanoma in patients with BRAF<sup>1</sup> V600 mutations in combination with Zelboraf (vemurafenib). The FDA granted cobimetinib Fast Track Designation, for the treatment of patients with unresectable or metastatic melanoma, on August 15, 2014, and orphan drug designation, for the proposed indication of Stage IIb to IV melanoma with BRAF V600 mutation, on January 31, 2014. Priority Review was granted on February 12, 2015.

The Division of Oncology Products 2 (DOP2) consulted the Division of Pediatric and Maternal Health (DPMH) on February 27, 2015, to review the Pregnancy and Lactation subsections of labeling to ensure compliance with the Pregnancy and Lactation Labeling Rule formatting requirements and to provide comments to be included in the labeling that will be sent to the applicant.

**BACKGROUND****Cobimetinib and Drug Characteristics**

Cobimetinib is a reversible, non-ATP competitive inhibitor of MEK 1 and MEK 2. The MEK 1 and 2 proteins are part of the mitogen-activated protein kinase (MAPK) pathway, which is a pathway that regulates cell growth and survival, participates in angiogenesis and cell migration and supports the growth and spread of tumors. Mutations in genes coding for proteins in the MAPK pathway are associated with the development and progression of cancer. Missense mutations, such as BRAF V600E (glutamic acid is substituted for valine) or V600K (lysine is substituted for valine) are associated with the development of melanoma.<sup>2</sup> Inhibition of BRAF-catalyzed MEK activation and kinase activity of MEK leads to decreased cellular proliferation of tumors with BRAF V600 mutations.<sup>3</sup>

Cobimetinib has the following characteristics: a molecular weight of 531 Daltons, a bioavailability of 46%, highly protein bound (95%), and an elimination half-life of 44 hours (range of 23-70 hours).<sup>4</sup> Trametinib, approved May 2013 for the treatment of unresectable of metastatic melanoma, has a similar mechanism of action.

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<sup>1</sup> BRAF is a human gene that makes a protein called B-Raf. The gene is also referred to as proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene homolog B, while the protein is more formally known as serine/threonine-protein kinase B-Raf. [http://en.wikipedia.org/wiki/BRAF\\_%28gene%29](http://en.wikipedia.org/wiki/BRAF_%28gene%29)

<sup>2</sup> Nonclinical Team Primary Review, Cotellic (cobimetinib), NDA 206192. Shawna Weis, PhD, Anwar Goheer, PhD. May 29, 2015. DARRTS Reference ID 3768701.

<sup>3</sup> Clinical Pharmacology Review. Cotellic (cobimetinib). NDA206192. May 11, 2015. Ruby Leong, PharmD DARRTS Reference ID 3751393.

<sup>4</sup> Cotellic (cobimetinib) applicant proposed labeling. Section 12 Clinical Pharmacology.

## Melanoma

Malignant melanoma (MM), a type of skin cancer that develops in melanocytes, is the fifth most common cancer in men and the seventh most common cancer in women. Four percent of all newly diagnosed cases of MM are metastatic. Once MM is metastatic, the five-year survival is less than 10%.<sup>5</sup> In 2014, there were 76,100 new cases and 9,710 deaths associated with MM.<sup>6</sup> Approximately 40-60% of cases of MM contain a mutation in the gene that encodes BRAF, and in 80-90% of these cases, the mutation is BRAF V600E.<sup>7</sup> FDA-approved treatment options for treatment of metastatic MM include the following<sup>8,9</sup>:

- Chemotherapy (dacarbazine)
- Immunotherapy
  - Checkpoint Inhibitors
    - human cytotoxic T-lymphocyte antigen 4 blocking antibody
      - Ipilimumab (approved in the U.S. in March 2011)
    - Programmed Cell Death-1 (PD-1) Inhibitors
      - Pembrolizumab (approved in the U.S. in September 2014)
      - Nivolumab (approved in the U.S. in March 2015)
  - Interleukin-2 (approved in the U.S. in 1998)
- Signal-transduction inhibitors
  - BRAF kinase inhibitors, for patients with BRAF V600E mutation
    - Vemurafenib (approved in the U.S. in August 2011)
    - Dabrafenib (approved in the U.S. in May 2013)
  - MEK 1 and 2 inhibitors, for patients with V600E and V600K mutations
    - Trametinib (approved in the U.S. in May 2013)

## Melanoma in Pregnancy

About one third of women diagnosed with MM are of childbearing age. MM is considered the most common malignant tumor found during pregnancy, corresponding to 31% of all diagnosed malignant neoplasms. There is a 3.3% incidence of MM during pregnancy in women between 16 and 49 year old.<sup>10</sup> One hypothesis, regarding the increase in MM in pregnancy, is that hormonal changes during pregnancy may be involved with the increased incidence, but according to Mestnik *et al.*, the most probable explanation is a delay in diagnosis. In pregnancy, pre-existing benign pigmented skin lesions may become darker and larger. Therefore, a new or enlarging malignant lesion in a pregnant woman may not be recognized as being malignant until later. In one article (Travers, *et al.*), the authors noted that in the medical records of women who were subsequently diagnosed with melanoma, several patients had presented with abnormal skin lesions during pregnancy but were advised

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<sup>5</sup> Clinical Team Secondary Review, Keytruda (pembrolizumab), BLA 125514, 2/27/2014, DARRTS Reference ID 3621494

<sup>6</sup> Melanoma. <http://www.cancer.gov/cancertopics/types/melanoma>. Accessed 6/3/2015.

<sup>7</sup> Melanoma and BRAF. <http://emedicine.medscape.com/article/2045059-overview>. Accessed 6/3/2015.

<sup>8</sup> Drugs@FDA: vemurafenib, dabrafenib, ipilimumab, trametinib, pembrolizumab, nivolumab. Accessed 6/3/2015.

<sup>9</sup> Melanoma Treatment. [http://www.cancer.gov/types/skin/hp/melanoma-treatment-pdq#link/\\_862\\_toc](http://www.cancer.gov/types/skin/hp/melanoma-treatment-pdq#link/_862_toc). Accessed 6/3/2015.

<sup>10</sup> Jhaveri *et al.* Melanoma in Pregnancy. *Clinical Obstetrics and Gynecology*. 2011; 54(4): 537-545.

to wait until after delivery to undergo excisional biopsy.<sup>11</sup> In another article (Jhaveri *et al.*), the authors propose a different hypothesis attributing the higher incidence of MM in pregnancy to immunosuppression that occurs during pregnancy. Pregnancy, however, does not significantly change the characteristics or prognosis of MM.<sup>12</sup>

### **Pregnancy and Nursing Mothers Labeling**

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,”<sup>13</sup> also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule<sup>14</sup> format to include information about the risks and benefits of using these products during pregnancy and lactation.

## **DISCUSSION**

### **Cobimetinib and Pregnancy**

The applicant did not conduct studies with cobimetinib in pregnant women. A search of published literature in Pubmed was performed, and no publications were found evaluating the use of cobimetinib in pregnant women.

In embryo-fetal development studies of pregnant Sprague Dawley rats, oral exposure of cobimetinib during organogenesis resulted in increases in post-implantation loss at a 0.9 and 1.4 times the recommended human dose (RHD). This dose caused maternal toxicity and was also associated with decreased fetal weight, malformations of the great vessels, and skeletal malformations (fused ribs, small eye sockets). Based on the current animal study and the drug’s mechanism of action, the Nonclinical Review team recommended that a warning for embryofetal risk be included in labeling. (The reader is referred to the Nonclinical Primary Review by Shawna Weis, PhD and Anwar Goheer, PhD and the Secondary Review by Whitney Helms, PhD for further details.)<sup>1516</sup>

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<sup>11</sup> Travers, et al. Increased thickness of pregnancy-associated melanoma. *British Journal of Dermatology*. 1995. 332: 876-883.

<sup>12</sup> Jhaveri *et al.* Melanoma in Pregnancy. *Clinical Obstetrics and Gynecology*. 2011; 54(4): 537-545.

<sup>13</sup> *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

<sup>14</sup> *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

<sup>15</sup> Nonclinical Team Primary Review, Cotellic (cobimetinib), NDA 206192. Shawna Weis, PhD, Anwar Goheer, PhD. May 29, 2015. DARRTS Reference ID 3768701.

<sup>16</sup> Nonclinical Team Secondary Review, Cotellic (cobimetinib), NDA 206192. Whitney Helms, PhD. May 29, 2015. DARRTS Reference ID 3769107.

*Reviewer Comments:*

*Although human pregnancy outcome data are not available for cobimetinib, animal reproduction studies show evidence of decreased fetal weight, malformations of the great vessels, and skeletal malformation, which is most likely secondary to maternal toxicity. Trametinib, which has a similar mechanism of action, demonstrated decreased fetal weight loss and an increase in post-implantation loss in rats and rabbits during animal reproductive studies. In rabbits, there was also an increased incidence of variations in ossification. There was no evidence of malformations of the great vessels, as seen with cobimetinib that was noted in animal reproduction studies with trametinib.*

*The warning about fetal harm that appears in section 8.1, Risk Summary, for trametinib and cobimetinib is based on the increased risk of post-implantation loss. In addition, the likelihood of adverse fetal and infant effects is high based on the drugs' mechanism of action.*

**Cobimetinib and Lactation**

The applicant did not provide human data on the use of cobimetinib during lactation. The Drugs and Lactation Database (LactMed)<sup>17</sup> and Pubmed were searched for available lactation data on the use of trametinib and cobimetinib, and no information was found. Serious adverse reactions (left ventricular dysfunction, serious retinopathy, and increases in alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase) were observed in adult patients in clinical trials with cobimetinib. In adult patients treated with trametinib, serious adverse reactions included: cutaneous malignancies (basal cell carcinoma, squamous cell carcinoma, and new primary melanoma), hemorrhage (intracranial or gastric), venous thromboembolism, cardiomyopathy, ocular toxicity (retinal vein occlusion, retinal pigment epithelial detachment, uveitis, and iritis), interstitial lung disease, and hyperglycemia.

*Reviewer Comments:*

*Although cobimetinib has a low bioavailability (46%) and is highly protein bound (drugs that are highly protein bound are less likely to be present in breast milk), cobimetinib has a molecular weight of 531 Daltons (drugs with molecular weights less than 800 Daltons can easily pass into breast milk) and a long half-life of 44 hours (ranges 23-70 hours), which increases the presence of the drug in the mother's circulation and may increase infant exposure to the drug via breast milk.<sup>18</sup> It is possible that cobimetinib may be present in breast milk.*

*Current trametinib and proposed cobimetinib lactation labeling states that the drug is not recommended during breastfeeding. Given the risk of potential serious adverse events seen in adult patients in clinical trials with trametinib and cobimetinib, breastfeeding with maternal use of trametinib and cobimetinib is not recommended due to the potential for*

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<sup>17</sup> <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

<sup>18</sup> Nice, F and Luo, Amy. Medications and breast-feeding: Current Concepts. Journal of the American Pharmacists Association. 2012; 51 (1): 86-94.

*serious adverse reactions in a breastfed infant. DPMH agrees with the applicant's recommendation against breastfeeding during treatment with cobimetinib, and recommends the addition of the phrase: "for two weeks after the final dose," which is calculated by multiplying the half-life (44 hours) by 6.*

### **Cobimetinib and Fertility**

Although there were no human or animal studies conducted to evaluate the effect of cobimetinib on fertility, effects on reproductive tissues were observed in general toxicology studies conducted in animals and suggest that there is a potential for cobimetinib to impair fertility. Findings observed in the female reproductive tract of rats included increased apoptosis/necrosis of corpora lutea and vaginal epithelial cell at doses two times the RHD of 60mg. The Nonclinical Review Team notes that these findings suggest the potential for transient effects on fertility in females who are exposed cobimetinib. In male dogs, testicular degeneration occurred at doses 0.1 times the RHD. (The reader is referred to the Nonclinical review by Shawna Weis, PhD and Anwar Goheer, PhD for further details.)<sup>19</sup>

#### *Reviewer Comments*

*Due to the potential for adverse fetal and infant effects (see reviewer comments above in discussion of Cobimetinib and Pregnancy), females of reproductive potential should use effective contraception during treatment with cobimetinib and for two weeks following completion of therapy to ensure low to no systemic drug levels in a female patient. The duration on contraception use is based on multiplying the half-life (44 hours is the average half-life) by 6. Cobimetinib was not found to be genotoxic in assays for genotoxicity; therefore, there is no recommendation for male contraception.*

*In addition, the applicant did not perform a dedicated fertility study in animals. The fertility results that were observed in females were based on general toxicology studies. The Nonclinical Team notes that the results seen in females are likely transient because there was no infertility noted in recovery animals. For males, the Nonclinical Team notes that the findings are mild and are unlikely to be permanent.*

### **CONCLUSIONS**

DPMH-MHT has the following recommendations for Cotellic labeling:

- **Warnings and Precautions, Section 5.3**
  - Based on the increased likelihood of adverse fetal and infant effects due to cobimetinib's mechanism of action and teratogenicity seen in animal reproduction studies, a subsection describing embryo- and/or fetal risks ("Embryofetal Toxicity") as well as mitigation measures must be placed in the Warnings and Precautions section of labeling as required by regulation (21 CFR 201.57(c)(9)(i)(A)(4).

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<sup>19</sup> Nonclinical Team Primary Review, Cotellic (cobimetinib), NDA 206192. Shawna Weis, PhD, Anwar Goheer, PhD. May 29, 2015. DARRTS Reference ID 3768701.

- **Pregnancy, Section 8.1**
  - The “Pregnancy” subsection of cobimetinib labeling was formatted in the PLLR format to include “Risk Summary” and “Data” subsections.<sup>20</sup>
- **Lactation, Section 8.2**
  - The “Lactation” subsection of cobimetinib labeling was formatted in the PLLR format to include the “Risk Summary” subsection.<sup>21</sup>
- **Females and Males of Reproductive Potential, Section 8.3**
  - The “Females and Males of Reproductive Potential” subsection of cobimetinib labeling was formatted in the PLLR format to include “Contraception” to advise females of reproductive potential to use effective contraception during treatment and for 2 weeks (6 half-lives) following completion of therapy because of the potential for adverse fetal and infant effects from maternal exposure. This subsection is consistent with the PLLR for drugs with a likelihood of embryofetal toxicity.<sup>22</sup> In addition, the “Infertility” subsection was added due to data from animal studies that raised concerns about impaired human fertility in females and males.
- **Patient Counseling Information, Section 17**
  - The “Patient Counseling Information” section of cobimetinib labeling was updated to correspond with changes made to sections 5.3, 8.1, 8.2 and 8.3 of labeling.

## RECOMMENDATIONS

DPMH revised subsections 5.3, 8.1, 8.2, 8.3 and 17 in Cotellic labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

- Embryofetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and use of effective contraception (5.3, 8.1, 8.3).

### -----USE IN SPECIFIC POPULATIONS-----

- Lactation: (b)(4) (8.2).

## FULL PRESCRIBING INFORMATION

### 5 WARNINGS AND PRECAUTIONS

#### 5.3 Embryofetal Toxicity

Based on its mechanism of action and findings from animal reproduction studies, COTELLIC can cause fetal harm when administered to a pregnant woman. In animal

<sup>20</sup> Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection A-8.1 Pregnancy, 2-Risk Summary.

<sup>21</sup> Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, B- 8.2 Lactation, 1- Risk Summary.

<sup>22</sup> Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format. December 2014. Part IV Specific Subsection, C-8.3 Females and Males of Reproductive Potential.

reproduction studies, oral administration of cobimetinib in pregnant rats during the period of organogenesis was teratogenic and embryotoxic at doses resulting in exposures (b) (4) in humans at the recommended human dose of 60 mg. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with COTELLIC and for at least 2 weeks following the final dose [see *Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1)*].

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

Based on (b) (4) findings from animal reproduction studies, COTELLIC can cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology (12.1)*]. There are no available data on the use of COTELLIC during pregnancy. In animal reproduction studies, oral administration of cobimetinib in pregnant rats during organogenesis was teratogenic and embryotoxic a (b) (4) in humans at the recommended human dose of 60 mg [see *Data*]. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

#### Data

##### *Animal Data*

Administration of cobimetinib to pregnant rats during the period of organogenesis resulted in increased post-implantation loss, including total litter loss, at exposures (AUC) of 0.9-1.4 times those in humans at the recommended dose of 60 mg. Postimplantation loss was primarily due to early resorptions. Fetal malformations of the great vessels and skull (eye sockets) occurred at the same exposures.

### **8.2 Lactation**

#### Risk Summary

There is no information regarding the presence of cobimetinib in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed infant, advise a nursing woman not to breastfeed during treatment with COTELLIC and for 2 weeks after the final dose.

### **8.3 Females and Males of Reproductive Potential**

#### Contraception

##### *Females*

COTELLIC can cause fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1)*]. Advise females of reproductive potential to use effective contraception during treatment with COTELLIC and for at least 2 weeks after the final dose.

## Infertility

### *Females and Males*

Based on findings in animals, COTELLIC may reduce fertility in females and males of reproductive potential [see *Nonclinical Toxicology (13.1)*.]

## **17 PATIENT COUNSELING INFORMATION**

### Embryo-fetal Toxicity

- Advise females of reproductive potential of the potential risk to a fetus [redacted] (b) (4) their healthcare provider [redacted] (b) (4) [see *Warnings and Precautions (5.3)*, *Use in Specific Populations (8.1)*].
- Advise females of reproductive potential to use effective contraception during treatment with COTELLIC and for at least 2 weeks after the final dose [see *Use in Specific Populations (8.3)*].

### Lactation

- Advise women not to breastfeed during treatment with COTELLIC and for 2 weeks after the final dose [see *Use in Specific Populations (8.2)*]

### **Patient Information Cotellic (cobimetinib)**

#### **Before you take COTELLIC, tell your healthcare provider if you:**

- are pregnant or plan to become pregnant. COTELLIC can harm your unborn baby.
  - Patients who take COTELLIC should use effective methods of birth control during treatment with COTELLIC and for at least 2 weeks after stopping COTELLIC
  - Talk to your healthcare provider about birth control methods that may be right for you.
  - Tell your healthcare provider right away if you become pregnant or think you are pregnant during treatment with COTELLIC.
- are breastfeeding or plan to breastfeed. It is not known if COTELLIC passes into your breast milk. Do not breastfeed during treatment with COTELLIC and for 2 weeks after the final dose. Talk to your healthcare provider about the best way to feed your baby during this time.

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/s/  
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MIRIAM C DINATALE  
07/07/2015

TAMARA N JOHNSON  
07/07/2015

LYNNE P YAO  
07/09/2015

MEMORANDUM

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

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**CLINICAL INSPECTION SUMMARY**

**DATE:** May 27, 2015

**TO:** Meredith Libeg, Regulatory Project Manager  
Ruthann Giusti, M.D., Medical Reviewer  
Division of Oncology Products 2

**FROM:** Lauren Iacono-Connors, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
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**THROUGH:** Susan Thompson, M.D.  
Team Leader  
Good Clinical Practice Assessment Branch  
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Kassa Ayalew, M.D., M.P.H.  
Branch Chief  
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**SUBJECT:** Evaluation of Clinical Inspections

**NDA:** 206192

**APPLICANT:** Genentech, Inc.

**DRUG:** Cotellic (Cobimetinib, GDC-0973)

**NME:** Yes

**THERAPEUTIC CLASSIFICATION:** Priority

**INDICATION:** For the treatment of unresectable or metastatic melanoma with BRAF V600 mutation.

CONSULTATION REQUEST DATE: February 10, 2015 (Draft); May 11, 2015 (Final)  
INSPECTION SUMMARY GOAL DATE: June 15, 2015 (Original); May 18, 2015 (Revised)  
DIVISION ACTION GOAL DATE: July 30, 2015  
PDUFA DATE: August 11, 2015

## I. BACKGROUND:

Genentech, Inc. seeks approval to market cobimetinib (GDC-0973), a mitogen-activated protein kinase (MEK) inhibitor, for the treatment of patients with unresectable or metastatic melanoma with BRAF (proto-oncogene B-Raf [for the protein known as serine/threonine-protein kinase B-Raf]) V600 mutation. The BRAF mutation is found in approximately 50% of malignant melanoma tumors, primarily at codon V600. Oncogenic mutations in BRAF result in constitutive activation of the RAF-MEK-ERK pathway in the absence of typical growth factors; dysregulated downstream signaling via MEK and ERK leads to excessive cell proliferation, and survival. The activity of BRAF inhibitors, such as vemurafenib (Zelboraf) or dabrafenib, in BRAF-mutated melanoma is characterized by rapid and high response rates but a relatively brief progression free survival (PFS). Several mechanisms of acquired resistance result in loss of efficacy of BRAF inhibitors. Preclinical models demonstrated that the addition of a MEK inhibitor to a BRAF inhibitor may overcome acquired resistance to BRAF inhibition. Cobimetinib, a synthetically manufactured small molecule, is a potent and highly selective, small molecule inhibitor of the mitogen-activated protein kinases MEK1 and MEK2, central components of the RAS/RAF/MEK/ERK signal transduction pathway. This signaling pathway is highly conserved and plays an important role in cell proliferation, survival, migration, cell-cycle regulation, and angiogenesis.

The key study supporting this application is Study GO28141. This study is an international, randomized, double-blind, placebo-controlled Phase III study evaluating the safety and efficacy of 60 mg once daily of cobimetinib in combination with 960 mg twice daily of vemurafenib, compared to 960 mg twice daily of vemurafenib alone. Planned enrollment was a total of 500 subjects; 495 subjects were randomized into the study: 248 in the placebo plus vemurafenib arm and 247 in the cobimetinib plus vemurafenib arm. Treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent. Investigator-assessed Progression Free Survival (PFS) was the primary endpoint. The PFS outcome measure was defined as the time from randomization to the first occurrence of disease progression (as determined by the investigator using RECIST v1.1) or death from any cause, whichever came first. Data for patients who did not have documented disease progression or death at the time of data cutoff (May 9, 2014) were censored at the date of the last evaluable tumor assessment. Secondary endpoints include PFS by independent review committee (IRC); overall response rate (ORR), and overall survival (OS), other secondary endpoints included duration of response and other safety, pharmacokinetic, and quality of life measures.

The trial was conducted at 132 clinical centers in Australia (15), Austria (3), Belgium (6), Canada (7), Czech Republic (8), France (9), Germany (19), Great Britain (11), Hungary (3), Italy (11), Israel (3), Netherlands (3), New Zealand (2), Norway (1), Russia (5), Spain (7), Switzerland (1), Sweden (3), and the United States (16).

The study was conducted under IND 109307.

Four clinical sites were chosen for inspection: Site 256859 (Dr. Gabriella Liskay, Budapest, Hungary), Site 253588 (Dr. Paolo Ascierio, Napoli, Italy), Site 257793 (Dr. Virginia Ferraresi, Rome, Italy) and Site 255078 (Dr. Michele Maio, Siena, Italy) based on enrollment of large numbers of study subjects and significant primary efficacy results pertinent to decision making. The study Sponsor, Genentech, was also inspected.

## II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
<b>CI#1: Gabriella Liskay</b> Rath Gyorgy u. 7-9. Budapest, Hungary, 1122	Protocol: GO28141  Site Number: 256859  Number of Subjects: 15	April 27-29, 2015	Pending  Interim classification: NAI
<b>CI#2: Paolo Ascierio</b> Via Mariano Semmola, Napoli, Napoli, Italy, 80131	Protocol: GO28141  Site Number: 253588  Number of Subjects: 30	May 4-8, 2015	Pending  Interim classification: VAI
<b>CI#3: Virginia Ferraresi</b> Via Elio Chianesi, 53, Roma, Roma, Italy, 00144	Protocol: GO28141  Site Number: 257793  Number of Subjects: 15	May 11-15, 2015	Pending  Interim classification: OAI
<b>CI#4: Michele Maio</b> Viale Mario Bracci, 16, Siena, Siena, Italy, 53100	Protocol: GO28141  Site Number: 255078  Number of Subjects: 15	April 27-May 1, 2015	Pending  Interim classification: NAI
<b>Sponsor: Genentech, Inc.</b> 1 DNA Way, MS 241A South San Francisco, CA 94080-4990	Protocol: GO28141  Number of Sites Audited: 13	May 8-15, 2015	Pending  Interim classification: NAI

### 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 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

**1. CI#1: Dr. Gabriella Liskay (Site 256859)**

- a. What was inspected:** The site screened thirty two subjects and fifteen were enrolled. At the time of this inspection, seven subjects had died, one had withdrawn, five were in follow-up, and two subjects were still actively receiving study treatment. The study records of all fifteen enrolled subjects were audited. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 206192, with particular attention paid to inclusion/exclusion criteria compliance, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, and monitoring reports.
- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. The inspection revealed no significant deficiencies. Records and procedures were clear, and generally well organized. The primary efficacy endpoints were verified. There was no evidence of underreporting of adverse events. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles, and drug accountability found no major discrepancies. A Form FDA 483 was not issued.
- c. Assessment of data integrity:** The data for Dr. Liskay's site, associated with Study GO28141 submitted to the Agency in support of NDA 206192, appear reliable based on available information.

**Note:** The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

**2. CI#2: Paolo Ascierio (Site 253588)**

- a. What was inspected:** The site screened one hundred and five subjects, thirty subjects were enrolled, and twenty nine were treated with study drug. At the time of this inspection, four subjects remain in the study. Study records of twenty one subjects were audited. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 206192. The following records were reviewed: drug accountability, protocol deviations, randomization, adverse events, vital signs, laboratory results, prior and current medications, inclusion/exclusion criteria, and the use of concomitant medications. The FDA investigator also assessed informed consent documents, monitoring reports, IRB/EC documentation and financial disclosure.
- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. Records and procedures were clear, and generally well organized. The inspection revealed no major deficiencies. The

primary efficacy endpoints were verified. There was no evidence of underreporting of adverse events. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles, and drug accountability found no major discrepancies. The inspection found evidence that several AEs that occurred prior to the data cut-off date of May 9, 2014, were not entered into the CRF until after the data cut-off date. As such the AEs were not included in the data listings submitted to the application. There were also a few protocol deviations in which the ECG was taken only once instead of three times in sequence, per protocol. In addition, the site did not always use the sponsor-provided ECG machine, but instead sometimes used the ECG data taken from an ECHO test. These issues were discussed with the site and not included in the Form FDA 483. The above issues did not appear to be a systemic practice at this site and should not importantly impact study safety outcome or subject safety. The site enrolled three study subjects who met the protocol specified exclusion criteria 8.c., (History of congenital long QT syndrome or mean (average of triplicate measurements) QTcF > 450 msec at baseline). A Form FDA 483 was issued citing one inspection observation.

**Observation 1.** An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically, Subjects 2019, 2025 and 2179 were randomized and treated with study drug, yet each subject was found to have a QTcF > 450 msec at baseline. Per Exclusion Criteria 8.c., subjects with a history of congenital long QT syndrome or mean (average of triplicate measurements) QTcF > 450 msec at baseline were to be excluded.

*OSI Reviewer Notes: According to the FDA field investigator, in each case, the principal investigator realized the enrollment errors and corrected the site study records to note the protocol deviations. These PDs are accurately reflected in the data listings submitted in the application.*

*Dr. Ascierio provided a written response to the Form FDA 483 inspectional observations dated May 19, 2015. He explained that Subjects 2019 and 2025 were enrolled with a mean of the three QTc of 452.3 and 451.6 msec respectively (2.3 and 1.6 msec above protocol requirement, respectively). These values (slightly above 450 msec) were considered "not clinically significant" by Dr. Ascierio and his sub-investigators. In addition, Dr. Ascierio consulted a local cardiologist who also corroborated the determination of NCS for this entry criteria. Therefore, at the time Dr. Ascierio believed the subjects to be eligible for entry into the study. In regard to Subject 2179, Dr. Ascierio explained that the subject's QTc mean is documented as 484 msec correctly, but that this value was inadvertently misinterpreted as 448 msec. The source documents in the patient's chart provide all correspondence with Sponsor at the time of discovery of the error.*

*In Dr. Ascierio's written response to the Form FDA 483 inspectional observations dated May 19, 2015, he further explained that once these deviations were discovered by*

*the Monitor (May and August 2013), the site was re-trained and the Sponsor was immediately contacted to determine if the subjects would need to be withdrawn for safety reasons. The Sponsor confirmed that all subjects were able to remain on study as there was no safety risk. Documentation of these decisions by the Sponsor was provided to the site in June and September 2013.*

- c. Assessment of data integrity:** Notwithstanding the inspectional observations noted above, the data for Dr. Ascierito's site, associated with Study GO28141 submitted to the Agency in support of NDA 206192, appear reliable based on available information.

**Note:** The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

### **3. CI#3: Virginia Ferraresi (Site 257793)**

- a. What was inspected:** The site screened nineteen subjects and fifteen subjects were enrolled. At the time of this inspection five subjects remain in the study, two discontinued due to AEs, and eight discontinued due to progression. Study records of eleven subjects were audited. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 206192. The following records were reviewed; drug accountability, protocol deviations, randomization, adverse events, vital signs, laboratory results, prior and current medications, inclusion/exclusion criteria, and the use of concomitant medications. The FDA investigator also assessed informed consent documents, monitoring reports, IRB/EC documentation, and financial disclosure.
- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be marginal. The inspection revealed numerous protocol deviations and GCP compliance deficiencies. The site enrolled one subject into the study without documentation of informed consent. Subsequently, this subject underwent study procedures and treatment with study drug. The site had instances where the protocol specified imaging for subjects were either not done or delayed to a point where the imaging was out of window for that cycle. For example, Subject 2011 did not have tumor assessments performed following protocol timeline (every 8 weeks +/- 1 week); at Cycle 7 the tumor assessment was not done, and at Cycle 9 and Cycle 11 tumor assessments were performed but were more than 21 days out of window.

There was also evidence of underreporting of adverse events. The firm had transcription errors where AEs were inadvertently not transcribed onto the eCRF, and in some cases AEs that occurred prior to the data analyses cutoff date were not transcribed onto the eCRF until after the data cut-off date, May 2014. Therefore, the AEs were not included in the datalistings submitted to the application. For example, AEs and concomitant medications that were

documented in subject medical records and subject diaries were not always entered in the case report forms. Subjects' diary data not entered into the CRF included headache, nausea, rash, diarrhea, and use of heparin. A Form FDA 483 was issued citing 5 inspectional observations.

**Observation 1.** Failure to report promptly to the sponsor adverse effects that may reasonably be regarded as caused by, or probably caused by, an investigational drug.

Specifically,

The Clinical Investigator did not follow the protocol specified timelines for reporting Serious Adverse Events (SAEs) to the sponsor. Per Protocol GO28141 section 5.2.2, SAEs are required to be reported by the investigator immediately to the sponsor (i.e. not more than 24 hours after learning of the event).

For example,

- Subject 2047 was hospitalized for diverticulitis on [REDACTED] (b) (6). This SAE was not reported to the sponsor until July 23, 2013.
- Subject 2047 was hospitalized for an intestinal perforation on [REDACTED] (b) (6). This SAE was not reported to the sponsor until June 5, 2013.
- Subject 2098 was hospitalized for a fractured rib on [REDACTED] (b) (6). This SAE was not reported to the sponsor until November 1, 2013.

**Observation 2.** Failure to report promptly to the IRB all unanticipated problems involving risk to human subjects or others.

Specifically,

The Clinical Investigator did not follow the required timelines and protocol specified procedures for reporting Serious Adverse Events (SAE) to the local Ethics Committee (EC/IRB) for Protocol GO28141 (Section 8.3, Institutional Review Board or Ethics Committee; all versions).

The Clinical Investigator failed to report promptly to the EC/IRB (Ethic Committee-Comitato Etico Centrale Istituti IRCSS Lazio Sezione IFO-Biett) all adverse drug reactions (ADRs) that are both serious and unexpected, as required by EC/IRB regulations.

For example, on [REDACTED] (b) (6), Subject 2047 was hospitalized for diverticulitis. On [REDACTED] (b) (6), Subject 2047 was hospitalized for an intestinal perforation. Entries made by the investigator in the subjects' medical records (source records), states that a relationship between the study drug and these events cannot be ruled out.

These serious adverse events (SAEs) were not reported to the EC/IRB until February 6, 2014.

**Observation 3.** The IRB did not approve a written summary of what was to be said to the subject or the subject's legally authorized representative, in a situation where a short form written consent document was prepared. Specifically,

On March 10, 2014, Subject 2269 gave verbal informed consent to a study investigator, at which time study drugs were given to the subject and study tests were administered to the subject. The only record of this verbal consenting process is entries made by the investigator in the subjects medical records.

A short form informed consent document did not state that the required elements of informed consent had been presented orally to the subject or the subject's legally authorized representative, was not signed by the subject or the subject's legally authorized representative, and was not signed by the witness.

There was no witness to the oral presentation of the elements of informed consent, and a written consent document was not prepared.

**Observation 4.** An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.

Specifically,

The Clinical Investigator did not follow the approved investigational study plan, Protocol GO28141 (all versions). For all eleven subjects audited during this inspection (Subjects 2011, 2026, 2047, 2049, 2070, 2081, 2085, 2098, 2260, 2269, and 2370), subject source documents revealed that numerous and repeated safety monitoring procedures were not conducted during subject study visits such as ECGs, ECHOS (LVEF), and dermatologic exams. The required study visit laboratory test panels were incomplete. In addition, study visit CT scans for tumor assessments were not conducted, or not conducted within the required study time frames.

**Observation 5.** Investigational drug disposition records are not adequate with respect to dates, quantity, and use by subjects.

Specifically,

The quantities of drugs reported used in subject diaries do not reconcile with the Investigational Product Accountability Logs and/or subject medical records for six study subjects audited (Subjects 2026, 2070, 2081, 2085, 2098, and 2269).

Subject 2098 was given the incorrect lot of the study drug Vermurafenib on October 11, 2013. Subject 2070 was given the incorrect lot of the study drug Vermurafenib on November 26, 2013.

*OSI Reviewer Notes: Site 257793 had a relatively large number of protocol deviations, and GCP compliance violations. Most notable are enrolling and treating a subject without documentation of informed consent, numerous instances of underreporting of AEs to the study sponsor and the local ethics committee, and numerous protocol violations some of which may have put the subject at undo risk. Regarding inspectional observation item 1., these SAEs for Subjects 2047 and 2098, identified as not having been reported to the sponsor within the protocol-specified time frame, were included in the study datalistsings submitted to NDA 206192. Subjects 2047 and 2098 were randomized to the Vemurafenib + cobimetinib treatment arm. Regarding inspectional observation item 5., Subjects 2098 and 2070 received the correct study drug, but the study drug was from the wrong lot number, on the specified dates. Therefore, there would be no impact on subject safety for this particular observation. This inspection was completed on May 15, 2015, as such; the final Establishment Inspection Report (EIR) has not been completed by the FDA field investigator for review by OSI. Therefore, the specific details of each item referred to in the Form FDA 483 inspectional observations are not yet available and cannot be assessed for impact on site-generated data reliability and whether subjects were exposed to undue risk at this site.*

*The totality of inspectional observations demonstrated poor ability of this site to adhere to the investigational plan and provide adequate oversight of the conduct of the study. For these reasons OSI recommends the review team considers doing sensitivity analyses with a set of plausible possibilities for the data from Dr. Ferraresi's site. OSI will conduct a detailed compliance review upon receipt of the Establishment Inspection Report.*

*It should be noted that the inspection of the sponsor, Genentech, Inc., conducted in support of this application, found no evidence to suggest the Site 257793 issues were systemic across the study.*

- c. Assessment of data integrity:** Although regulatory violations were noted as described above they are unlikely to significantly impact primary safety and efficacy analyses. Data from Dr. Ferraresi's site appear acceptable with the proposed plan to conduct sensitivity analyses.

**Note:** The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

**4. CI#4: Michele Maio (Site 255078)**

- a. What was inspected:** The site screened twenty four subjects and fifteen subjects were enrolled. At the time of this inspection, four subjects remain in the study, one withdrew consent before disease progression, one withdrew consent after progression of the disease, and nine discontinued due to disease progression. Study records of all fifteen subjects were audited. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 206192. The following records were reviewed: drug accountability, protocol deviations, randomization, adverse events, vital signs, laboratory results, prior and current medications, inclusion/exclusion criteria, and the use of concomitant medications. The FDA investigator also assessed informed consent documents, monitoring reports, IRB/EC documentation and financial disclosure.
- b. General observations/commentary:** Generally, records and procedures were adequate, and generally well organized. The inspection revealed no significant deficiencies. Records and procedures were clear, and generally well organized. The primary efficacy endpoints were verified. There was no evidence of underreporting of adverse events. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles, and drug accountability found no major discrepancies. A Form FDA 483 was not issued.
- c. Assessment of data integrity:** The data for Dr. Maio's site, associated with Study GO28141 submitted to the Agency in support of NDA 206192, appear reliable based on available information.

**Note:** The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

**5. Sponsor: Genentech, Inc.**

- a. What was inspected:** The inspection focused on thirteen study sites. The inspection included but was not limited to assessment of adverse events/serious adverse events reporting, efficacy endpoint data, Principal Investigator site qualification (financial disclosure, IRB, and curriculum vitae), study specific training for investigators and monitors, Form FDA 1572 and investigator agreements, and monitoring reports.
- b. General observations/commentary:** Records and procedures were clear, and generally well organized. The sponsor maintained adequate oversight over the study. There was no evidence of under-reporting of AEs/SAEs by the sponsor. The primary efficacy endpoint data were verifiable. No significant discrepancies were noted. Compliance with the investigational plan appeared to be adequate.

Monitoring appeared adequate and non-compliant sites were escalated by the monitors to the Sponsor. No study sites were closed due to non-compliance. There was no evidence to suggest that the compliance issues observed during the associated inspection of Dr. Ferraresi's site (257793) were systemic across study clinical sites. No Form FDA 483 was issued.

- c. Assessment of data integrity:** The data from this sponsor submitted to the Agency associated with Study GO28141 in support of NDA 206192 appear reliable based on available information.

**Note:** The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for clinical investigators Dr. Gabriella Liszkay (Site 256859), Dr. Paolo Ascierio (Site 253588), Dr. Michele Maio (Site 255078), and the study sponsor, Genentech, Inc., the Study GO28141 data submitted to the Agency in support of NDA 206192, appear reliable based on available information. Based on the review of preliminary inspectional findings for Dr. Ferraresi's site the Study GO28141 data appear acceptable with the proposed plan to conduct sensitivity analyses.

Site 257793 (Dr. Virginia Ferraresi) had a number of protocol deviations, and GCP compliance violations. The preliminary inspection observations were provided to the OSI reviewer Lauren Iacono-Connors on May 18, 2015. The final Establishment Inspection Report was not available at the time this CIS was finalized. The inspectional observations demonstrated poor ability of this site to adhere to the investigational plan and provide adequate oversight of study conduct. For these reasons OSI recommends the review team considers doing sensitivity analyses with a set of plausible possibilities for the data from Dr. Ferraresi's site because of poor ability of the site to adhere to the investigational plan and provide adequate oversight of study conduct.

The inspectional findings of the study sponsor found no significant issues. The sponsor inspection found no evidence to suggest that the inspectional observations and issues raised at Dr. Ferraresi's site were systemic across study clinical sites. The data submitted to the Agency in support of NDA 206192, appear reliable.

**Note:** The observations noted above are based on the preliminary communications provided by the FDA field investigators. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

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/s/  
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LAUREN C IACONO-CONNORS  
05/27/2015

SUSAN D THOMPSON  
05/27/2015

KASSA AYALEW  
05/27/2015

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**LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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**Date of This Review:** May 20, 2015  
**Requesting Office or Division:** Division of Oncology Products 2 (DOP2)  
**Application Type and Number:** NDA 206192  
**Product Name and Strength:** Cotellic (cobimetinib) Tablets, 20 mg  
**Product Type:** Single Ingredient Product  
**Rx or OTC:** Rx  
**Applicant/Sponsor Name:** Genentech, Inc.  
**Submission Date:** December 11, 2014 and April 6, 2015  
**OSE RCM #:** 2014-2484  
**DMEPA Primary Reviewer:** Otto L. Townsend, PharmD  
**DMEPA Team Leader:** Chi-Ming (Alice) Tu, PharmD

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## 1 REASON FOR REVIEW

As part of the New Drug Application review, we assessed the proposed prescribing information, container label, and carton labeling for areas vulnerable to medication errors.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	B – N/A
Previous DMEPA Reviews	C – N/A
Human Factors Study	D – N/A
ISMP Newsletters	E – N/A
Other	F – N/A
Labels and Labeling	G
Recommendations for the Prescribing Information	H

N/A=not applicable for this review

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We identified the following areas of vulnerability that could lead to medication errors:

- The Prescribing Information Section 2.2 (Dose Modifications) is difficult to follow. In the filing communication to Genentech, the Agency recommended revision of this section.
- The Patient Information section of the PI contains treatment schedule instructions that may be confusing to patients.
- The carton labeling contains a tablet image that does not truly reflect the actual tablet.

## 4 CONCLUSION & RECOMMENDATIONS

The proposed container label, carton labeling, and prescribing information can be improved to provide clarity and promote safe use of the product.

### 4.1 RECOMMENDATIONS FOR THE DIVISION

See Appendix H for our recommendations for the PI to promote the safe use of Cotellic (cobimetinib). DMEPA will participate in labeling meetings to provide further rationale for these recommendations. In addition, we provide the following general comments:

1. The PI contains sections that are written in passive voice. We defer to SEALD and the review team for appropriate recommendations on the use of active voice throughout the PI as communicated in the February 23, 2015 Filing Communication.
2. Delete the brackets surrounding the proprietary name, Cotellic.
3. We recommend the use of a table to more clearly present dose modification guidelines. We have proposed a table for your consideration as in-line track changes in Appendix H.
4. We defer to the Division of Medical Policy Programs (Patient Labeling) for the appropriateness of the following. The “How should I take [COTELLIC] ?” subsection of the Patient Information section of the PI contains the statement, “[COTELLIC] is usually taken for 21 days followed by a 7 day rest period (no drug) for a 28 day cycle.” This statement could be confusing to patients.

#### **4.2 RECOMMENDATIONS FOR GENETECH**

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

##### Carton Labeling



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<sup>1</sup> Guidance for Industry: Safety considerations for container labels and carton labeling design to minimize medication errors (Draft Guidance). April 2013.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for cobimetinib that Genentech, Inc. submitted on April 6, 2015.

<b>Table 2. Relevant Product Information for Cobimetinib</b>	
<b>Initial Approval Date</b>	N/A
<b>Active Ingredient</b>	cobimetinib
<b>Indication</b>	Use in combination with Zelboraf <sup>®</sup> (vemurafenib) for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutation.
<b>Route of Administration</b>	Oral
<b>Dosage Form</b>	Tablet
<b>Strength</b>	20 mg
<b>Dose and Frequency</b>	60 mg (3 tablets) orally once daily for 21 consecutive days followed by a 7-day rest period in combination with Zelboraf.
<b>How Supplied</b>	20 mg film-coated tablets in bottles of 63 tablets.
<b>Storage</b>	At or below 86°F (30°C).
<b>Container Closure</b>	70 mL nominal-volume, white, (b) (6) square, high-density polyethylene (HDPE) bottle with a plastic (b) (6) screw cap (b) (6).

## **APPENDIX G. LABELS AND LABELING**

### **G.1 List of Labels and Labeling Reviewed**

Using the principles of human factors, Failure Mode and Effects Analysis,<sup>2</sup> and postmarket medication error data, we reviewed the following cobimetinib labels and labeling submitted by Genentech on December 11, 2014 and April 6, 2015.

- Container label submitted December 11, 2014
- Carton labeling submitted December 11, 2014
- Prescribing Information submitted April 6, 2015

### **G.2 Label and Labeling Images**

(b) (4)



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

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<sup>2</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/  
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OTTO L TOWNSEND  
05/20/2015

CHI-MING TU  
05/20/2015

## Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

<b>IND or NDA</b>	NDA 206192
<b>Brand Name</b>	Cotellic
<b>Generic Name</b>	Cobimetinib
<b>Sponsor</b>	Roche, Genentech
<b>Indication</b>	Unresectable or metastatic melanoma with BRAF V600 mutation
<b>Dosage Form</b>	hard gelatin capsule
<b>Drug Class</b>	Inhibitor of mitogen-activated protein kinase (MEK)
<b>Therapeutic Dosing Regimen</b>	60 mg orally daily for 21 consecutive days followed by a 7-day rest period in combination with Zelboraf
<b>Duration of Therapeutic Use</b>	Chronic
<b>Maximum Tolerated Dose</b>	MTD is dependent on the dosing scheme. 21 days dosing and 7 days off; 60 mg 14 days dosing and 14 days off: 100 mg
<b>Submission Number and Date</b>	SDN # 002 , 3/2/2015
<b>Review Division</b>	Division of Oncology Products (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

This study includes data from cancer patients enrolled in three cobimetinib clinical studies who received cobimetinib once daily (QD) across various dose levels. Based on data from Studies MEK4592g, GO28141 and NO25395, no large changes (i.e., > 20 ms) in the QTcF intervals were detected when administered cobimetinib 60 mg - 125 mg, vemurafenib with and without co-administration cobimetinib 60 mg, and cobimetinib 60 mg co-administered with vemurafenib 720 mg and 960 mg, respectively. The sponsor did not obtain placebo and positive control (moxifloxacin) arms. Therefore, no assay sensitivity was established.

There are 114, 435, and 123 subjects from Studies MEK4592g, GO28141 and NO25395, respectively, who received cobimetinib 60 mg – 125 mg, vemurafenib with and without co-administration of cobimetinib 60 mg, and cobimetinib 60 mg co-administered with vemurafenib 720 mg and 960 mg. Overall summary of findings is presented in Table 1.

**Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Cobimetinib and the Largest Lower Bound for Moxifloxacin (FDA Analysis)**

Treatment Group	$\Delta$ QTcF (ms)	Std Dev	90% CI (ms)
Cobimetinib 60 mg (Study MEK4592g)	-2.2	11.0	(-3.7, -0.7)
Cobimetinib 80 mg (Study MEK4592g)	-0.3	13.9	(-4.6, 4.1)
Cobimetinib 100 mg (Study MEK4592g)	2.2	10.4	(0.9, 3.5)
Cobimetinib 125 mg (Study MEK4592g)	-11.2	16.7	(-16.2, -6.3)
Vemurafenib 960 mg BID + Placebo (Study GO28141)	13.1	16.5	(12.2, 13.9)
Cobimetinib 60 mg + Vemurafenib 960 mg b.i.d. (Study GO28141)	7.8	16.1	(6.9, 8.6)
Cobimetinib 60 mg + Vemurafenib 720 mg b.i.d. (Study NO25395)	6.2	20.8	(4.7, 7.7)
Cobimetinib 60 mg + Vemurafenib 960 mg b.i.d. (Study NO25395)	6.8	18.1	(5.8, 7.9)

Applicant's vemurafenib concentration- $\Delta$ QTcF analysis of trial GO28141 confirms the known positive relationship between vemurafenib exposure and increase in QT interval. Furthermore, data from the same trial show that there is no evident concentration-QTc relationship for cobimetinib. In cobimetinib monotherapy study MEK4592g, a significant relationship between cobimetinib exposure and  $\Delta$ QTcF was not observed either.

However, that finding was not confirmed in Study NO25395 in the sponsor's pooled analysis of all three trials. The reviewer's analysis of NO25395 confirmed the significant relationship between vemurafenib concentration and QT prolongation. The analysis also showed that there was a significant slope between cobimetinib exposure and  $\Delta$ QTcF in NO25395, although the QT effect of cobimetinib seems small. However, there are limitations of concentration-QTc analysis for a combination therapy<sup>1</sup> because of the correlation between the concentrations of the two drugs.

## 1.2 QT INTERDISCIPLINARY REVIEW TEAM'S COMMENTS

- The exploratory analysis cannot fully rule out cobimetinib's QT prolongation risk.

<sup>1</sup> Zhu, Hao, and Yaning Wang. "Evaluation of false positive rate based on exposure-response analyses for two compounds in fixed-dose combination products." *Journal of pharmacokinetics and pharmacodynamics* 38, no. 6 (2011): 671-696.

- Because cobimetinib is proposed to be used in combination with vemurafenib (Zelboraf®) which prolongs QT at the therapeutic dose, no additional QT assessment is needed for this combination product.
- A dedicate QT study will be needed if cobimetinib is further developed as a monotherapy or in combination with other drugs.

## 2 PROPOSED LABEL

*Our proposed language is a recommendation only. We defer final labeling language to the Division.*

Full prescribing information

Used alone, the QT effect of cobimetinib at doses up to 125 mg daily appears to be <20 ms. Clinically relevant QT prolongation has been reported with vemurafenib, but when vemurafenib and cobimetinib 60 mg are combined, substantial further increase in QTc was not observed. Monitor ECG and electrolytes before initiating treatment and routinely during treatment with the combination. See vemurafenib's label for details.

## 3 BACKGROUND

### 3.1 PRODUCT INFORMATION

Cobimetinib (also known as GDC-0973, XL518, and RO5514041) is a potent and selective, non-competitive small molecule inhibitor of mitogen-activated protein kinase (MEK). Cobimetinib in combination with vemurafenib (Zelboraf®) is under development for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation. (b) (6).

### 3.2 MARKET APPROVAL STATUS

Cobimetinib is not approved for marketing in any country. Vemurafenib is approved in USA, EU, and other countries.

### 3.3 PRECLINICAL INFORMATION

Cobimetinib can inhibit the hERG channel with potency (IC50) of 266 ng/mL. However, the IC50 estimate is 19-fold the unbound  $C_{max,ss}$  of cobimetinib following dosing of 60 mg q.d. (14 ng/mL). Total  $C_{max,ss}$  is estimated at 253 ng/mL following the same dosing regimen.

Vemurafenib can prolong QTc interval prolongation in a concentration-dependent manner. The concentration-effect slope is estimated at 0.184 ms per  $\mu\text{g/mL}$ . However, there have not been any cases of TdP in any vemurafenib-treated patient in metastatic melanoma studies.

Potential for additive inhibition of hERG channel was evaluated with the vemurafenib-cobimetinib combination. The determined IC50 value suggests an additive effect of on hERG inhibition.

### 3.4 PREVIOUS CLINICAL EXPERIENCE

Cobimetinib has been administered to 75 healthy subjects in 5 clinical pharmacology studies. Furthermore, cobimetinib has been administered in an additional 5 clinical trials, including 4 combination trials with other drugs, and 2 single-patient INDs. Total number of patients exposed to cobimetinib alone or in combination with other products is 842.

### 3.5 CLINICAL PHARMACOLOGY

Following oral dosing of 60 mg in cancer patients, cobimetinib showed a moderate rate of absorption with a median  $T_{max}$  of 2.4 hours. The mean steady-state  $C_{max}$  and  $AUC_{0-24}$  were 273 ng/mL and 4340 ng.h/mL respectively. The mean accumulation ratio at steady state was approximately 2.4-fold.

Cobimetinib has linear pharmacokinetics in the dose range of ~3.5 mg to 100 mg.

The pharmacokinetics of cobimetinib are not altered when administered in the fed state (high-fat meal) compared with the fasted state in healthy subjects.

Cobimetinib was extensively metabolized and eliminated in feces; no single metabolite was predominant. Oxidation by CYP3A and glucuronidation by UGT2B7 appear to be the major pathways of cobimetinib metabolism. Cobimetinib is the predominant moiety in plasma. No oxidative metabolites > 10% of total circulating radioactivity or human specific metabolites were observed. Unchanged drug in feces and urine accounted for 6.6% and 1.6% of the administered dose, respectively, indicating that Cobimetinib is primarily metabolized with very little renal elimination.

The mean elimination half-life following oral dosing of cobimetinib was 43.6 hours (range: 23.1 to 69.6 hours).

Cobimetinib is metabolized by CYP3A and cobimetinib AUC increased approximately 7-fold in the presence of a potent CYP3A inhibitor (itraconazole) in healthy subjects. Since cobimetinib is a sensitive substrate of CYP3A, it is likely that cobimetinib exposures will be significantly lower in the presence of CYP3A inducers. Therefore concomitant administration of strong CYP3A inducers and inhibitors is not recommended. Caution should be exercised when cobimetinib is co-administered with moderate CYP3A inducers and inhibitors.

*Source: from the proposed label.*

## 4 SPONSOR'S SUBMISSION

### 4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conduct of this study, under IND 109307. The sponsor submitted the report "Concentration-QTc Interval Analysis for Cobimetinib", including electronic datasets and waveforms to the ECG warehouse. The sponsor's report is based on the following studies identified by their protocol number: MEK4592g, NO25395, and GO28141.

## 4.2 TQT STUDY

### 4.2.1 Title

Concentration-QTc Interval Analysis for Cobimetinib

### 4.2.2 Protocol Number

MEK4592g, NO25395, and GO28141

### 4.2.3 Study Dates

Study ID: MEK4592g

Title: A phase I dose-escalation study of the safety and pharmacokinetics of gdc-0973/x1518 administered orally daily to subjects with solid tumors

Dates: 3 May 2007 to 25 May 2012

Study ID: NO25395

Title: A Phase Ib, open label, dose-escalation study evaluating the safety, tolerability and pharmacokinetics of vemurafenib in combination with GDC-0973 (cobimetinib) when administered in BRAFV600E mutation-positive patients previously treated (but without prior exposure to BRAF or MEK inhibitor therapy) or previously untreated for locally advanced/unresectable or metastatic melanoma or those who have progressed after treatment with vemurafenib.

Dates: First patient entered: 17 Feb 2011  
Last patient entered: 23 July 2013  
Data cut-off: 01 Oct 2013

Study ID: GO28141

Title: A Phase III double-blind, placebo-controlled study of vemurafenib versus vemurafenib plus GDC-0973 in previously untreated BRAF600-mutation positive patients with unresectable locally advanced or metastatic melanoma

Dates: First patient entered: 8 January 2013  
Last patient entered: 31 January 2014  
Data cut-off: 9 May 2014

### 4.2.4 Objectives

The primary objective of this analysis was to characterize the relationship between plasma cobimetinib and vemurafenib concentrations and baseline-adjusted QTc interval corrected for heart rate using Fridericia method ( $\Delta QTcF$ ) to determine if:

- Cobimetinib prolongs the QTcF interval when administered as a single agent in Study MEK4592g; and
- QTcF interval prolongation with vemurafenib administration is augmented when vemurafenib is co-administered with cobimetinib in Study GO28141.

As a secondary objective, data from these clinical studies were pooled with data from Study NO25395 to develop a C-QTc model to support the results of the individual studies and to assess the effects of patient- and study-level covariates.

## 4.2.5 Study Description

MEK4592g: A Phase I dose escalation and expansion study in patients with solid tumors. Cobimetinib doses ranged from 2.1 to 125 mg once daily (QD) on two schedules, 21/7 (21 days on and 7 days off) and 14/14 (14 days on and 14 days off).

GO28141: A phase III, double-blind, placebo-controlled study of vemurafenib (Zelboraf®) (960 mg twice daily (BID) on a 28/0 schedule) versus vemurafenib (960 mg BID on a 28/0 schedule) plus cobimetinib (60 mg on a 21/7 schedule) in previously untreated BRAF V600 mutation-positive patients with unresectable locally advanced or metastatic melanoma.

NO25395: A Phase Ib dose escalation and expansion study in advanced melanoma patients with BRAF V600E mutation in combination with vemurafenib. Cobimetinib doses ranged from 60 to 100 mg QD on three schedules, 14/14, 21/7 and 28/0 (28 days on and 0 days off) and vemurafenib doses were 720 and 960 mg BID on a 28/0 schedule.

### 4.2.5.1 Design

#### MEK4592g:

This is a Phase I, nonrandomized, open-label, safety and PK dose-escalation study. The study consisted of 4 treatment stages listed below.

- |            |   |
|------------|---|
| Stage I:   | Dose-escalation cohorts were treated on a 21-days-on, 7-days-off schedule to determine the MTD.   |
| Stage IA:  | Dose-escalation cohorts, starting at the MTD of the 21-days-on, 7-days-off schedule, were treated on a 14-days-on, 14-days-off schedule to determine the MTD on an alternate dosing regimen.                                  |
| Stage II:  | Expansion cohort with the MTD determined in Stage I in approximately 20 patients with FDG-PET-avid tumors harboring a BRAF, NRAS, or KRAS mutation (as discussed in the Protocol Section 1.1.1) and with FDG-PET-avid disease |
| Stage IIA: | Expansion cohort with the MTD determined in Stage IA in approximately 20 patients with FDG-PET-avid tumors harboring a BRAF, NRAS, or KRAS mutation   |

#### GO28141:

Study GO28141 was a Phase III randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of vemurafenib in combination with cobimetinib as

compared to vemurafenib alone, in previously untreated BRAFV600 mutation-positive patients with unresectable locally advanced or metastatic melanoma.

A total of 500 patients were planned for enrollment; 495 patients were randomized into the study: 248 in the placebo plus vemurafenib arm and 247 in the cobimetinib plus vemurafenib arm.

Arm A (control arm): vemurafenib 960 mg by mouth (PO) twice daily (BID) on Days 1–28 and placebo PO once daily (QD) on Days 1–21 of each 28-day treatment cycle

Arm B (investigational arm): vemurafenib 960 mg PO BID on Days 1–28 and cobimetinib 60 mg PO QD on Days 1–21 of each 28-day treatment cycle

Study drug was administered until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurred earliest.

#### NO25395:

Phase Ib, open label, dose-escalation study to evaluate the safety, tolerability, and pharmacokinetics of cobimetinib in combination with vemurafenib in BRAFV600E mutation-positive (as detected by cobas 4800 BRAF V600 Mutation Test) patients previously treated (but without prior exposure to BRAF or MEK inhibitor therapy) or previously untreated for locally advanced/unresectable or metastatic melanoma or those who have progressed after treatment with vemurafenib.

Dose-escalation stage: 10 dose-escalation cohorts of 3–6 patients each were enrolled in order to identify a safe and tolerable dose of each agent to be administered during the cohort-expansion stage, i.e., the potential recommended Phase II/III dose combination.

Cohort-expansion stage: After a cohort was declared safe and tolerable, cohort-expansion was instituted for that specific cohort. Expansion Cohort 1 was open to patients whose melanoma had progressed while on vemurafenib immediately preceding enrollment in this trial (vemurafenib-PD patients). Expansion Cohort 2 enrolled patients without prior treatment for locally advanced/unresectable or metastatic melanoma or those who were previously treated but without prior exposure to any BRAF or MEK inhibitor therapy (BRAFi-naïve patients). Expansion cohorts allowed for the gathering of additional safety and PK data and the opportunity to better describe the PD effects of the combination.

#### **4.2.5.2 Controls**

The submitted report is not based on a TQT study; no placebo control and positive control were used.

#### **4.2.5.3 Blinding**

Study NO25395 and MEK4592g were open label studies. Study GO28141 was randomized and double blind.

#### **4.2.6 Treatment Regimen**

An overview of treatment regimens is shown in Table 2.

**Table 2: Overview of Clinical Studies**

Study	Phase	n <sup>a</sup> (N)	Population	Cobimetinib dose and schedule	Other anti-cancer drugs delivered in combination
MEK4592g	I	57 (114)	Solid tumors with RAS- or RAF-mutant tumors	QD 14/14: 60-125 mg QD 21/7: 2.135-80 mg	
GO28141	III	435 (495)	BRAF V600-mutation positive advanced melanoma	QD 21/7 : 60 mg or placebo	Vemurafenib 960mg BID
NO25395	Ib	123 (131)	BRAF V600-mutation positive advanced melanoma	QD 14/14: 60-100 mg QD 21/7 : 60 mg QD 28/0 : 60 mg	Vemurafenib 720 or 960mg BID

*a* Number of subjects available for analysis with time-matched PK and  $\Delta$ QTcF values. *n* = number of subjects in the analysis; *N* = number of subjects in the clinical study

RAS= Rat sarcoma; RAF= Rapidly Accelerated Fibrosarcoma; BRAF=Human gene that makes a protein called B-Raf; QD=Daily dose; BID= Twice daily, 14/14 = 14 days on and 14 days off; 21/7 = 21 days on and 7 days off; 28/0 = 28 days on and 0 days off.

Source: Sponsor's report, Table 3-1.

#### 4.2.6.1 Sponsor's Justification for Doses

This is not a TQT study. The sponsor did not provide justification for doses. The applicant provides the following justification for the overall strategy regarding assessment of QT prolongation.

Cobimetinib cannot be administered (on a once-daily [QD] schedule to assess the effect at steady-state) to healthy subjects at therapeutic doses due to risk-benefit profile; therefore triplicate ECG monitoring was performed during the course of clinical studies to evaluate the corrected QT (QTc) prolongation potential. This report addresses the C-QTc modeling of cobimetinib (GDC-0973 or RO5514041 or XL518) and vemurafenib (RO5185426 or PLX4032) either given as single agents or in combination

*Reviewer's comment: Applicant's strategy to combined results from multiple trials has been found acceptable for the combination therapy in the previous review by QT-IRT dated June 20, 2012 as well as January 6, 2014. This reviewer concurs with that assessment.*

#### 4.2.6.2 Instructions with Regard to Meals

Both cobimetinib/placebo and vemurafenib and were to be taken with a glass of water, with or without a meal.

*Reviewer's Comment: Food has no impact on cobimetinib PK. Instructions with or without regard meals are therefore appropriate.*

#### 4.2.6.3 ECG and PK Assessments

The PK and ECG sampling scheme varied between the three studies. Sampling schedule for study MEK4592g is shown in Table 3.

**Table 3: Time-Matched PK and Triplicate ECG Assessments in Study MEK4592g**

Stage	Cycle 1							Cycle 2-	Cycles
	1	2	8	14	15	21	22	3	4+
Stage I	X <sup>a</sup>		X		X	X		X	X
Stage Ia	X <sup>b</sup>	X	X	X <sup>b</sup>				X	X
Stage II	X <sup>b</sup>	X				X <sup>b</sup>			
Stage IIa	X <sup>b</sup>	X		X <sup>b</sup>					

*a: Pre-dose and 4-hours post-dose*

*b: Pre-dose, 1.5, 3 and 6 hours post-dose*

*All are pre-dose measurements except where noted.*

*Source: Applicant's report, Table 5-1.*

#### Study GO28141:

Standard 12-lead surface ECGs were performed in triplicate for each assessment time-point.

Time-matched PK and ECGs were obtained pre-dose on Cycle 1, Day 15 ± 3 days of study treatment; 2 – 4 hours post-dose on Cycle 1, Day 15 ± 3 days of study treatment; Cycle 2, Day 15 ± 3 days of study treatment.

#### Study NO25395:

Triplicate 12-lead ECG monitoring had to be performed more frequently if clinically indicated. ECG on Day -1 was not required for previously treated (but without prior exposure to BRAF or MEK inhibitor therapy) or previously untreated for locally advanced/unresectable or metastatic melanoma patients.

Time-matched PK/ECGs were performed at Day –1, Hour 0 (pre-vemurafenib dose); Cycle 1, Day 1, Hour 4 (4 hours post-cobimetinib dose); Day 2, Hour 0 (pre-dose); Day 14, Hour 0 (predose) and Hours 2, 4, and 8 post-dose; Cycle 2, Day 1; and at disease progression (or final visit).

*Reviewer's Comment: The PK and ECG sampling schedule is not optimized for a typical TQT study. Given the proposed indication and the difficulties of performing a TQT in healthy volunteers, the sampling schedule seems reasonable.*

#### **4.2.6.4 Baseline**

The sponsor used the averaged pre-dose QTc values as baselines.

#### **4.2.7 ECG Collection**

Triplicate 12-lead ECGs were performed consecutively within a total time of no more than 2 minutes to appropriately average the QTc intervals.

#### **4.2.8 Sponsor's Results**

##### **4.2.8.1 Study Subjects**

There are 114, 435, and 123 subjects from Studies MEK4592g, GO28141 and NO25395, respectively, who received cobimetinib 60 mg - 125 mg, vemurafenib 960 mg b.i.d. with and without co-administration of cobimetinib 60 mg, and cobimetinib 60 mg co-administered with vemurafenib 720 mg b.i.d. and 960 mg b.i.d.

##### **4.2.8.2 Statistical Analyses**

###### **4.2.8.2.1 Primary Analysis**

The sponsor did not perform E14 analysis.

*Reviewer's Comments: We will provide our independent analysis result in Section 5.2. Statistical reviewer performed summary statistics and analyses of  $\Delta QTcF$  for studies of MEK4592g, NO25395, and GO2814.*

###### **4.2.8.2.2 Assay Sensitivity**

No positive control arm included in these studies, therefore, no assay sensitivity established.

###### **4.2.8.2.3 Categorical Analysis**

The sponsor did not perform categorical analysis.

##### **4.2.8.3 Safety Analysis**

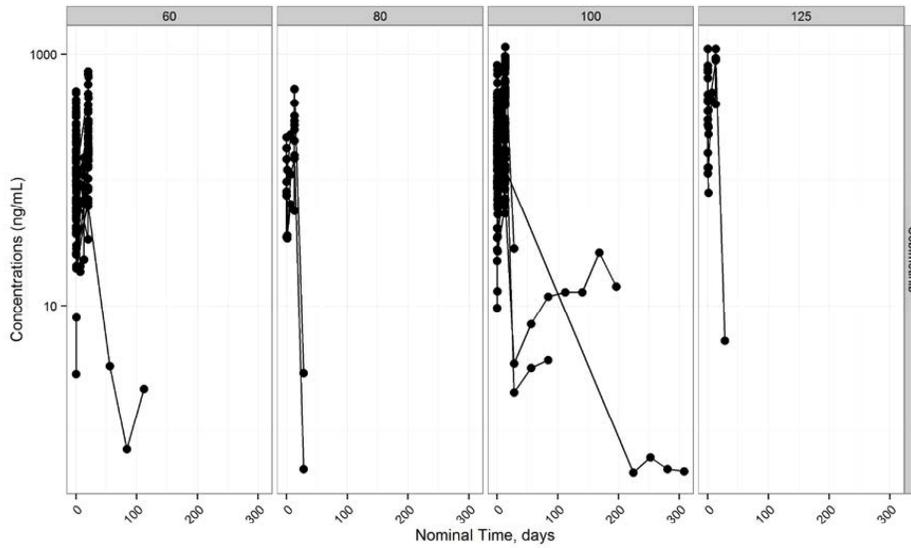
The sponsor did not conduct a safety analysis.

##### **4.2.8.4 (ClinPharm) Clinical Pharmacology**

###### **4.2.8.4.1 Pharmacokinetic Analysis**

The applicant has not performed a PK analysis due to the nature of the PK sampling schedule. A plot of the available PK from is shown in Figure 1.

**Figure 1: Scatter Plots of Concentrations versus Nominal Time**  
Study MEK4592g

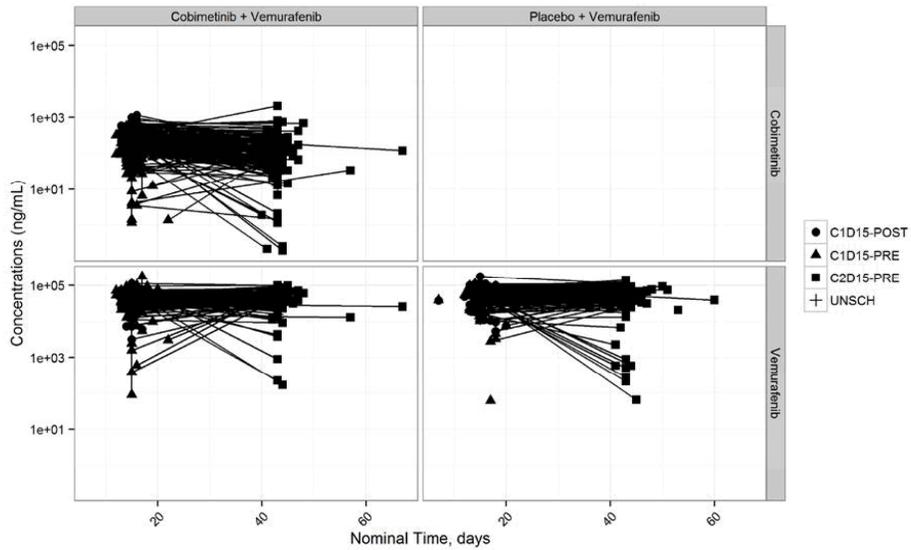


Individual subject data are connected by the solid line

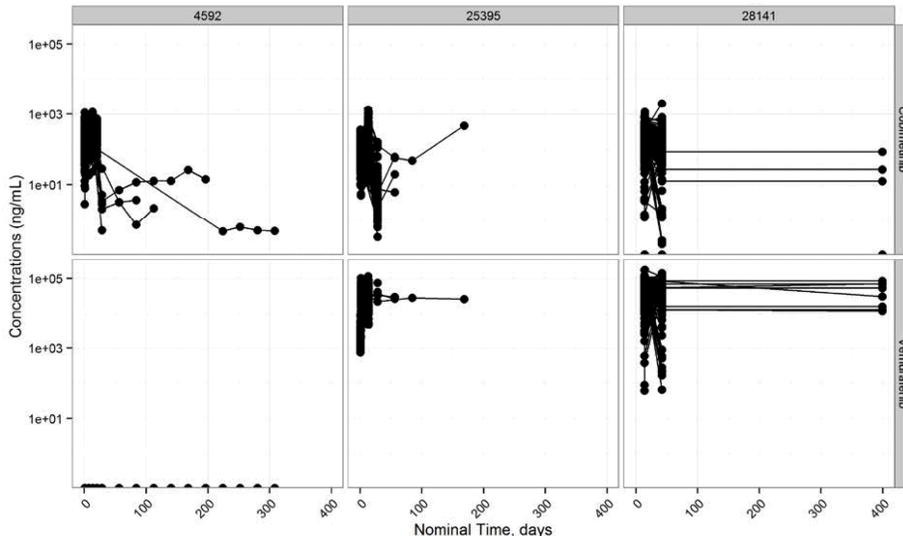
Source: Applicant's report, Figure 11-1

Note: Each panel shows individual concentration time points from subjects receiving the 60, 80, 100, or 125 mg dose of the product.

Study GO28141



## Pooled Studies



Source: Applicant's report, Figure 11-10.

Note: Each panel represent patients from one of the three studies, MEK4592g=4592, GO28141=28141, NO25395=25395

### 4.2.8.4.2 Exposure-Response Analysis

The applicant has performed the following exposure response analyses.

#### C-QTc relationship for cobimetinib administered as monotherapy using data from Study MEK4592g

The applicant fitted a linear mixed effect model with  $\Delta QTcF$  as the dependent variable and plasma concentration of cobimetinib as the independent variable. The final model included random effects on slope and intercept. Intercept was fixed to zero. Slope parameter was not significantly different from zero.

#### the C-QTc relationship for vemurafenib with and without coadministration of cobimetinib using data from study GO28141

The applicant fitted a linear mixed effect model with  $\Delta QTcF$  as the dependent variable and plasma concentrations of vemurafenib as the independent variable using both arms of study GO28141 (arm A=placebo+vemurafenib, arm B =cobimetinib+vemurafenib). The final model included random effects on intercept but not slope. The applicant did not fit a random effect parameter on slope because when that parameter could not be estimated with good precision. The slope parameter was estimated to be statistically significant with an estimate of 0.148 ms per  $\mu\text{g/mL}$ , 95% CI: (0.105, 0.190). The effect on study arm B on the slope parameter was estimated to -0.0805, 95% CI: (-0.125,-0.0356). The final model is shown in the equation below.

$$\Delta QTcF = \text{Intercept} + \eta_1 + (\text{Vem Slope} + \text{ARM B}) * \text{Vem} + \text{Residual Error}$$

In the next step of the analysis the applicant added the effect of cobimetinib concentration on the model shown in the equation above resulting in the effect of study arm B on the vemurafenib slope no longer being significant. The estimated cobimetinib slope was negative. The applicant makes the following interpretation: "...subjects who received cobimetinib plus vemurafenib (Arm B) had less QTcF prolongation than those subjects who received placebo plus vemurafenib (Arm A)."

The final model parameters are shown in Table 4.

**Table 4: Cobimetinib and Vemurafenib C-QTc Model Parameters (GO28141)**

Parameter	Estimate	SE	RSE %	95% CI
Intercept (ms)	5.03	1.31	26.0	(2.46, 7.60)
Vem Slope (ms per µg/mL)	0.118	0.0208	17.6	(0.0768, 0.158)
Cobi Slope (ms per ng/mL)	-0.018	0.00299	16.6	(-0.0239, -0.0121)
BSV Intercept (SD) (ms)	12.5	0.552	4.42	(11.4, 13.6)
Residual Error (SD) (ms)	9.57	0.277	2.89	(9.04, 10.1)

*Model QT5.Sub2:  $\Delta QTcF = \text{Intercept} + \eta_1 + \text{Vem-Slope} * \text{Vem} + \text{Cobi-Slope} * \text{Cobi} + \text{Residual Error}$*

*Abbreviations: Vem=vemurafenib; Cobi=cobimetinib;  $\Delta QTcF$ =change from baseline in QTcF; SE=standard error; RSE=relative standard error; CI=confidence interval; BSV=between-subject variability; SD=standard deviation*

*Number of observations=1031, Number of subjects=433*

*Source: Applicant's report, Table 6-3*

### **C-QTc Analysis of Cobimetinib and Vemurafenib Using Pooled Data from Studies MEK4595g, NO25395 and GO28141**

The  $\Delta QTcF$  and concentration data from Studies MEK4592g and GO28141 were combined with the  $\Delta QTcF$  and concentration data from Study NO25395.

A stand-alone analysis was not performed for Study NO25395 since no single agent data were available for either cobimetinib or vemurafenib in this study.

The structural model for the pooled studies was similar to the Cobimetinib and Vemurafenib C-QTc model developed based on data from study GO28141 with the exception of an added covariate that estimated the effect of vemurafenib progressive disease patients (PD) on vemurafenib slope and a study effect (NO25395) on cobimetinib slope. Model structure and final parameter estimates are shown in Table 5.

Other study covariates were tested in the model (e.g., cohort, dose level, cycle, region, patient type, sex). However, none of the covariates could explain the positive cobimetinib slope estimate in Study NO25395

**Table 5: Cobimetinib and Vemurafenib C-QTc Model Parameters (Pooled Studies)**

Parameter	Estimate	SE	RSE %	95% CI
Intercept (ms)	1.87	0.852	45.6	(0.203, 3.54)
Vem Slope (ms per µg/mL)	0.161	0.0170	10.6	(0.128, 0.194)
Effect of PD on Vem Slope (ms per µg/mL)	-0.221	0.0422	19.1	(-0.304, -0.138)
Cobi Slope (ms per ng/mL)	-0.009	0.00341	37.9	(-0.0157, -0.00231)
Effect of NO25395 on Cobi Slope (ms per ng/mL)	0.0292	0.00591	20.2	(0.0176, 0.0407)
BSV Vem Slope (SD) (ms per µg/mL)	0.124	0.0192	15.5	(0.0915, 0.167)
BSV Cobi Slope (SD) (ms per ng/mL)	0.0262	0.00335	12.8	(0.0205, 0.0336)
BSV Intercept (SD) (ms)	10.2	0.598	5.86	(9.07, 11.4)
Residual Error (SD) (ms)	9.39	0.197	2.10	(9.01, 9.78)

Model QT11.All:  $\Delta QTcF = \text{Intercept} + \eta_1 + (\text{Vem Slope} + V\text{Flag} + \eta_2) * \text{Vem} + (\text{Cobi Slope} + S\text{Flag} + \eta_3) * \text{Cobi} + \text{Residual Error}$

Abbreviations: Vem=vemurafenib; Cobi=cobimetinib;  $\Delta QTcF$ =change from baseline in QTcF; SE=standard error; RSE=relative standard error; CI=confidence interval; BSV=between-subject variability; SD=standard deviation; VFlag=indicator for Vemurafenib-PD patients; SFlag=indicator for study NO25395. Number of observations=2005, Number of subjects=613

Source: *Applicant's report, Table 6-4.*

The applicant used their model to predict the  $\Delta QTcF$  at Steady State Cmax of Cobimetinib and Vemurafenib. The following scenarios were considered: 1) Cobimetinib 60 mg q.d. dosing, 2) Vemurafenib 960 mg b.i.d., and 3) Cobimetinib 60 mg q.d. + Vemurafenib 960 mg b.i.d. Results for the different scenarios are shown in the following table.

**Table 6: Model-Predicted  $\Delta$ QTcF at Steady State Cmax of Cobimetinib and Vemurafenib**

	Mean (90% CI) Cobimetinib C <sub>max,ss</sub> , ng/mL <sup>a</sup>	Mean (90% CI) Vemurafenib C <sub>max,ss</sub> , µg/mL <sup>a</sup>	Predicted Median (90%CI) $\Delta$ QTcF, ms
Cobimetinib 60 mg QD	253 (241, 266)	0	-0.407 (-2.15, 1.31)
Vemurafenib 960 mg BID	0	65 (63, 66)	12.3 (11.0, 13.7)
Cobimetinib 60 mg + Vemurafenib 960 mg BID	253 (241, 266)	59 (58, 61)	9.04 (2.19, 16.1)
Cobimetinib 60 mg + Vemurafenib 960 mg BID with study effect of NO25395 on Cobi-slope	253 (241, 266)	59 (58, 61)	16.4 (9.38, 23.8)

Source: *Applicant's report, Table 6-5.*

The applicant makes the following conclusions based on the pooled analysis:

When cobimetinib was administered alone in Study MEK4592g at doses ranging from 60 mg QD to 125 mg QD or co-administered at 60 mg QD with vemurafenib in Study GO28141, there was no evidence for a concentration-dependent increase in  $\Delta$ QTcF. The mean slope estimate was -0.009 ms per ng/mL cobimetinib. There was, however, a positive cobimetinib slope estimate in Study NO25395. The effect of Study NO25395 on cobimetinib slope was +0.0292 ms per ng/mL. Cohort, dose level, cycle, region, patient type, and sex were tested as covariates on cobimetinib slope, but none could explain the variability or study effect.

The positive cobimetinib slope estimate in this study could be a spurious because the slope estimate is inconsistent with Studies MEK4592g and GO28141 where cobimetinib was administered as single agent at doses up to 125 mg or administered at 60 mg QD in combination with vemurafenib 960 mg BID

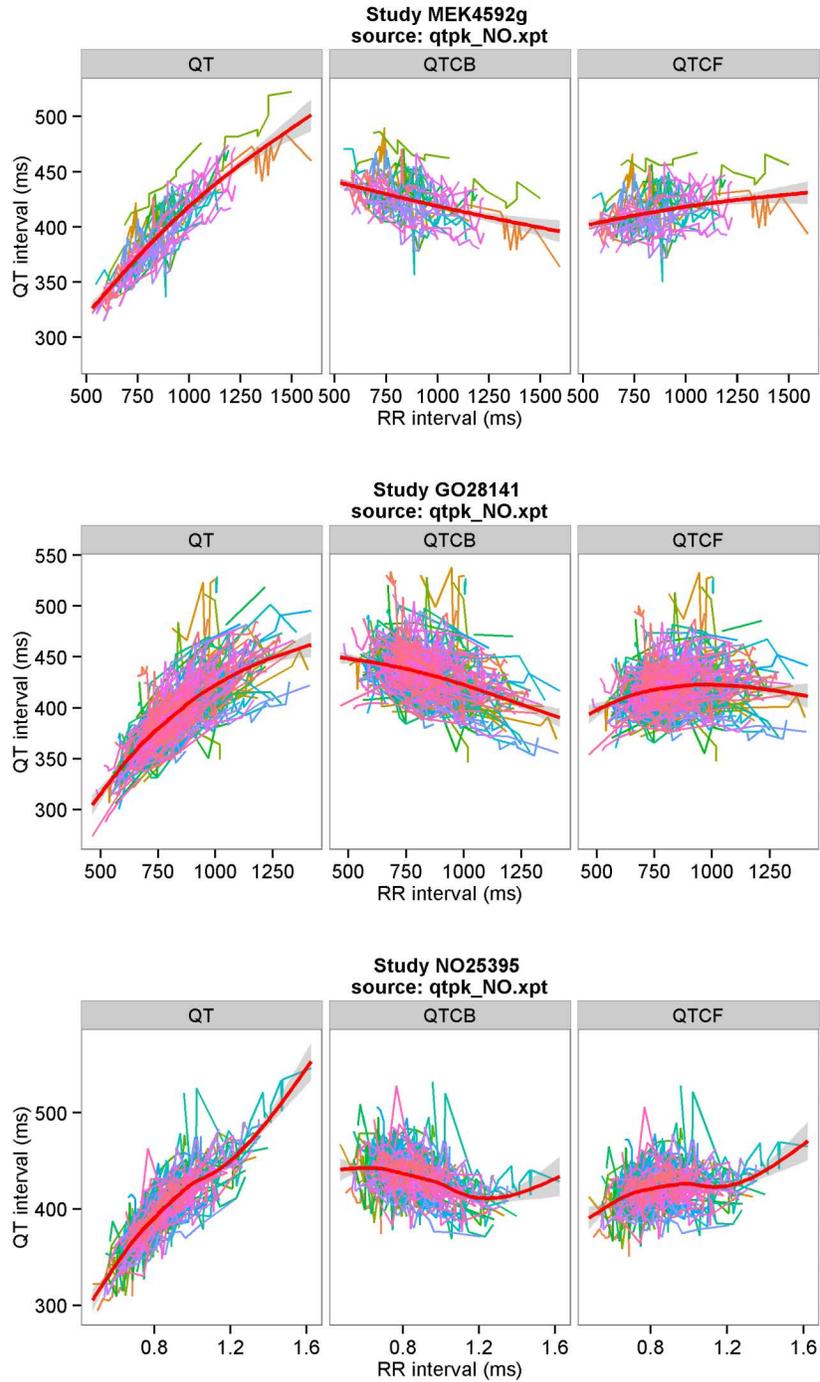
*Reviewer's Analysis: A plot of  $\Delta$ QTcF vs. drug concentrations is presented in Figure 3.*

## 5 REVIEWERS' ASSESSMENT

### 5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The relationship between different correction methods and RR is presented in Figure 2. This review did not formally evaluate of the QT/RR correction method because the sponsor only provided QTcB and QTcF correction intervals. QTcF is used in the primary analysis.

**Figure 2: 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 the Study Drug

The primary endpoint is change from baseline of QTcF. The descriptive statistics are listed in Table 7, Table 8 and Table 9 in studies MEK4592g, GO28141 and NO25395, respectively. Based on data from studies MEK4592g, GO28141 and NO25395, no large change (i.e., > 20 ms) in the QTcF interval were detected when administered cobimetinib 60 mg - 125 mg, co-administrated vemurafenib 960 mg b.i.d with and without cobimetinib 60 mg, and cobimetinib 60 mg co-administered with vemurafenib 720 mg b.i.d. and 960 mg b.i.d., respectively.

**Table 7: Analysis Results of  $\Delta$ QTcF for Cobimetinib 60 mg - 125 mg (Study MEK4592g)**

Treatment Group	Total N	*Contributed PK/ $\Delta$ QTcF observations	Mean	Std Dev	90% CI for Mean
Cobimetinib 60 mg	20	148	-2.2	11.0	(-3.7, -0.7)
Cobimetinib 80 mg	3	30	-0.3	13.9	(-4.6, 4.1)
Cobimetinib 100 mg	26	177	2.2	10.4	(0.9, 3.5)
Cobimetinib 125 mg	3	33	-11.2	16.7	(-16.2, -6.3)

- 20 subjects receiving 60 mg contributed 148 paired PK/ $\Delta$ QTcF observations;
- 3 subjects receiving 80 mg contributed 30 paired PK/ $\Delta$ QTcF observations;
- 26 subjects receiving 100 mg contributed 177 paired PK/ $\Delta$ QTcF observations; and
- 3 subjects receiving 125 mg contributed 33 paired PK/ $\Delta$ QTcF observations.

**Table 8: Analysis Results of  $\Delta$ QTcF for Vemurafenib 960 mg BID with and without Cobimetinib 60 mg (Study GO28141)**

Treatment	N	Mean	Std Dev	90% CI for Mean
Arm A (Placebo + Vemurafenib 960 mg b.i.d.)	242	13.1	16.5	(12.2, 13.9)
Arm B (Cobimetinib 60 mg + Vemurafenib 960 mg b.i.d.)	235	7.8	16.1	(6.9, 8.6)

- 242 subjects receiving arm A=placebo+vemurafenib contributed 966 observations;
- 235 subjects receiving arm B=cobimetinib+vemurafenib contributed 963 observations;

**Table 9: Analysis Results of  $\Delta$ QTcF for Cobimetinib 60 mg co-administered with Vemurafenib 720 mg and 960 mg (Study NO25395)**

Treatment	Total N	*Contributed PK/ $\Delta$ QTcF observations	Mean	Std Dev	90% CI for Mean
Cobimetinib 60 mg + Vemurafenib 720 mg b.i.d.	51	508	6.2	20.8	(4.7, 7.7)
Cobimetinib 60 mg + Vemurafenib 960 mg b.i.d.	77	857	6.8	18.1	(5.8, 7.9)

- 51 subjects receiving Vemurafenib 720 mg contributed 508 paired PK/ $\Delta$ QTcF observations;
- 77 subjects receiving Vemurafenib 960 mg contributed 857 paired PK/ $\Delta$ QTcF observations;

### 5.2.1.2 Assay Sensitivity Analysis

No assay sensitivity established because no positive control arm include in this submission.

### 5.2.1.3 Categorical Analysis

Table 10, Table 11 and Table 12 list the number of subjects as well as the number of observations whose QTcF values are  $\leq$  450 ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and  $>$  500 ms. No subject's QTcF was above 500 ms.

**Table 10: Categorical Analysis for QTcF (Study MEK4592g)**

TREAT	QTcF		
	450 ms<Value<=480 ms	Value<=450 ms	Total
Cobimetinib 100 mg	2	27	29
Cobimetinib 125 mg	0	6	6
Cobimetinib 60 mg	2	21	23
Cobimetinib 80 mg	0	3	3
<b>Total</b>	4	57	61
<b>Frequency Missing = 32</b>			

**Table 11: Categorical Analysis for QTcF  
(Study GO28141)**

Table of TREAT by QTcF					
TREAT	QTcF				
	450 ms<Value<=480 ms	480 ms<Value<=500 ms	Value<=450 ms	Value>500	Total
Arm A (Placebo + Vemurafinib 960 mg BID)	22	6	212	2	242
Arm B (Cobimetinib 60 mg + Vemurafinib 960 mg)	28	3	201	3	235
<b>Total</b>	50	9	413	5	477

**Table 12: Categorical Analysis for QTcF  
(Study NO25395)**

Table of TREATV by QTcF					
TREATV	QTcF				
	450 ms<Value<=480 ms	480 ms<Value<=500 ms	Value<=450 ms	Value>500	Total
Vemurafinib 720 mg	9	1	40	1	51
Vemurafinib 960 mg	16	1	60	1	78
<b>Total</b>	25	2	100	2	129
Frequency Missing = 2					

Table 13 - Table 15 lists the categorical analysis results for  $\Delta$ QTcF. No subject's change from baseline was above 90 ms.

**Table 13: Categorical Analysis of  $\Delta$ QTcF  
(Study MEK4592g)**

Table of TREAT by QTcF_CFB			
TREAT	QTcF_CFB		
	30 ms<Value<=60 ms	Value<=30 ms	Total
Cobimetinib 100 mg	2	25	27
Cobimetinib 125 mg	0	5	5
Cobimetinib 60 mg	0	22	22
Cobimetinib 80 mg	0	3	3
<b>Total</b>	2	55	57
Frequency Missing = 36			

**Table 14: Categorical Analysis of  $\Delta$ QTcF  
(Study GO28141)**

Table of TREAT by QTCF_CFB				
TREAT	QTCF_CFB			Total
	30 ms<Value<=60 ms	Value<=30 ms	Value>60 ms	
Arm A (Placebo + Vemurafenib 960 mg BID)	50	181	2	233
Arm B (Cobimetinib 60 mg + Vemurafenib 9)	36	183	5	224
<b>Total</b>	86	364	7	457
Frequency Missing = 20				

**Table 15: Categorical Analysis of  $\Delta$ QTcF  
(Study NO25395)**

Table of TREATV by QTCF_CFB				
TREATV	QTCF_CFB			Total
	30 ms<Value<=60 ms	Value<=30 ms	Value>60 ms	
Vemurafenib 720 mg	11	36	2	49
Vemurafenib 960 mg	14	57	5	76
<b>Total</b>	25	93	7	125
Frequency Missing = 6				

### 5.2.2 HR Analysis

The primary endpoint is change from baseline of HR. The descriptive statistics are listed in Table 16, Table 17 and Table 18. Based on data from Studies MEK4592g, GO28141 and NO25395, no large change (i.e., > 20 ms) in the HR interval were detected when administrated cobimetinib 60 mg - 125 mg, co-administrated vemurafenib 960 mg b.i.d with and without cobimetinib 60 mg, and cobimetinib 60 mg co-administered with vemurafenib 720 mg and 960 mg, respectively. Table 19, Table 20 and Table 21 presented the categorical analysis of HR for Studies MEK4592g, GO28141 and NO25395. There are 4, 12, and 2 subjects from Studies MEK4592g, GO28141 and NO25395, respectively, who experienced HR interval greater than 100 bpm.

**Table 16: Analysis Results of  $\Delta$ HR for Cobimetinib 60 mg - 125 mg (Study MEK4592g)**

Treatment Group	Total N	Mean	Std Dev	90% CI for Mean
Cobimetinib 60 mg	20	-1.7	11.3	(-2.8, -0.7)
Cobimetinib 80 mg	3	1.2	6.9	(-0.3, 2.7)
Cobimetinib 100 mg	26	-1.2	11.4	(-2.4, 0.1)
Cobimetinib 125 mg	3	-0.5	8.3	(-2.8, 1.9)

**Table 17: Analysis Results of  $\Delta$ HR for Vemurafenib 960 mg BID with and without Cobimetinib 60 mg (Study GO28141)**

Treatment	Total N	Mean	Std Dev	90% CI for Mean
Arm A (Placebo + Vemurafenib 960 mg b.i.d.)	242	0.4	11.8	(-0.2, 1.0)
Arm B (Cobimetinib 60 mg + Vemurafenib 960 mg b.i.d.)	235	-2.8	11.6	(-3.4, -2.2)

**Table 18: Analysis Results of  $\Delta$ HR for Cobimetinib co-administered with Vemurafenib 720 mg and 960 mg (Study NO25395)**

Treatment	Total N	Mean	Std Dev	90% CI for Mean
Cobimetinib 60 mg + Vemurafenib 720 mg	51	-4.1	11.6	(-5.0, -3.3)
Cobimetinib 60 mg + Vemurafenib 960 mg	78	-1.8	12.8	(-2.5, -1.1)

**Table 19: Categorical Analysis for HR (Study MEK4592g)**

Table of TREAT by HR			
TREAT	HR		
	HR <= 100 bpm	HR >100 bpm	Total
Cobimetinib 100 mg	28	1	29
Cobimetinib 125 mg	6	0	6
Cobimetinib 60 mg	45	3	48
Cobimetinib 80 mg	10	0	10
<b>Total</b>	89	4	93

**Table 20: Categorical Analysis for HR  
(Study GO28141)**

Table of TREAT by HR			
TREAT	HR		
	HR <= 100 bpm	HR >100 bpm	Total
Arm A (Placebo + Vemurafinib 960 mg BID)	234	8	242
Arm B (Cobimetinib 60 mg + Vemurafinib 9	231	4	235
<b>Total</b>	465	12	477

**Table 21: Categorical Analysis for HR  
(Study NO25395)**

Table of TREATV by HR			
TREATV	HR		
	HR <= 100 bpm	HR >100 bpm	Total
Vemurafinib 720 mg	49	2	51
Vemurafinib 960 mg	78	0	78
<b>Total</b>	127	2	129
<b>Frequency Missing = 2</b>			

### 5.2.3 PR Analysis

The primary endpoint is change from baseline of PR. The descriptive statistics are listed in Table 22, Table 23 and Table 24. Based on data from Studies MEK4592g, GO28141 and NO25395, no large change (i.e., > 20 ms) in the PR interval were detected when administrated cobimetinib 60 mg - 125 mg, co-administrated vemurafenib 960 mg b.i.d with and without cobimetinib 60 mg, and cobimetinib 60 mg co-administered with vemurafenib 720 mg and 960 mg, respectively. Table 25, Table 26 and Table 27 presented the categorical analysis of PR. There are 7, 25, and 8 subjects from Studies MEK4592g, GO28141 and NO25395, respectively, who experienced PR interval greater than 200 ms.

**Table 22: Analysis Results of  $\Delta$ PR for Cobimetinib 60 mg - 125 mg (Study MEK4592g)**

Treatment Group	Total N	Mean	Std Dev	90% CI for Mean
Cobimetinib 60 mg	20	8.7	15.8	(7.2, 10.2)
Cobimetinib 80 mg	3	7.7	10.5	(5.4, 9.9)
Cobimetinib 100 mg	26	5.2	10.9	(4.1, 6.4)
Cobimetinib 125 mg	3	9.6	7.9	(7.2, 11.9)

**Table 23: Analysis Results of  $\Delta$ PR for Vemurafenib 960 mg BID with and without Cobimetinib 60 mg (Study GO28141)**

Treatment	Total N	Mean	Std Dev	90% CI for Mean
Arm A (Placebo + Vemurafenib 960 mg b.i.d.)	242	-3.9	12.8	(-4.6, -3.2)
Arm B (Cobimetinib 60 mg + Vemurafenib 960 mg b.i.d.)	235	7.7	15.7	(6.8, 8.5)

**Table 24: Analysis Results of  $\Delta$ PR for Cobimetinib co-administered with Vemurafenib 720 mg and 960 mg (Study NO25395)**

Treatment	Total N	Mean	Std Dev	90% CI for Mean
Cobimetinib 60 mg + Vemurafenib 720 mg b.i.d.	51	6.5	13.8	(5.5, 7.6)
Cobimetinib 60 mg + Vemurafenib 960 mg b.i.d.	77	4.6	12.3	(3.9, 5.3)

**Table 25: Categorical Analysis for PR  
(Study MEK4592g)**

Table of TREAT by PR			
TREAT	PR		
	PR <= 200 ms	PR >200 ms	Total
Cobimetinib 100 mg	27	1	28
Cobimetinib 125 mg	5	0	5
Cobimetinib 60 mg	43	5	48
Cobimetinib 80 mg	9	1	10
<b>Total</b>	<b>84</b>	<b>7</b>	<b>91</b>
Frequency Missing = 2			

**Table 26: Categorical Analysis for PR  
(Study GO28141)**

Table of TREAT by PR			
TREAT	PR		
	PR <= 200 ms	PR >200 ms	Total
Arm A (Placebo + Vemurafinib 960 mg BID)	228	9	237
Arm B (Cobimetinib 60 mg + Vemurafinib 9	216	16	232
<b>Total</b>	<b>444</b>	<b>25</b>	<b>469</b>
Frequency Missing = 8			

**Table 27: Categorical Analysis for PR  
(Study NO25395)**

Table of TREATV by PR			
TREATV	PR		
	PR <= 200 ms	PR >200 ms	Total
Vemurafinib 720 mg	46	4	50
Vemurafinib 960 mg	74	4	78
<b>Total</b>	<b>120</b>	<b>8</b>	<b>128</b>
Frequency Missing = 3			

#### 5.2.4 QRS Analysis

The primary endpoint is change from baseline of QRS. The descriptive statistics are listed in Table 28, Table 29 and Table 30. Based on data from Studies MEK4592g, GO28141 and NO25395, no large change (i.e., > 20 ms) in the QRS interval were

detected when administrated cobimetinib 60 mg - 125 mg, co-administrated vemurafenib 960 mg b.i.d with and without cobimetinib 60 mg, and cobimetinib 60 mg co-administered with vemurafenib 720 mg b.i.d. and 960 mg b.i.d., respectively. Table 31, Table 32 and Table 33 presented the categorical analysis of QRS. There are 14, 32, and 10 subjects from Studies MEK4592g, GO28141 and NO25395, respectively, who experienced QRS interval greater than 110 ms.

**Table 28: Analysis Results of  $\Delta$ QRS for Cobimetinib 60 mg - 125 mg (Study MEK4592g)**

Treatment	Total N	Mean	Std Dev	90% CI for Mean
Cobimetinib 60 mg	20	0.8	8.6	(0.0, 1.7)
Cobimetinib 80 mg	3	2.5	6.8	(1.1, 3.9)
Cobimetinib 100 mg	26	2.2	5.8	(1.6, 2.8)
Cobimetinib 125 mg	3	-1.2	5.7	(-2.8, 0.4)

**Table 29: Analysis Results of  $\Delta$ QRS for Vemurafenib 960 mg with or without co-administration of Cobimetinib 60 mg (Study GO28141)**

Treatment	Total N	Mean	Std Dev	90% CI for Mean
Arm A (Placebo + Vemurafenib 960 mg b.i.d.)	242	0.6	6.6	(0.2, 0.9)
Arm B (Cobimetinib 60 mg + Vemurafenib 960 mg b.i.d.)	235	2.1	8.1	(1.7, 2.5)

**Table 30: Analysis Results of  $\Delta$ QRS for Cobimetinib co-administered with Vemurafenib 720 mg and 960 mg (Study NO25395)**

Treatment	Total N	Mean	Std Dev	90% CI for Mean
Cobimetinib 60 mg + Vemurafenib 720 mg b.i.d.	51	3.6	7.0	(3.1, 4.1)
Cobimetinib 60 mg + Vemurafenib 960 mg b.i.d.	78	2.2	8.1	(1.8, 2.7)

**Table 31: Categorical Analysis for QRS  
(Study MEK4592g)**

Table of TREAT by QRS			
TREAT	QRS		
	QRS <= 110 ms	QRS > 110 ms	Total
Cobimetinib 100 mg	22	7	29
Cobimetinib 125 mg	5	1	6
Cobimetinib 60 mg	42	6	48
Cobimetinib 80 mg	10	0	10
<b>Total</b>	<b>79</b>	<b>14</b>	<b>93</b>

**Table 32: Categorical Analysis for QRS  
(Study GO28141)**

Table of TREAT by QRS			
TREAT	QRS		
	QRS <= 110 ms	QRS > 110 ms	Total
Arm A (Placebo + Vemurafinib 960 mg BID)	229	13	242
Arm B (Cobimetinib 60 mg + Vemurafinib 9	216	19	235
<b>Total</b>	<b>445</b>	<b>32</b>	<b>477</b>

**Table 33: Categorical Analysis for QRS  
(Study NO25395)**

Table of TREATV by QRS			
TREATV	QRS		
	QRS <= 110 ms	QRS > 110 ms	Total
Vemurafinib 720 mg	47	4	51
Vemurafinib 960 mg	72	6	78
<b>Total</b>	<b>119</b>	<b>10</b>	<b>129</b>
<b>Frequency Missing = 2</b>			

### 5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

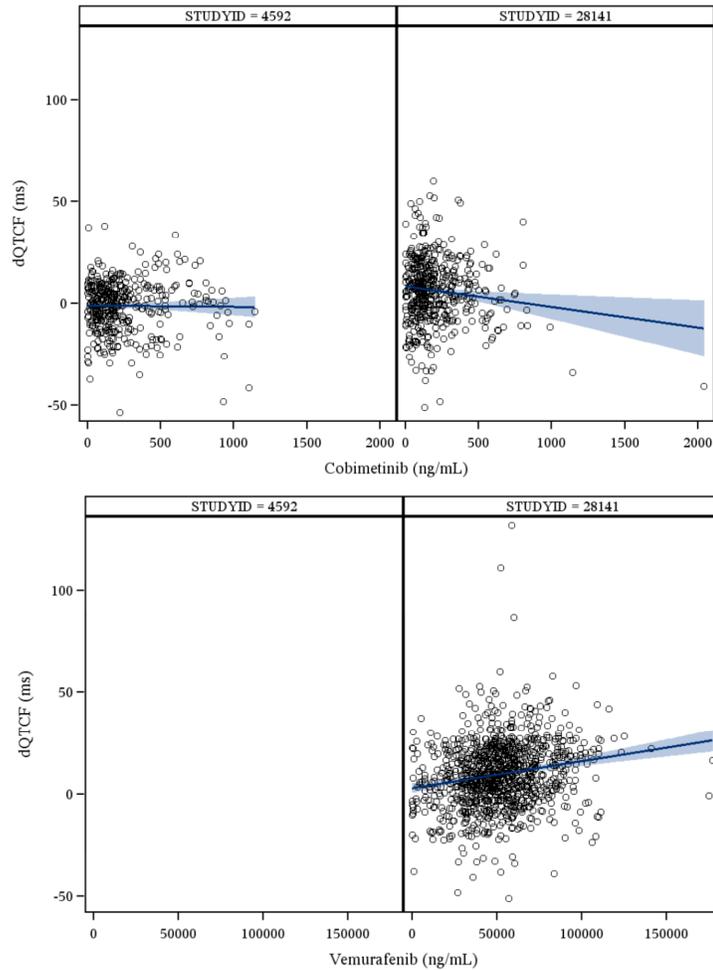
Number of subjects that received each treatment is shown in Table 34. The relationships between  $\Delta$ QTcF and cobimetinib and vemurafinib concentrations are visualized in Figure 3 for Trial MEK4592g and GO28141. No evident relationship between  $\Delta$ QTcF and cobimetinib concentrations was observed.

**Table 34: Drug Combinations and Dose Strengths in Trials NO25395, MEK4592g, GO28141**

<b>Administered doses of cobimetinib and vemurafinib</b>	<b>N</b>	<b>Study</b>
Cobimetinib 100 mg + Vemurafinib 720 mg b.i.d.	4	NO25395
Cobimetinib 60 mg	2	NO25395
Cobimetinib 60 mg + Vemurafinib 720 mg b.i.d.	43	NO25395
Cobimetinib 60 mg + Vemurafinib 960 mg b.i.d.	73	NO25395
Cobimetinib 80 mg + Vemurafinib 720 mg b.i.d.	4	NO25395
Cobimetinib 80 mg + Vemurafinib 960 mg b.i.d.	5	NO25395
Arm A (Placebo + Vemurafinib 960 mg b.i.d.)	247	GO28141
Arm B (Cobimetinib 60 mg + Vemurafinib 960 mg b.i.d.)	246	GO28141
Cobimetinib 10 mg	3	MEK4592g
Cobimetinib 100 mg	29	MEK4592g
Cobimetinib 11.9 mg	1	MEK4592g
Cobimetinib 12.18 mg	1	MEK4592g
Cobimetinib 125 mg	6	MEK4592g
Cobimetinib 16.14 mg	1	MEK4592g
Cobimetinib 2.135 mg	1	MEK4592g
Cobimetinib 2.18 mg	1	MEK4592g
Cobimetinib 20 mg	3	MEK4592g
Cobimetinib 3.295 mg	1	MEK4592g
Cobimetinib 3.975 mg	1	MEK4592g
Cobimetinib 40 mg	6	MEK4592g
Cobimetinib 5.65 mg	1	MEK4592g
Cobimetinib 60 mg	51	MEK4592g
Cobimetinib 8.55 mg	1	MEK4592g
Cobimetinib 80 mg	10	MEK4592g
Cobimetinib 9.59 mg	1	MEK4592g
<b>Total</b>	<b>742</b>	

Note: Data source: *qtpk\_NO.xpt, qtpk\_GO.xpt, qtpk\_MEK.xpt*

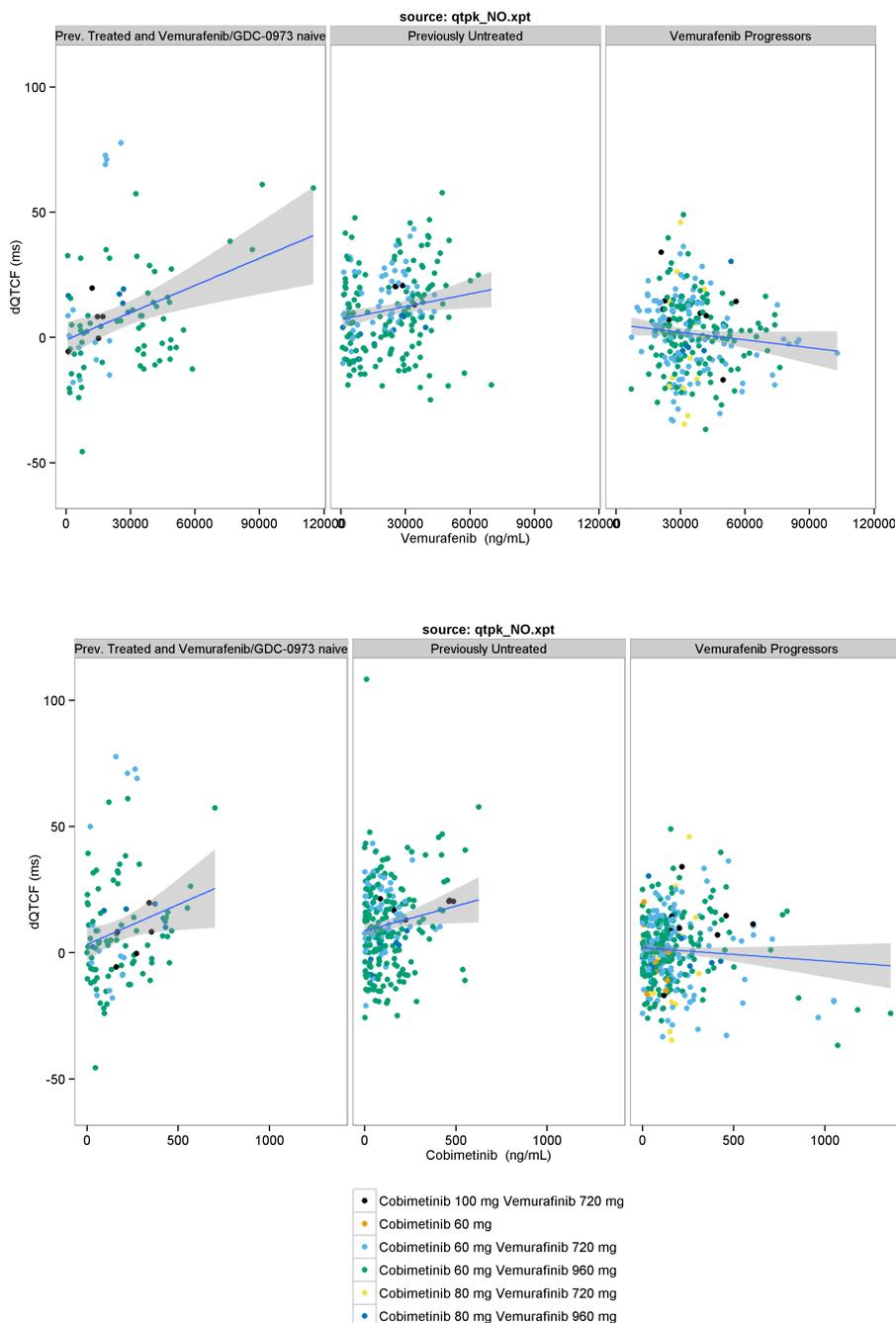
**Figure 3:  $\Delta$  QTcF vs. Cobimetinib and Vemurafenib Concentration (Trial MEK4592g and GO28141)**



*Note: The solid line is generated by a linear regression and the shaded area is the 95% CI of the mean*

Data from trial NO25395 was analyzed with a linear mixed effect model as a sensitivity analysis of the applicant's assessment. Patients who were identified as vemurafenib progressors were excluded from the analysis because of the higher QT at baseline with vemurafenib treatment. The relationship between  $\Delta$ QTcF and cobimetinib and vemurafenib concentrations in trial NO25395 is visualized in Figure 4.

**Figure 4:  $\Delta$  QTcF vs. Cobimetinib and Vemurafenib Concentration in Trial NO25395**

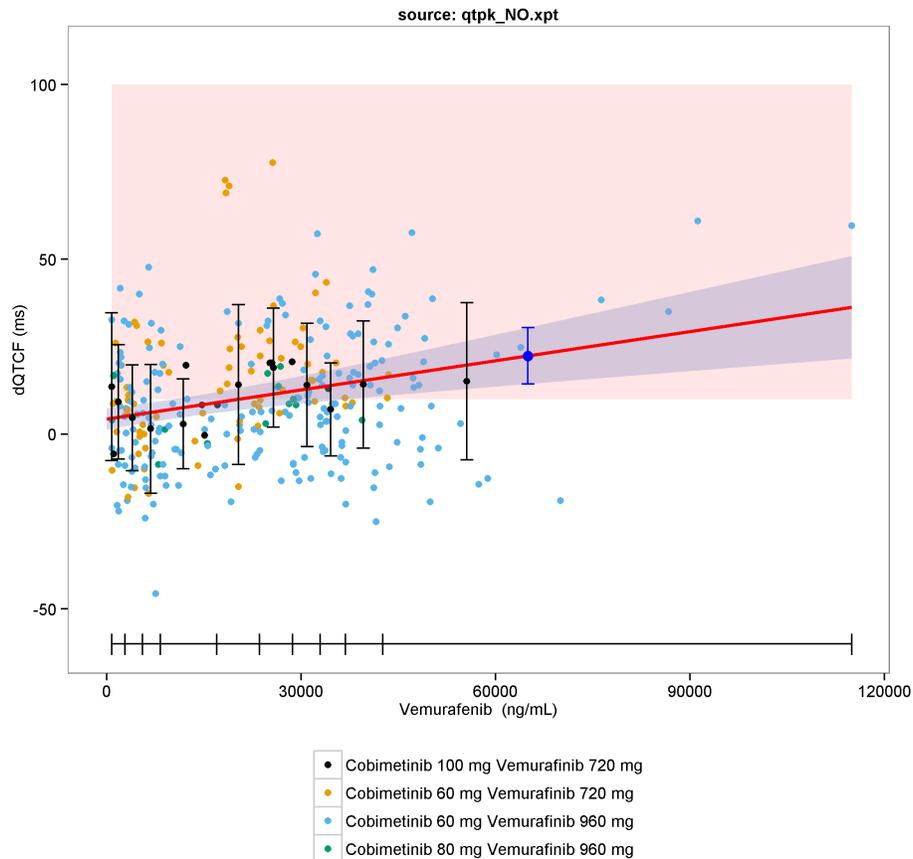


*Note: The solid line is generated by a linear regression and the shaded area is the 95% CI of the mean*

Univariate concentration-response analysis for vemurafenib was evaluated based on a linear mixed effect model that included random effects (subject) on slope and intercept. A significant relationship between vemurafenib concentration and  $\Delta$ QTcF was found with a slope of 0.0003 ms per ug/mL, 95% CI (0.0001, 0.0005). At  $C_{max}$  of 59000 ng/mL, a QT prolongation of 21 ms with 95% CI (12, 30) is projected. A log-linear model was not found to be superior to the linear model based on similar AIC value. The relationship

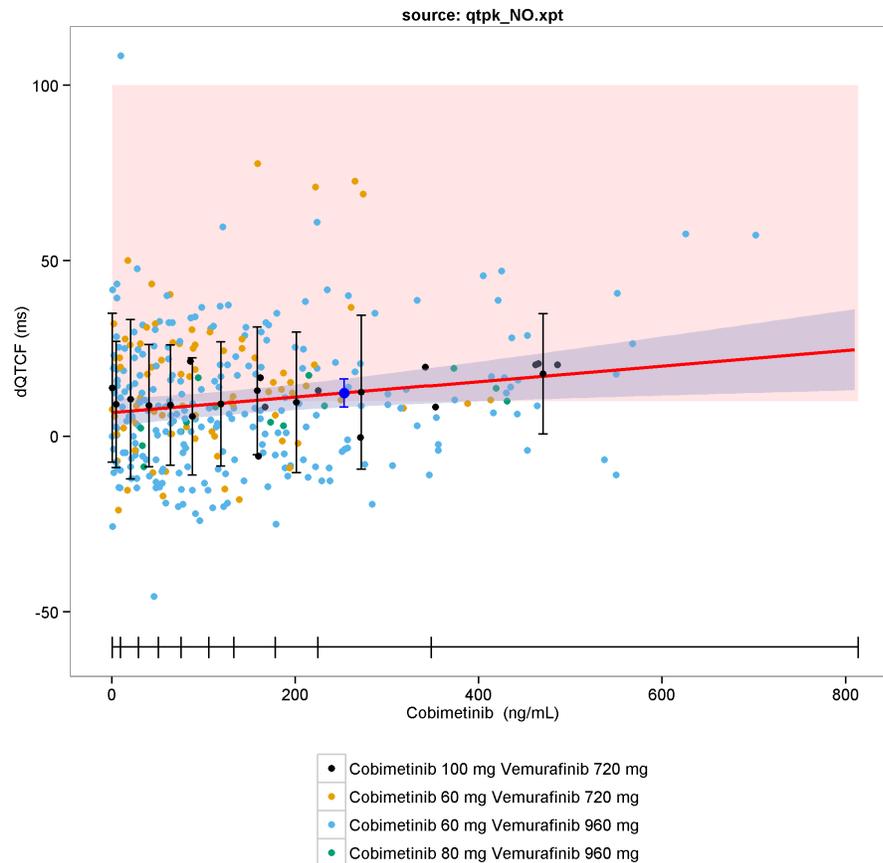
between  $\Delta\text{QTcF}$  and vemurafenib is visualized in Figure 5. In trial NO25395, the QT effect of vemurafenib (when treated with cobimetinib) seems slightly larger compared to that in Study GO28141 and those we previously observed in NDA 202429 when vemurafenib was administered alone (see QT-IRT's review dated 6/2/2011).

**Figure 5: Vemurafenib Concentration  $\Delta\text{QTcF}$  Analysis in Patients That Were Not Identified as Vemurafenib Progressors. Blue Point and Error Bar Indicate Prediction of  $\Delta\text{QTcF}$  at Vemurafenib  $C_{\text{max}}$  Following a 960-Mg b.i.d. Regimen**



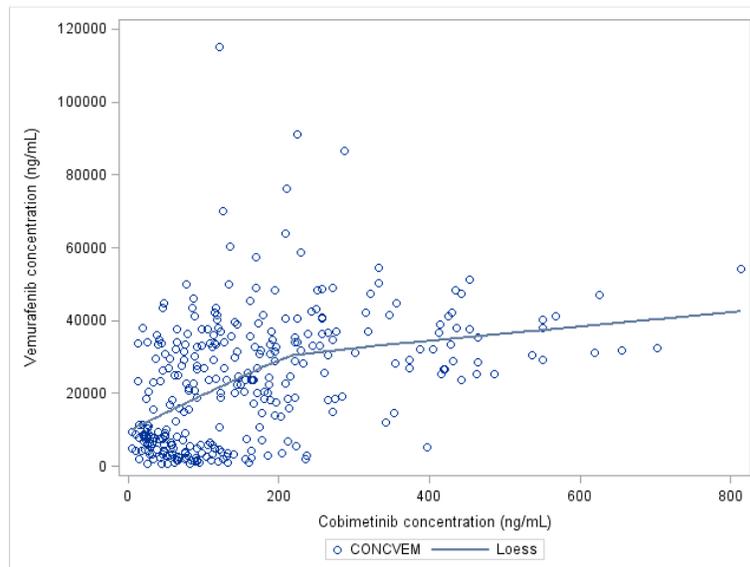
Univariate concentration-response analysis for cobimetinib was evaluated based on a linear mixed effect model that included random effects (subject) on slope and intercept. A significant relationship between cobimetinib concentration and  $\Delta\text{QTcF}$  was found with a slope of 0.020 ms per ng/mL, 95% CI (0.001, 0.038). At  $C_{\text{max}}$  of 253 ng/mL, a QT prolongation of 12 ms with 95% CI (8, 17) is projected. A log-linear model was not found to be superior to a linear model based on increased AIC value of 17.2 points. The relationship between  $\Delta\text{QTcF}$  and cobimetinib is visualized in Figure 6.

**Figure 6: Cobimetinib Concentration  $\Delta$ QTcF Analysis in Patients That Were Not Identified as Vemurafenib Progressors. Blue point and Error Bar Indicate Prediction of  $\Delta$ QTcF at Vemurafenib  $C_{max}$  Following a 60 mg q.d. regimen.**



However, cobimetinib and vemurafenib concentrations are correlated in NO25395 dataset (Figure 7). Therefore, a multivariate linear mixed effect model including both cobimetinib and vemurafenib concentrations was explored. A significant relationship between cobimetinib concentration and  $\Delta$ QTcF was still observed with a slope of 0.019 ms per ng/mL, 95% CI (0.001, 0.037). However, the QT effect at cobimetinib  $C_{max}$  of 253 ng/mL is projected to be 6.7 ms with 95% CI (3.1, 10.3) at vemurafenib concentration of 0 ng/mL, which seems to indicate that the QT effect at cobimetinib is relatively small.

**Figure 7: Correlation between Cobimetinib and Vemurafenib in Patients That Were Not Identified as Vemurafenib Progressors.**



## 5.4 CLINICAL ASSESSMENTS

### 5.4.1 Safety assessments

No pooled summary of the safety data was included as part of the sponsor's integrated review of QT effects.

### 5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

### 5.4.3 PR and QRS Interval

No clinically significant effects were seen on PR or QRS intervals.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DEVI KOZELI on behalf of DINKO REKIC  
05/08/2015  
Signing for Dinko because he is on leave

JIANG LIU  
05/08/2015

MOH JEE NG  
05/08/2015

QIANYU DANG  
05/08/2015

MICHAEL Y LI  
05/08/2015

NORMAN L STOCKBRIDGE  
05/08/2015