

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202429Orig1s000

OTHER REVIEW(S)

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: July 28, 2011

TO: Theresa Ferrara, MPH, Regulatory Project Manager
Division of Drug Oncology Products

Y. Max Ning, M.D., PhD.
Medical Officer (Application CDTL)
Division of Drug Oncology Products

FROM: Robert Young,
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH: Lauren Iacono-Connors, Ph.D.
Acting Team Leader, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

SUBJECT: Evaluation of Clinical Inspections

NDA: 202 429

APPLICANT: Hoffmann-La Roche, Inc.
Nutley, NJ 07110

DRUG: Zelboraf (vemurafenib)

NME: Yes

THERAPEUTIC CLASSIFICATION: Accelerated Priority Review

INDICATIONS: BRAF V600 mutation-positive unresectable or metastatic melanoma

CONSULTATION REQUEST DATE: 5/02/2011
INSPECTION SUMMARY GOAL DATE: 7/22/2011
DIVISION ACTION GOAL DATE: 7/29/2011
PDUFA DATE: 10/28/2011

I. BACKGROUND:

The investigational new drug is RO5185426 (also known as PLX4032) a compound that selectively inhibits oncogenic BRAF kinase. Oncogenic mutations in BRAF kinase, predominantly V600E, have been observed in approximately 8% of all solid tumors, including 50% of metastatic melanomas, 30% to 70% of thyroid carcinomas, 30% of ovarian carcinomas, and 10% of colorectal carcinomas. The BRAF mutations result in constitutive activation of BRAF kinase, which causes dysregulated downstream signaling leading to excessive cell proliferation and survival.

Protocol BRIM 3 was a randomized, open-label, multi-center, active treatment controlled, Phase 3 trial to evaluate the efficacy and safety of RO5185426 compared to dacarbazine in previously untreated adult patients with histologically confirmed *BRAFV600* mutation-positive metastatic melanoma (unresectable Stage IIIC or Stage IV). Patients were randomized in a 1:1 ratio to either:

- Experimental Arm A: oral RO5185426 administered twice (bid) daily at a dose of 960 mg or
- Control Arm B: Dacarbazine administered intravenously 1000 mg/m² on Day 1 every 3 weeks (3 week cycle)

While the protocol specified primary endpoint was overall survival and disease progression free survival, based on discussions with DDOP reviewers the review division will consider overall survival the primary efficacy endpoint of interest. A total of 675 subjects were enrolled at 104 sites with 60% from Western Europe and 25% from North America.

Four clinical sites were chosen for inspection. Sites were chosen based on high enrollment numbers at site, high regional rate of enrollment, and high rate of treatment responders at site (Site #201202; Site #200991).

II. RESULTS (by Site):

All classifications are preliminary and based on preliminary review of Establishment Inspection Reports (EIR) of the two domestic clinical investigator audits, or written or oral conversations with the FDA field investigator who conducted the overseas inspections in Italy and Germany and issued Form FDA 483, where one was issued.

These preliminary classifications are subject to revision based on final review of the relevant EIR and associated exhibits and any response to Form FDA 483 observations that may be submitted by the inspected entity. An inspection summary addendum will be generated if

conclusions change upon receipt and complete review of the EIRs.

Name of CI or Sponsor	# of Subjects	Inspection Date	Preliminary Classification
Jeffrey Sosman Vanderbilt University Medical Center Nashville, TN 37232	9	6/13-17/2011	NAI
Kim Margolin, University of Washington 825 Eastlake Ave. E. Seattle, WA, 98109	7	6/15-27/2011	VAI
Alessandro Testori Istituto Europeo di Oncologia Via Ripamonti, 435 Milano, 20141 ITALY	14	7/11-15/2011	VAI
Carmen Loquai Universitaetsklinikum Mainz Mainz, RP, 55131 GERMANY	12	7/18-22/2011	VAI
Hoffmann-LaRoche, Inc. 340 Kingsland St. Nutley, NJ 07110	Sponsor/Mon itor oversight of sites listed above was focused on during inspection	6/27/2011 – 7/8/2011	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. Jeffrey Sosman
Site #200991

- a. What was inspected: At this site 36 patients were screened and 9 enrolled into the study. The records of all subjects were reviewed.
- b. General observations/commentary: No significant deviations were identified and no Form FDA 483 was issued. This investigator had been inspected in 2010 and the inspection was classified Official Action Indicated (OAI); regulatory violations identified previously were not observed during review of records for Study BRIM 3.
- c. Assessment of data integrity: The data collected by this site are acceptable to support approval of the pending application.

2. Kim Margolin
Site #200997

- a. What was inspected: At this site 24 patients were screened and 7 enrolled into the study. The records of all subjects were reviewed.
- b. General observations/commentary: Several significant deviations were found and shared with the clinical investigator on an issued Form FDA 483. For example:
 - Subjects kept a diary, but these diaries were not always carefully reviewed by the study staff and the site thereby, missed reporting: one incident of alopecia from 11/30/2010 – 12/20/2010 in Subject #90938-3507, two incidents of the use of Ibuprofen for pain, and stiff joints in two subjects, and three daily (9/22-24/2010) uses of Lasix for swelling in one subject.
 - Early in the study the site failed to obtain protocol required oxygen saturation levels in six of the subjects (#90334-3502, cycles 3 and 6; #90540-3503, cycle 3; #90740-3504, cycles 3, 4, 6, and 9; #90740-3505, cycles 1, 2, 3, 4, and 6; #90914-3506, cycles 1 and 2; and #90938-3507, cycles 1, 2, and 4) and hematology and/or chemistry studies in three subjects on day 7 of cycle 1 (#90170-3501, #90540-3503, and #90914-3506). Once these failures were called to the site's attention necessary corrections were made.

The clinical investigator responded to the issued Form FDA 483, acknowledged the lapses and implemented procedures to avoid future repeat deficiencies.

- c. Assessment of data integrity: Although there were lapses in the conduct of the study the lapses were identified early and necessary procedural corrections were made, e.g. collection of oxygen saturation, chemistry and hematology studies. The information missed in patient diaries were sporadic and limited in number. While regulatory violations as noted above occurred at this site, they are unlikely to significantly impact

primary efficacy and safety data, nor do they appear to have had a significant impact on the protection of subjects' rights or welfare. Notwithstanding the regulatory violations noted above, the data generated at this site are acceptable in support of an approval of the pending application.

3. Alessandro Testori
Site #201192

- a. What was inspected: Of the 14 subjects enrolled, the records for half of the enrolled subjects were reviewed during the site inspection.
- b. General observations/commentary: During the inspection it was discovered that the original investigator had left the site. A sub-investigator served as the most responsible party for the study during the inspection. It appears that the subjects were real, participated in the study, and were subject to the protocol including the assessment of their disease by CT scans. Significant deviations in study conduct were identified during the inspection and a Form FDA 483 was issued at the conclusion of the inspection. Form FDA 483 observations included:
 - Failure to maintain complete/accurate case histories relating to measurements of target lesions for all seven subjects' records reviewed. Source CT scans for baseline assessments were not present at the site. In addition, personnel at the site were not able to accurately identify the target lesions measured from time point to time point during the study that were reported on in the CRF; therefore, actual measurements of target lesions were also not able to be verified.
 - Pharmacokinetic (PK) samples were not placed on ice as required when transported from subject to laboratory and documentation of the receipt of samples and their processing was not available.
 - The site refused to produce records showing that corrective actions promised in relation to deficiencies identified in a previous inspection had been implemented.
- c. Assessment of data integrity: Radiographic data related to assessment of target lesion sizes could not be verified at this site; therefore, OSI can not provide an assessment of reliability of these data submitted in the NDA and the review division may wish to consider the impact of this finding on disease progression endpoint assessment. Survival data from the site appears to have been accurately reported in the NDA. The impact of failure to follow protocol specified PK sample storage/transport procedures should also be considered in assessment of pharmacokinetic data from this site. The balance of data reported for Study BRIM3 from this site appears to have been adequately captured/reported and may be considered reliable in support of the pending application.

4. Carmen Loquai
Site #201202

- a. What was inspected: Twelve subjects were enrolled at this site. Clarity on specific records reviewed during the inspection has been requested from the ORA field investigator.
- b. General observations/commentary: Preliminary communications from the ORA field investigator for this inspection include that several non-serious adverse events were unreported to the sponsor. In addition, survival was confirmed for 7 of 12 subjects enrolled at this site. CT scans and source records were retained at the site and were available for inspection.
- c. Assessment of data integrity: While inspectional observations from this site remain pending, based on preliminary communications from the field investigator, it appears that with the exception several instances of failure to report non-serious adverse events, no regulatory violations were observed and data from this site are acceptable in support of the pending application.

5. Hoffman LaRoche, Inc

- a. What was inspected: The Sponsor was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. In addition to conduct of routine aspects of this program, the Sponsor's adequacy of oversight of Drs. Loquai, Testori, Margolin, and Sosman was specifically evaluated.
- b. General observations/commentary: No substantial violative conditions were found. No Form FDA 483 issued.
- c. Assessment of data integrity: Notwithstanding regulatory violations discussed in prior sections of this review, the data from this Sponsor submitted to the agency as part and in support of NDA 202429 appear generally reliable.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for clinical investigators Dr. Loquai, Dr. Margolin, Dr. Testori, Dr. Sosman, and Hoffman LaRoche, Inc., survival data and safety data reported in the NDA appear reliable.

At Dr. Testori's site radiographic data related to assessment of target lesion sizes could not be verified; therefore, OSI can not provide an assessment of reliability of these data submitted in the NDA and the review division may wish to consider the impact of this finding on the disease progression endpoint assessment. In addition, at Dr. Testori's site the impact of failure to follow protocol specified PK sample storage/transport procedures should also be considered

in assessment of pharmacokinetic data from this site.

At Dr. Margolin's site, while regulatory violations were noted, they were limited in number and significance (e.g. one missed report of one month of alopecia, two uses of Ibuprofen for joint pain unrelated to the investigational new drug, missed oxygen saturation, chemistry and hematology testing, etc.) and they are unlikely to significantly impact primary efficacy and safety data, nor do they appear to have had a significant impact on the protection of subjects' rights or welfare.

Note: All observations noted above are based on the preliminary communications provided by the FDA field investigators and preliminary review of available Form FDA 483, inspectional observations. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

Follow-Up Actions: OSI will generate an inspection summary addendum if the conclusions change significantly upon final review of the EIRs and supporting inspection evidence and exhibits.

{ See appended electronic signature page }

Robert Young
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE: { See appended electronic signature page }

Jean Mulinde, M.D.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

/s/

ROBERT S K YOUNG
07/28/2011

JEAN M MULINDE
07/28/2011

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 # 202429 BLA#	NDA Supplement #:S- N/A BLA STN #	Efficacy Supplement Type SE- N/A
Proprietary Name: Zelboraf Established/Proper Name: vemurafenib Dosage Form: Oral Strengths: 240 mg		
Applicant: Hoffman La-Roche Inc Agent for Applicant (if applicable):		
Date of Application: April 27, 2011 Date of Receipt: April 28, 2011 Date clock started after UN:		
PDUFA Goal Date: October 28, 2011	Action Goal Date (if different): July 29, 2011	
Filing Date: June 27, 2011	Date of Filing Meeting: May 24, 2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) NME – Type 1		
Proposed indication(s)/Proposed change(s): BRAF mutation positive unresctable or metastatic melanoma		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
<i>If 505(b)(2): Draft the “505(b)(2) Assessment” form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499 and refer to Appendix A for further information.</i>		
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i>		
<i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input checked="" type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system <input type="checkbox"/> Pre-filled biologic delivery device/system <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Drug/Biologic <input checked="" type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	
<i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>		

<input type="checkbox"/> Fast Track <input checked="" type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): N/A				
List referenced IND Number(s): 73620				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the Application and Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163970.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	X			Priority, accelerated
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			Orphan designation

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>			<p>X</p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the (b)(2) review staff in the Immediate Office of New Drugs</i></p>			<p>X</p>																	
<p>Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1457 1349 1591"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration															<p>X</p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 108(b)(2). Unexpired, 3-year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</p>		<p>X</p>																		

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

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

1

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

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
If no, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?			X	
If yes, BLA #				
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	X			
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	X			
<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>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?		X		Don't see it under the NDA, only the IND
<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>				
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature?	X			

<p>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].</p> <p>Note: Debarment Certification should use wording in FDCA 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...”</p>				
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>			X	e-CTD submission

Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment
<p><u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?</p> <p><i>If yes, date consult sent to the Controlled Substance Staff:</i></p> <p><u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff :</i></p>		X		

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)²</i></p> <p><i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i></p>		X		Received orphan designation
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>			X	

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

If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>			X	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>			X	
BPCA (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>		X		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	X			
REMS	YES	NO	NA	Comment
Is a REMS submitted? <i>If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox</i>		X		Applicant submitted Risk Management Plan
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" 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 in 74-day letter.</i>	X			
Is the PI submitted in PLR format? ⁴	X			

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

⁴ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	X			
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted? <i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>	X			Env.Assess. – sent 3.31.11 QT-IRT - sent 5.5.11 DSI - sent 5.3.11 DDMAC – sent 4.29.11 OSE DMEPA – sent 5.9.11 OSE DRISK – sent 5.9.11 Internal center (CDRH) - sent 10.18.10
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s) Date(s): EOP2 - May 15, 2009; CMC EOP2 – July 17, 2009 <i>If yes, distribute minutes before filing meeting</i>	X			

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): January 21, 2011 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>		X		

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 24, 2011

BLA/NDA/Supp #: NDA 202429

PROPRIETARY NAME: Zelboraf

ESTABLISHED/PROPER NAME: vemurafenib

DOSAGE FORM/STRENGTH: 250 mg

APPLICANT: Hoffman-La Roche Inc

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): BRAF mutation positive recurrent or metastatic melanoma

BACKGROUND: Pre NDA meeting held January 21, 2011, where it was stated rolling NDA submission is acceptable. Non-clinical module submitted February 14, 2011 and received February 15 2011. CMC portion submitted and received 3/31/11. Clinical module submitted April 27, 2011 and received April 28, 2011.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Theresa Ferrara	Y
	CPMS/TL:	Alice Kacuba	N
Cross-Discipline Team Leader (CDTL)	Max Ning		Y
Clinical	Reviewer:	Amy McKee, Geoffrey Kim	Y
	TL:	John Johnson	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:	N/A	
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:	N/A	
	TL:		

Clinical Pharmacology	Reviewer:	Jeanne Fourie	Y
	TL:	Qi Liu	Y
Biostatistics	Reviewer:	Qiang (Casey) Xu	Y
	TL:	Shenghui Tang	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	David McGuinn Robeena Aziz	Y
	TL:	Whitney Helms	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	N/A	
	TL:		
Product Quality (CMC)	Reviewer:	Anne Marie Russell	Y
	TL:	Haripada Sarker	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:	N/A	
	TL:		
CMC Labeling Review	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	EES	
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Lubna Merchant	Y
	TL:	Melina Griffis	N
OSE/DRISK (REMS)	Reviewer:	Joyce Weaver	Y
	TL:	Suzanne Berkman- Robottom	
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:	Robert Young	
	TL:	Jean Mulinde	
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:		
Other reviewers CDRH	Donna Roscoe		
Other attendees			

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments: expect PMRs</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO Bob Young (DSI) 5.24.11 All inspection assignments are out. At least one domestic inspection will be done in June and the two foreign inspections should run the middle of July.
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: strong efficacy results with acceptable risks; 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
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
CLINICAL MICROBIOLOGY	<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
CLINICAL PHARMACOLOGY	<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>Comments: expect PMRs</p> <ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
BIOSTATISTICS	<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
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	<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
Comments:	

<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>PRODUCT QUALITY (CMC)</p> <p>Comments: Three months stability data available.</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
<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments: EA requested to CDER OPS IO Environmental; June 20, 2011 inspection</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Richard Pazdur, MD, Director, Office of Oncology Drug Products</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
<input checked="" type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input checked="" type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027822]
<input type="checkbox"/>	Other

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

/s/

THERESA A FERRARA
07/27/2011

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.

PMR/PMC Description: **1803-2: Submit the final analysis of safety in the ongoing trial (Protocol NO25026:BRIM3) to provide the potential for new safety data signals from longer duration of exposure.**

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>09/2009 (submitted)</u>
	Study/Trial Completion:	<u>03/2014</u>
	Final Report Submission:	<u>10/2014</u>
	Other:	<u>MM/DD/YYYY</u>

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

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

The approval of vemurafenib is based on a randomized clinical trial of vemurafenib vs. dacarbazine in metastatic melanoma that demonstrated an overall survival benefit of vemurafenib; however, long term safety data in patients treated with vemurafenib is not available. This trial has met its primary endpoint of demonstrating an advantage in overall and progression free survival of vemurafenib over dacarbazine and has a favorable risk/benefit profile. It would therefore be inappropriate to have this be a pre-approval requirement.

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 approval of vemurafenib is based on a randomized clinical trial of vemurafenib vs. dacarbazine in metastatic melanoma that demonstrated an overall survival benefit of vemurafenib. There was a median follow-up of 6.2 months for patients treated with vemurafenib. Longer follow up of patients may reveal additional safety signals which were not previously apparent.

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.

This is a currently ongoing randomized clinical trial.
--

Required

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

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
A final determination of the overall survival of all subjects will allow for accurate determination of the magnitude of the overall survival benefit of vemurafenib.
 - Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

PMR/PMC Description:

1803-3: Submit an analysis for secondary malignancies from the proposed adjuvant melanoma trial [GO27826: Phase III, Randomized, Double-Blind, Placebo-Controlled Study of Vemurafenib (RO5185426) Adjuvant Therapy in Patients with Surgically-Resected, Cutaneous BRAF Mutant Melanoma at High Risk for Recurrence] annually and for one year after the last patient has completed clinical trial treatment.

PMR/PMC Schedule Milestones:	Draft protocol submission	<u>08/2011</u>
	Final Protocol Submission:	<u>02/2012</u>
	Interim Report Submission	<u>02/2013</u>
	Interim Report Submission	<u>02/2014</u>
	Interim Report Submission	<u>02/2015</u>
	Interim Report Submission	<u>02/2016</u>
	Interim Report Submission	<u>02/2017</u>
	Study/Trial Completion:	<u>03/2017</u>
	Final Report Submission:	<u>09/2017</u>
	Other: _____	<u>MM/DD/YYYY</u>

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

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

This PMR is based on the safety concern of the development of secondary malignancies in patients treated with vemurafenib and will be addressed in a study that is being planned in the adjuvant melanoma population. Since the risk/benefit profile is favorable for the metastatic melanoma population and there has yet to be a clear safety signal of non-cutaneous secondary malignancies, it is inappropriate to have this as a pre-approval requirement.

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.”

Treatment with vemurafenib is associated with the development of cutaneous squamous cell carcinoma. While the exact mechanism is unknown, the high incidence of RAS mutations found in these lesions suggest that the drug may be driving proliferation of primed pre-malignant cells. The incidence of non-cutaneous squamous cell cancers or other RAS-mutation associated cancers in patients treated with vemurafenib is not known. The resectable melanoma population have a significantly longer life expectancy than that of the unresectable or metastatic melanoma population. The development of these secondary malignancies over a presumably longer exposure to vemurafenib is a serious safety concern in this population.

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.

The planned study in papillary thyroid cancer is an uncontrolled study. The planned study in the adjuvant setting for melanoma is a randomized controlled trial.

Required

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

Continuation of Question 4

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

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

PMR/PMC Description:

1803-4: Follow-up for secondary malignancies from the planned papillary thyroid cancer trial [NO25530: An Open-Label, Multi-Center Phase II Study of the BRAF Inhibitor RO5185426 in Patients with Metastatic or Unresectable Papillary Thyroid Cancer (PTC) positive for the BRAF V600 Mutation and Resistant to Radioactive Iodine] annually and for one year after the last patient has completed clinical trial treatment.

PMR/PMC Schedule Milestones:	Protocol amendment* Submission:	11/2011
	<i>*Study N025530 is ongoing</i>	
	Interim Report Submission	11/2012
	Interim Report Submission	11/2013
	Interim Report Submission	11/2014
	Interim Report Submission	11/2015
	Trial Completion:	08/2015
	Final Report Submission:	02/2016
	Other: _____	MM/DD/YYYY

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

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

This PMR is based on the safety concern of the development of secondary malignancies in patients treated with vemurafenib and will be addressed in a study that is being planned in the papillary thyroid population. Since the risk/benefit profile is favorable for the metastatic melanoma population and there has yet to be a possible safety signal of secondary malignancies besides non-cutaneous squamous cell carcinoma, it is inappropriate to have this as a pre-approval requirement.

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.”

Treatment with vemurafenib is associated with the development of cutaneous squamous cell carcinoma. While the exact mechanism is unknown, the high incidence of RAS mutations found in these lesions suggest that the drug may be driving proliferation of primed pre-malignant cells. The incidence of non-cutaneous squamous cell cancers or other RAS-mutation associated cancers in patients treated with vemurafenib is not known. The papillary thyroid population has a significantly longer life expectancy than that of the unresectable or metastatic melanoma population and the development of these secondary malignancies over a presumably longer exposure to vemurafenib is a serious safety concern.

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.

The planned study in papillary thyroid cancer is an uncontrolled study. The planned study in the adjuvant setting for melanoma is a randomized controlled trial.

Required

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

Continuation of Question 4

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

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

PMR/PMC Description: 1803-8: Submit updated overall survival results from the ongoing trial (Protocol NO25026:BRIM3) with a minimum follow-up of 24 months after the last patient was enrolled into the trial.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>09/2009 (Submitted)</u>
	Trial Completion:	<u>12/2012</u>
	Final Report Submission:	<u>07/2013</u>
	Other:	<u>MM/DD/YYYY</u>

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

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

The approval of vemurafenib is based on a randomized clinical trial of vemurafenib vs. dacarbazine in metastatic melanoma that demonstrated an overall survival benefit of vemurafenib; however, the magnitude of the duration of the overall survival in patients treated with vemurafenib is not available. This trial has met its primary endpoint of demonstrating an advantage in overall and progression free survival of vemurafenib over dacarbazine and has a favorable risk/benefit profile. It would therefore be inappropriate to have this be a pre-approval requirement.

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 approval of vemurafenib is based on a randomized clinical trial of vemurafenib vs. dacarbazine in metastatic melanoma that demonstrated an overall survival benefit of vemurafenib. The duration of the overall survival benefit is not known and longer follow up for overall survival would provide this information.

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.

This is a currently ongoing randomized clinical trial.
--

Required

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

Continuation of Question 4

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

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- Other
A final determination of the overall survival of all subjects in the pivotal phase 3 trial.
-

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR/PMC Development Template

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

PMR/PMC Description: **1803-9: Develop an Investigational Use Only, Companion Diagnostic (IUO CoDx) that reliably detects V600K BRAF mutation in patients with unresectable or metastatic melanoma and conduct an open-label single arm trial with overall response rate and duration of response as the primary endpoints in this population as determined by the diagnostic test.**

PMR/PMC Schedule Milestones:	Draft protocol submission	<u>06/2012</u>
	Final Protocol Submission*:	<u>10/2012</u>
	*To coincide with completion of 1 year paperwork for IUO development	
	Trial Completion:	<u>01/2015</u>
	Final Report Submission:	<u>07/2015</u>
	Other:	<u>MM/DD/YYYY</u>

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

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

The cobas[®] 4800 BRAF^{V600} Mutation Test is the companion diagnostic that will be approved with vemurafenib and was used to select patients for the Phase 2 and Phase 3 trials. This test is designed to detect the V600E mutation but can cross react with some, but not all, V600K mutations. This PMC will address those patients who have a V600K mutation but whose tumors do not test positive by the current iteration of the cobas test. Since the favorable risk benefit of vemurafenib has been established for the V600E population (~90% of V600 mutations are V600E) it would be inappropriate to require this PMC as a pre-approval requirement.

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 companion diagnostic test to vemurafenib was designed to be highly sensitive for the V600E mutation, but is able to detect a proportion of patients with the V600K mutation. In the phase 3 trial, a total of 19 patients were determined to have a V600K mutation by Sanger sequencing (DTIC = 9; Vem = 10) and 9 patients were identified as having a V600K mutation in the phase 2 trial. Seven out of 16 (43.8%) patients identified as having a V600k mutation who were treated with vemurafenib had a confirmed response, suggesting that this drug has similar efficacy in the V600K population. Currently, there is a subset of patients with V600K mutations who will not be detected by the current companion diagnostic test, but may benefit from treatment with vemurafenib.

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.

The agreed upon trial is an open-label single-arm trial in patients with unresectable or metastatic melanoma with the BRAF V600K mutation as determined by an Investigational Use Only, Companion Diagnostic (IUO CoDx) that reliably detects V600K BRAF mutation. The primary endpoints of this trial will be response rates and duration of response.

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)
Development of an Investigational Use Only Companion Diagnostic that reliably detects the BRAF V600K mutation.
-
- 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.

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PMR/PMC Development Template

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

PMR/PMC Description: **1803-10: Assess changes in NRAS mutation status at both baseline and disease progression in biopsy accessible lesions in patients with advanced melanoma positive for the V600E BRAF mutation who have been treated with vemurafenib. This assessment should include all patients with available biopsy specimens and may be derived from completed and ongoing trials in patients treated with vemurafenib. These trials are:**

- *PLX06-02: A Study to Assess Safety, Pharmacokinetics, and Pharmacodynamics of PLX4032 in Patients with Solid Tumors
 - *NP22657: An Open-Label, Multi-Center, Phase II Study of Continuous Oral Dosing of RO5185426 in Previously Treated Patients With Metastatic Melanoma
 - *NO25026: A Randomized, Open-label, Controlled, Multicenter, Phase III Study in Previously Untreated Patients With Unresectable Stage IIIC or Stage IV Melanoma with V600E BRAF Mutation Receiving RO5185426 or Dacarbazine
 - *NP25163: A Phase I, Randomized, Open-label, Multi-center, Multiple Dose Study to Investigate the Pharmacokinetics and Pharmacodynamics of RO5185426 Administered as 240 mg Tablets to Previously Treated BRAF V600E Positive Metastatic Melanoma Patients
 - *NP25396: A Phase I, Randomized, Open-label, Multi-center, Two Period Crossover Study to Investigate the Effect of Food on the Pharmacokinetics of a Single Oral Dose of RO5185426, Followed by Administration of 960 mg RO5185426 Twice Daily to BRAF^{V600E} Positive Metastatic Melanoma Patients
-

PMR/PMC Schedule Milestones:

Trial Completion:	<u>5/2012</u>
Final Report Submission:	<u>9/2012</u>
Other:	<u>MM/DD/YYYY</u>

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

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

This PMC addresses a scientific concern regarding the role of RAS mutations in conferring primary and secondary mechanisms of resistance. The benefit/risk profile of vemurafenib has been established as favorable in the patients who have provided biopsy specimens. Thus it would be inappropriate to have this PMC as a pre-marketing requirement.

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

In both nonclinical models and in patient samples, RAS mutations have been reported in progressive lesions that arose during vemurafenib treatment that did not exist prior to therapy. Although rare, concomitant RAS and BRAF mutations have been reported in melanoma and pre-melanoma lesions. It is important to assess the incidence of concomitant RAS and BRAF mutations and to determine whether progressive lesions alter their genotype in response to vemurafenib treatment.

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.

This will be a nonclinical study assessing RAS mutational status in biopsy specimens that have been collected at baseline and at progression in patient's treated with vemurafenib.

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)
Assess RAS mutation status in baseline and progression biopsy samples and archival tissue acquired through the exploratory biomarker program.
 - Other
-

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

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

/s/

THERESA A FERRARA
08/04/2011

KATHERINE M FEDENKO
08/15/2011

PMR 1
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.

PMR/PMC Description: 1803-5: Conduct a drug interaction trial to evaluate the effect of a strong CYP3A inducer (e.g., rifampin) on the pharmacokinetics of vemurafenib.

PMR/PMC Schedule Milestones:	Draft protocol Submission	02/2012
	Final Protocol Submission:	07/2012
	Trial Completion:	04/2014
	Final Report and Dataset Submission:	10/2014
	Other:	MM/DD/YYYY

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

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

In vitro screens showed that CYP3A4 is responsible for the metabolism of vemurafenib into mono-hydroxyl metabolites. The bioavailability of vemurafenib in humans is not known. If vemurafenib has a low oral bioavailability in humans, CYP3A4 mediated metabolism could contribute significantly to its clearance. Thus, co-administration of vemurafenib with strong CYP3A inducers can lead to decreased vemurafenib concentrations and efficacy concerns. No clinical drug-drug interaction trial has been conducted to address this issue. Therefore, a drug interaction trial with a strong CYP3A inducer, such as rifampin, is required to identify the appropriate dose when vemurafenib is co-administered with a potent CYP3A inducer.

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.”

CYP3A4 is responsible for the metabolism of vemurafenib into mono-hydroxyl metabolites. A clinical trial with a potent CYP3A inducer, such as rifampin, is needed to accurately determine the magnitude of vemurafenib exposure changes when a strong CYP3A4 inducer is co-administered with vemurafenib. Depending on the results, a safe and efficacious dose of vemurafenib will be identified when it is co-administered with potent CYP3A inducers.

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.

The required drug-drug interaction trial may be a crossover or parallel trial to evaluate the effect of a strong CYP3A inducer (e.g., rifampin) on the pharmacokinetics of vemurafenib.

Required

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

Continuation of Question 4

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

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR 2
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.

PMR/PMC Description: 1803-6: Conduct a drug interaction trial to evaluate the effect of a strong CYP3A4 inhibitor (e.g., ketoconazole) on the pharmacokinetics of vemurafenib.

PMR/PMC Schedule Milestones:	Draft protocol Submission	02/2012
	Final Protocol Submission:	07/2012
	Trial Completion:	04/2014
	Final Report and Datasets Submission:	10/2014
	Other:	MM/DD/YYYY

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

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

In vitro screens showed that CYP3A4 is responsible for the metabolism of vemurafenib into mono-hydroxyl metabolites. The bioavailability of vemurafenib in humans is not known. If vemurafenib has a low oral bioavailability in humans, CYP3A4 mediated metabolism could contribute significantly to its clearance. Thus, co-administration of vemurafenib with strong CYP3A inhibitors can lead to an increase in vemurafenib concentrations and risk of toxicity. However, no clinical drug-drug interaction trial has been conducted to address this issue. Therefore, a drug interaction trial with a strong CYP3A inhibitor, such as ketoconazole, is required.

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.”

CYP3A4 is responsible for the metabolism of vemurafenib into mono-hydroxyl metabolites. A clinical trial with a strong CYP3A inhibitor, such as ketoconazole, is needed to accurately determine the magnitude of vemurafenib exposure changes when a strong CYP3A4 inhibitor is co-administered with vemurafenib. Depending on the results, a safe dose of vemurafenib will be identified when co-administered with strong CYP3A inhibitors.

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.

The required drug-drug interaction trial may be a crossover or parallel trial to evaluate the effect of a CYP3A4 inhibitor, ketoconazole, on the pharmacokinetics of vemurafenib.

Required

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

Continuation of Question 4

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

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR 3
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.

PMR/PMC Description: 1803-7: Conduct a clinical trial in patients with normal hepatic function and patients with pre-existing severe hepatic impairment to assess the effect of severe hepatic impairment on the pharmacokinetics of vemurafenib.

PMR/PMC Schedule Milestones:	Draft protocol Submission	<u>05/2012</u>
	Final Protocol Submission:	<u>09/2012</u>
	Trial Completion:	<u>02/2017</u>
	Final Report and Datasets Submission:	<u>08/2017</u>
	Other: _____	<u>MM/DD/YYYY</u>

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

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

Insufficient clinical and pharmacokinetic data are available to determine if a starting dose adjustment is needed for patients with pre-existing severe hepatic impairment. Therefore, a clinical trial in patients with normal hepatic function and patients with pre-existing severe hepatic impairment is required to identify the appropriate dose for patients with severe hepatic impairment.

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.”

A change in vemurafenib exposure is expected to be in individuals with pre-existing severe hepatic impairment, compared to patients with normal hepatic function. Therefore, a clinical trial in patients with normal hepatic function and patients with pre-existing severe hepatic impairment is required to identify the appropriate dose for patients with 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.

The required clinical trial will be a trial designed to assess the pharmacokinetics of vemurafeinb in patients with pre-existing severe hepatic impairment compared to those with normal hepatic function.

Required

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

Continuation of Question 4

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

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

PMR 4
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.

PMR/PMC Description: 1803-1: Perform an *in vitro* screen to determine if vemurafenib is an inhibitor of human CYP2C8 and CYP2B6. Based on results from the *in vitro* screen, a clinical drug-drug interaction trial may be needed.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>11/2011</u>
	Study Completion:	<u>01/2012</u>
	Final Report Submission:	<u>03/2012</u>
	Other:	<u>MM/DD/YYYY</u>

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

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

The potential of vemurafenib to inhibit human CYP2C8 and CYP2B6 *in vitro* was not reported in the NDA submission. An *in vitro* screen to determine if vemurafenib inhibits CYP2C8 and CYP2B6 will help determine the likelihood of drug-drug interactions in which vemurafenib may increase concentrations of sensitive CYP2C8 and CYP2B6 substrates *in vivo*.

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 potential of vemurafenib to inhibit human CYP2C8 and CYP2B6 *in vitro* was not reported in the NDA submission. An *in vitro* screen to determine if vemurafenib inhibits CYP2C8 and CYP2B6 will help determine the likelihood of drug-drug interactions in which vemurafenib may increase concentrations of sensitive CYP2C8 and CYP2B6 substrates *in vivo*.

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.

The required study will be an *in vitro* screen of the effect of vemurafenib on human CYP2C8 and CYP2B6. The study may be done using human liver microsomes.

Required

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

Continuation of Question 4

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

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

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/s/

JEANNE FOURIE
07/21/2011

QI LIU
07/21/2011

NAM ATIQRUR RAHMAN
07/25/2011

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

PATIENT LABELING REVIEW

Date: **July 22, 2011**

To: Robert Justice MD, Director,
Division of Drug Oncology Products (DDOP)

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)

Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Risk Management

From: Latonia M. Ford, RN, BSN, MBA
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name (established name): ZELBORAF(vemurafenib)

Dosage Form and Route: tablet

Application Type/Number: NDA 202429

Applicant: Hoffmann-La Roche, Inc.

OSE RCM #: 2011-1491

1 INTRODUCTION

This review is written in response to a request by the Division of Drug Oncology Products (DDOP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide for Zelboraf (vemurafenib) tablet.

On April 27, 2011, Hoffmann-La Roche submitted an original New Drug Application, NDA 202-429 for Zelboraf (vemurafenib) tablet. The proposed indication for Zelboraf (vemurafenib) tablet is for the treatment of unresectable or metastatic melanoma with the BRAF^{V600E} mutation as detected by an FDA-approved test.

2 MATERIAL REVIEWED

- Draft ZELBORAF (vemurafenib) tablet Medication Guide (MG) received on April 27, 2011, and sent to DRISK on July 15, 2011.
- Draft ZELBORAF (vemurafenib) tablet prescribing information (PI) received April 27, 2011 revised by the Review Division throughout the current review cycle and received by DRISK on July 15, 2011; further revised and received by DRISK on July 20, 2011.

3 REVIEW METHODS

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

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

In our review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the prescribing information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated (tracked and clean) versions of the MG are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.
- Please consult with SEALD regarding PI section 17. Under PLR labeling guidelines, the MG should not receive a subsection number; instead it should immediately follow the text at the end of section 17. Additionally, there should be a statement at the beginning of the section that references the FDA-approved Medication Guide.

Please let us know if you have any questions.

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/s/

LATONIA M FORD
07/22/2011

LASHAWN M GRIFFITHS
07/22/2011

Internal Consult

Pre-decisional Agency Information

To: Theresa Ferrara, RPM, Division of Drug Oncology Products, (DDOP)

From: Marybeth Toscano, Regulatory Reviewer Officer
Richard Lyght, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

CC: Karen Rulli, Professional Review Group II Leader, DDMAC
Amy Toscano, DTC Review Group IV Leader, DDMAC

Date: July 22, 2011

Re: Comments on draft labeling (Package Insert) for Zelboraf
(vemurafenib) tablets, oral
NDA 202429

In response to your consult request dated April 29, 2011, we have reviewed the draft version of the Package Insert for Zelboraf (vemurafenib) tablets. We offer the following comments. Please note some of these comments may have been addressed during labeling meetings.

Section	Statement from draft	Comment
<ul style="list-style-type: none">1 Indications and Usage, and Highlights12.1 Mechanism of Action	<p>Limitations of Use: ZELBORAF (b) (4) in patients with wild-type BRAF^{V60} melanoma.</p> <p>Vemurafenib is a low molecular weight, orally available, inhibitor of mutated (b) (4) Vemuratenib also inhibits other kinases such as CRAF, ARAF, SRMS, ACK1, MAP4K5 and FGR at (b) (4) concentrations (b) (4)</p>	<p>Section 12.1 of the Full Prescribing Information states vemurafenib (b) (4) wild-type BRAF, but the Indications and Usage section states (b) (4)</p> <p>DDMAC recommends making this consistent (addressed at labeling meeting 7/19/11).</p>

<ul style="list-style-type: none"> 5.1 Warnings and Precautions 	<p>Cutaneous Squamous Cell Carcinoma (cuSCC) Cases of cuSCC have been reported in patients treated with vemurafenib [see Adverse Reactions (6.1)]. The incidence of cuSCC in vemurafenib-treated patients (b) (4) 24%. CuSCC usually occurred early in the course of treatment with a median time to the first appearance of 7 to 8 weeks. Of the patients who experienced cuSCC, approximately 33% experienced > 1 occurrence with median time between occurrences of 6 weeks. Potential risk factors associated with cuSCC in vemurafenib clinical studies included age (≥ 65 years), prior skin cancer, and chronic sun exposure. In the clinical trials, cases of cuSCC were managed with excision, and patients were able to continue treatment without dose adjustment. It is recommended that all patients receive a dermatologic evaluation prior to initiation of therapy and every two months while on therapy. Any suspicious skin lesions should be excised, sent for dermatopathologic evaluation and treated as per standard of care. Monitoring should continue for 6 months following discontinuation of vemurafenib (b) (4)</p> <p>(b) (4)</p>	<p>We note that there is no verbiage on (b) (4) in the Highlights, Warnings and Precautions section. DDMAC recommends adding this warning to the Warnings and Precautions section of the Highlights.</p> <p>Additionally, the section on cuSCC recommends a dermatologic evaluation every two months, (b) (4)</p> <p>Please consider choosing every two for evaluation, as this lack of consistency may cause confusion.</p> <p>(Addressed at labeling meeting 7/19/11)</p>
<ul style="list-style-type: none"> 8.1 Use in Specific Populations, Pregnancy 	<p>(b) (4)</p>	<p>DDMAC recommends this sentence be revised to remove “Based on mechanism of action”. In addition, we recommend adding this revised sentence to the Highlights, Use in Specific Populations section (addressed at labeling meeting 7/19/11).</p>
<ul style="list-style-type: none"> 8.7, Hepatic Impairment 8.8 Renal Impairment 	<p>No adjustment to the starting dose is needed for patients with pre-existing mild and moderate hepatic impairment.</p> <p>No adjustment to the starting dose is needed for patients with pre-existing mild and moderate renal</p>	<p>Both sections discuss use in severe hepatic or renal impairment after use use in mild or moderate impairment. DDMAC recommends reversing the order of this</p>

	impairment.	information to list severe first.
• 14 Clinical Studies	Table 4, Efficacy of Vemurafenib in Treatment-Naïve Patients with BRAFV600E Mutation-Positive Melanoma	DDMAC recommends the rows for HR and Median PFS be reversed so the PFS values appear before their corresponding HRs
• 14 Clinical Studies	<p><u>Treatment-Naïve Patients</u></p> <p>The confirmed, investigator-assessed best overall response rate (b) (4) was 48.4% (95% CI: 41.6%, 55.2%) in the vemurafenib arm compared to 5.5% (95% CI: 2.8%, 9.3%) in the dacarbazine arm</p> <p><u>Patients Who Received Prior Systemic Therapy</u></p> <p>The confirmed best overall response rate (b) (4) as assessed by an independent review committee (IRC) was 52% (95% CI: 43%, 61%).</p>	DDMAC recommends reporting the actual number of CRs and PRs in both of these patients
• 14 Clinical Studies	<p><u>Patients Who Received Prior Systemic Therapy</u></p> <p>The median time to response was 1.4 months with 75% of responses occurring by month 1.6 of treatment.</p>	This statement may be used in promotion. Was the response a PR, CR, etc.? Please provide a clarification.
• General Comment	<p>ZELBORAF and vemurafenib are used interchangeably throughout the Prescribing Information</p> <p>Some sections have ZELBORAF bolded</p>	Please confirm which sections use the brand name and which ones refer to the generic name and bolding of the brand name.

HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

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/s/

MARYBETH TOSCANO
07/19/2011

RICHARD A LYGHT
07/19/2011

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	indicated for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma. Pivotal Study #2 Indication:				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and				

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?		X		The sponsor has proposed a dedicated phase 2 study in pediatric patients.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____ Yes ____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Amy McKee; Geoffrey Kim

5/23/11

Reviewing Medical Officer

Date

Clinical Team Leader

Date

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/s/

GEOFFREY S KIM
07/19/2011

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

IND or NDA	NDA 202429
Generic Name	RO5185426 (Vemurafenib)
Sponsor	Hoffman-La Roche, Inc.
Indication	SRAF V600 mutation-positive unresectable or metastatic melanoma
Dosage Form	240 mg film-coated tablets
Drug Class	Tyrosine kinase inhibitor
Therapeutic Dosing Regimen	960 mg twice daily
Maximum Tolerated Dose	960 mg
Submission Date	28 April 2011
Review Division	DDOP / HFD 150

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No large changes in QTc interval (i.e., >20 ms) was detected in the trial following the treatment of vemurafenib (RO5185426) 960 mg twice daily, even though vemurafenib appears to prolong QTc interval in a concentration-dependent manner (P <0.0001). The largest upper bound of the 2-sided 90% confidence interval (CI) for the mean change from baseline was 14.8 ms, observed at 6 hours post-dose on Day 15 (i.e., at steady state) in Cycle 1.

This is an open-label, multi-center, single-agent, uncontrolled, phase 2 study in 132 previously treated patients with metastatic melanoma, whose tumors were *BRAF*^{V600E}-positive by the cobas® 4800 BRAF V600 Mutation Test. The patients were continually dosed with oral vemurafenib 960 mg b.i.d. in multiple treatment cycles. 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 RO5185426 (960 mg BID) (FDA Analysis)

Treatment	Day	Time (hour)	Δ QTcP (ms)	90% CI (ms)
RO5185426 (960mg BID)	15	6	11.9	(9.1, 14.8)

The dose tested in the trial, which represents both the anticipated therapeutic dose and the maximum tolerated dose, is sufficient for QT evaluation.

2 PROPOSED LABEL

2.1 SPONSOR PROPOSED LABEL

The sponsor proposed the following label language.

Full prescribing information



2.2 Dose Modifications

Management of symptomatic adverse drug reactions or prolongation of QTc may require dose reduction, treatment interruption, or treatment discontinuation of vemurafenib (Table 1). Dose modifications or interruptions are not recommended for cutaneous squamous cell carcinoma (cuSCC) adverse reactions [see *Warnings and Precautions* (5.2) and *Adverse Reactions* (6.1)]. Dose reductions resulting in a dose below 480 mg twice daily are not recommended. (See CSR NO25026, Section 5.4.3.3) (See CSR NO25026, Section 6.1.2.1) (See SCS, Section 1.1.2.3)

Table 1 Dose Modification Information

(See SCS, Section 1.1.2.3) (See CSR NO25026, Section 3.5.7.1)

(See CSR NP22657, Section 2.4.7)

Grade (CTC-AE)*	Recommended Vemurafenib Dose Modification
Grade 1 or Grade 2 (tolerable)	Maintain vemurafenib at a dose of 960 mg twice daily
Grade 2 (Intolerable) or Grade 3	
1 st Appearance	Interrupt treatment until grade 0 – 1. Resume dosing at 720 mg twice daily.
2 nd Appearance	Interrupt treatment until grade 0 – 1. Resume dosing at 480 mg twice daily
3 rd Appearance	Discontinue permanently
Grade 4	
1 st Appearance	Discontinue permanently or interrupt vemurafenib treatment until grade 0 – 1. Resume dosing at 480 mg twice daily
2 nd Appearance	Discontinue permanently

*The intensity of clinical adverse events graded by the Common Terminology Criteria for Adverse Events v4.0 (CTC-AE)

5.4 QT Prolongation

Exposure-dependent QT prolongation was observed in an uncontrolled, open-label Phase 2 QT sub-study in previously treated patients with BRAF V600 mutation-positive metastatic melanoma (See CSR NP22657, Section 3.5.6.1) [redacted] (b) (4) [redacted]. QT prolongation may lead to an increased risk of ventricular arrhythmias, including Torsade de Pointes. Treatment with vemurafenib is not recommended in patients with uncorrectable electrolyte abnormalities, long QT syndrome, or who are

taking medicinal products known to prolong the QT interval. (See CSR NO25026 Section 5.4.3.3) (See CSR NO25026 Section 4.6) (See IB, Section 1.5)

ECG and electrolytes should be monitored before treatment with vemurafenib or after dose modification. ^{(b) (4)} monitoring should occur monthly during the first 3 months of treatment followed by every 3 months thereafter or as clinically indicated. Initiation of treatment with vemurafenib is not recommended in patients with QTc >500 ms. If during treatment the QTc exceeds 500 ms (CTC-AE ≥ Grade 3), vemurafenib treatment should be temporarily interrupted, electrolyte abnormalities should be corrected, and cardiac risk factors for QT prolongation (e.g. congestive heart failure, bradyarrhythmias) should be controlled. Re-initiation of treatment should occur at a lower dose once the QTc decreases below 500 ms [see *Dose Modifications (2.2)*]. Permanent discontinuation of vemurafenib treatment is recommended if after correction of associated risk factors, the QTc increase meets values of both >500 ms and >60 ms change from pre-treatment values. (See CSR NO25026 Section 5.4.3.3) (See CSR NO25026 Section 6.1.2.1)(See IB, Section 1.5).



2.2 QT-IRT PROPOSED LABEL

We have the following label recommendations on Section 5.4 and Section 12.2 which are suggestions only. We defer the final labeling decisions to the review division.

5.4 QT Prolongation

Exposure-dependent QT prolongation was observed in an uncontrolled, open-label Phase 2 QT sub-study in previously treated patients with BRAF V600 mutation-positive metastatic melanoma (See CSR NP22657, Section 3.5.6.1) [see *Pharmacodynamics (12.2)*]. QT prolongation may lead to an increased risk of ventricular arrhythmias, including Torsade de Pointes. Treatment with vemurafenib is not recommended in patients with uncorrectable electrolyte abnormalities, long QT syndrome, or who are taking medicinal products known to prolong the QT interval. (See CSR NO25026 Section 5.4.3.3) (See CSR NO25026 Section 4.6) (See IB, Section 1.5) ECG and electrolytes should be monitored before treatment with vemurafenib or after dose modification. Further monitoring should **start in 15 days of the treatment and should** occur monthly during the first 3 months of treatment followed by every 3 months thereafter or as clinically indicated. Initiation of treatment with vemurafenib is not recommended in patients with QTc >500 ms. If during treatment the QTc exceeds 500 ms (CTC-AE \geq Grade 3), vemurafenib treatment should be temporarily interrupted, electrolyte abnormalities should be corrected, and cardiac risk factors for QT prolongation (e.g. congestive heart failure, bradyarrhythmias) should be controlled. Re-initiation of treatment should occur at a lower dose once the QTc decreases below 500 ms [see *Dose Modifications (2.2)*]. Permanent discontinuation of vemurafenib treatment is recommended if after correction of associated risk factors, the QTc increase meets values of both >500 ms and >60 ms change from pre-treatment values. (See CSR NO25026 Section 5.4.3.3) (See CSR NO25026 Section 6.1.2.1)(See IB, Section 1.5).

(b) (4)



3 BACKGROUND

Also see previous QT-IRT reviews under IND 73620 dated January 12, 2011, August 9, 2010 and May 11, 2009.

3.1 PRODUCT INFORMATION

Vemurafenib (RO5185426) is a small molecule, selective inhibitor of the activated form of the BRAF serine-threonine kinase enzyme. The proposed indication for vemurafenib is for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma.

3.2 MARKET APPROVAL STATUS

Vemurafenib is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

Reviewed previously in QT-IRT review dated May 11, 2009. IC_{50} for hERG was 1.24 μ M.

Mean C_{max} with multiple dosing is 172 μ M.

3.4 PREVIOUS CLINICAL EXPERIENCE

Source: Summary of Clinical Safety eCTD 2.7.4

Overall, the safety population includes a total of 866 patients who received at least one dose of study drug, RO5185426 (N=584) or dacarbazine (DTIC) (N=282).

In the pivotal Phase 3 study (N025026), as of the clinical cutoff date for the Phase 3 NO25026 study, the sponsor reports a total of 42 patients (13%) in the RO5185426 group had died during the course of the study, and 22 of these patients (6.5%) died within 28 days of their last RO5185426 dose. In the dacarbazine group, a total of 66 patients (23%) died during the study; 16 (5.5%) within 28 days of the last dacarbazine dose (Table 2).

Table 2: Summary of Deaths by Primary Cause (Phase 3 [NO25026] Study, All Treated Patients)

Primary Cause of Death	DTIC N = 289 No. (%)	RO5185426 N = 336 No. (%)
Total No. of Deaths	66 (23)	42 (13)
DISEASE PROGRESSION	63 (22)	35 (10)
OTHER	2 (<1)	3 (<1)
ADVERSE EVENTS	1 (<1)	2 (<1)
UNKNOWN	-	2 (<1)

Investigator text for Cause of Death encoded using MedDRA version 13.1.
Percentages are based on N.
DD11 17FEB2011:07:03:04
Source: dd11 ([page 553](#))

Source: Table 27, SCS

A total of 53 patients (32%) in the pooled safety population died during the course of the Phase 1 PLX06-02 and Phase 2 NP22657 studies and 21 of these patients (40%) died within 28 days of their last dose of RO5185426. With the exception of two deaths, one resulting from pneumonia (study NP22657, patient 107006,) and one from acute renal failure (study NP22657, patient 109003), the sponsor reports that all deaths resulted from disease progression.

The following serious cardiac AEs were reported (Table 3 and Table 4):

Table 3: Summary of Serious Adverse Events by Body System and Treatment Arm (Phase 3 [NO25026] Study, Safety Population)

Body System/ Adverse Event	DTIC	RO5185426
	N = 282 No. (%)	N = 336 No. (%)
CARDIAC DISORDERS		
Total Pts With at Least one AE	3 (1)	6 (2)
ATRIAL FIBRILLATION	-	2 (<1)
CARDIOPULMONARY FAILURE	2 (<1)	-
CARDIAC FAILURE	-	1 (<1)
CARDIAC TAMPONADE	1 (<1)	-
MYOCARDIAL INFARCTION	-	1 (<1)
PERICARDIAL EFFUSION	-	1 (<1)
PERICARDITIS	-	1 (<1)
Total Number of AEs	3	6

Source: Table 28, SCS

Table 4: Summary of Serious Adverse Events by Body System and NCI CTCAE Grade (Phase 1[PLX06-02]/Phase 2 [NP22657] Studies and Pooled Safety Population)

ael5_s Summary of Serious Adverse Events, by Body System and NCI CTCAE Grade
 Serious Adverse Events
 Protocol(s) : PLX0602 NP22657
 Analysis: SAFETY Center: ALL CENTERS
 Adverse Event Onset between Time of Very First Drug Intake and Study Day 9999, Time 23:59

Body System/ Adverse Event	PLX06-02					NP22657					Pooled							
	N = 32					N = 132					N = 164							
	Grade:	1	2	3	4	5	Grade:	1	2	3	4	5	Grade:	1	2	3	4	5
Total	No.	No.	No.	No.	No.	Total	No.	No.	No.	No.	No.	Total	No.	No.	No.	No.	No.	
CARDIAC DISORDERS																		
Total Pts With at Least one AE	2	-	-	2	-	-	4	-	1	3	-	-	6	-	1	5	-	-
PERICARDIAL EFFUSION	1	-	-	1	-	-	2	-	-	2	-	-	3	-	-	3	-	-
PERICARDITIS	1	-	-	1	-	-	1	-	1	-	-	2	-	-	2	-	-	
ANGINA PECTORIS	-	-	-	-	-	-	1	-	1	-	-	1	-	1	-	-	-	
ATRIAL FLUTTER	-	-	-	-	-	-	1	-	1	-	-	1	-	-	1	-	-	
Total Number of AEs	2	-	-	2	-	-	5	-	1	4	-	-	7	-	1	6	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
 Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
 Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
 AElS 28JAN2011:22:16:39 (3 of 6)

Source: Table 29, SCS

Adverse events related to QT prolongation are as follows (Table 5 and Table 6):

Table 5: Summary of “QT Prolongation-related” Adverse Events (Phase 3 [NO25026] Study, Safety Population)

Adverse Event	Total		1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Treatment: DTIC; N = 282												
TORSAD EPOINTE S/Q T P R O L O N G A T I O N												
Total Pts With at Least one AE	16	(5.7)	13	(4.6)	2	(0.7)	1	(0.4)	-	-	-	-
DIZZINESS	10	(3.5)	10	(3.5)	-	-	-	-	-	-	-	-
SYNCOPE	3	(1.1)	1	(0.4)	1	(0.4)	1	(0.4)	-	-	-	-
LOSS OF CONSCIOUSNESS	2	(0.7)	1	(0.4)	1	(0.4)	-	-	-	-	-	-
VENTRICULAR TACHYCARDIA	1	(0.4)	1	(0.4)	-	-	-	-	-	-	-	-
Total Number of AEs	16		13		2		1		-	-	-	-
Treatment: RO5185426; N = 336												
TORSAD EPOINTE S/Q T P R O L O N G A T I O N												
Total Pts With at Least one AE	28	(8.3)	21	(6.3)	6	(1.8)	3	(0.9)	-	-	-	-
DIZZINESS	20	(6.0)	17	(5.1)	3	(0.9)	-	-	-	-	-	-
ELECTROCARDIOGRAM QT P R O L O N G E D	6	(1.8)	4	(1.2)	2	(0.6)	-	-	-	-	-	-
SYNCOPE	3	(0.9)	-	-	1	(0.3)	2	(0.6)	-	-	-	-
LOSS OF CONSCIOUSNESS	1	(0.3)	-	-	-	-	1	(0.3)	-	-	-	-
Total Number of AEs	30		21		6		3		-	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity. AE17 15MAR2011:19:27:11
Source: ael7_si3c (page 1065)

Source: Table 49, SCS

Table 6: Summary of “QT Prolongation-related” Adverse Events by Preferred Term and NCI CTCAE Grade (Pooled Safety Population)

ael7_si Summary of Adverse Events of Special Interest (AESI) by Preferred Term and NCI CTCAE Grade
Protocol(s): FL00602 NP22697
Analysis: SAFETY Center: ALL CENTERS
Pooled: N = 164
Adverse Event Onset between Time of Very First Drug Intake and Study Day 9999, Time 23:59

Body System/ Adverse Event	Total		1		2		3		4		5	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
TORSAD EPOINTE S/Q T P R O L O N G A T I O N												
Total Pts With at Least one AE	14	(8.5)	12	(7.3)	2	(1.2)	1	(0.6)	-	-	-	-
DIZZINESS	10	(6.1)	8	(4.9)	2	(1.2)	-	-	-	-	-	-
ELECTROCARDIOGRAM QT P R O L O N G E D	5	(3.0)	5	(3.0)	-	-	-	-	-	-	-	-
SYNCOPE	1	(0.6)	-	-	-	-	1	(0.6)	-	-	-	-
Total Number of AEs	16		13		2		1		-	-	-	-

Investigator text for Adverse Events encoded using MedDRA version 13.1.
Percentages are based on N.
Only the most severe intensity is counted for multiple occurrences of the same adverse event in one individual.
Any difference between the total number and sum of AEs is due to missing investigators assessment of intensity.
AE17 11FEB2011:17:54:16
Source output: ael7_si (page 2038)

Source: Table 50, SCS

In the Phase 3 NO25026 study, the mean change from baseline in QT, QTc, QTcB, and QTcF intervals was greater in the RO518546 group than in the dacarbazine group at all times after dosing. A similar proportion of patients in RO5185426 and dacarbazine groups exhibited a treatment-emergent maximum individual QTcB and QTcF change from baseline of >60 ms, and no maximum individual QTcF values of >500 ms were seen in either treatment group.

In the pooled safety population, two patients (2%) developed treatment-emergent absolute QTcP (QT analysis corrected population) values >500 ms, and one of these patients also had a QTcP change from baseline of >60 ms.

The sponsor reports that no patients discontinued treatment due to a “QT prolongation” AE and one patient required dose modification. Three “QT prolongation-related” AEs were serious. These included loss of consciousness in two patients (dacarbazine patient 1908 and RO5185426 patient 1453) and syncope in one patient (RO5185426 patient 6102). ECGs reported in closest temporal proximity to the event had normal QTc but were not recorded at the time of the event.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of RO5185426’s clinical pharmacology.

4 SPONSOR’S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the analysis plan for this study under IND 73620, but did not review the study protocol. The sponsor submitted the study report 1038633 for the study drug, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

An Open-Label, Multi-Center, Phase II Study of Continuous Oral Dosing of RO5185426 in Previously Treated Patients With Metastatic Melanoma

4.2.2 Protocol Number

NP22567

4.2.3 Study Dates

September 2009 to September 2010

4.2.4 Objectives

The primary objective of this study was to evaluate the efficacy of RO5185426 in previously treated metastatic melanoma patients with *BRAF*_{V600} mutation-positive mutation by Best Overall Response Rate (BORR) as assessed by an independent review committee (IRC) using RECIST version 1.1 criteria for metastatic melanoma.

4.2.5 Study Description

4.2.5.1 Design

An open-label, multi-center, single agent, uncontrolled, Phase 2 study in which previously treated patients with metastatic melanoma, whose tumors were *BRAF*_{V600E}-positive by the cobas® 4800 BRAF V600 Mutation Test. The patients were continually dosed with oral RO5185426 960 mg b.i.d. until progression of disease, unacceptable toxicity, withdrawal of consent, or other reason as determined by the investigator.

4.2.5.2 Controls

There was no placebo or moxifloxacin used in this study.

4.2.5.3 Blinding

This study was an open-label study.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

This was a single-arm study; thus, each patient received RO5185426 960 mg BID.

4.2.6.2 Sponsor's Justification for Doses

“Selection of the dose used in this study was based primarily on the clinical efficacy observed at the maximum tolerated dose (MTD) of 960 mg b.i.d. in the dose escalation phase of the multiple ascending dose Phase 1 trial, PLX06-02, following an assessment of safety in the first 6 patients treated with the 960 mg b.i.d. dose for at least 28 days. This dose maintained maximum pathway inhibition and demonstrated anti-tumor response in *BRAF*^{V600E}-positive patients. Safety and efficacy data from the extension phase of this trial in patients with metastatic melanoma, which was ongoing at the time of initiation of Study NP22657, were also used to support the dose of 960 mg b.i.d.

“The choice of the MTD at 960 mg b.i.d. was well supported by preclinical efficacy xenograft models with varied response sensitivity. Tumor stasis was observed at exposures (AUC_{0-24h}) of 100 to 200 $\mu M \cdot h$ in the Colo205 model, and tumor shrinkage was not observed until drug concentrations of $>400 \mu M \cdot h$ was achieved. In the more resistant HT29 model, 90% TGI was achieved at exposures (AUC_{0-24h}) of $>2000 \mu M \cdot h$. This high level of exposure is more consistent with the MTD (960 mg b.i.d.) in which the mean AUC_{0-24h} in patients was $1740 \mu M \cdot h$.

“There was no plateau in response in the xenograft models; higher RO5185426 concentrations were associated with greater tumor shrinkage and longer duration survival.”

Reviewer's Comment: The sponsor's rationale for dose selection seems to be reasonable.

4.2.6.3 Instructions with Regard to Meals

“Starting on Day 1 of the study treatment phase, patients received continuous oral doses of RO5185426 960 mg b.i.d. without scheduled dose interruption. Patients took four 240-mg tablets in the morning and four 240-mg tablets in the evening (960 mg b.i.d. for a total daily dose of 1920 mg).

“After 8 hours of fasting on PK collection days (Day 1 and 15 of cycle 1, and Day 1 of all subsequent cycles), RO5185426 was administered to patients as part of the scheduled study visit in the clinic; patients then had 4 hours of post-dose fasting.

“On the morning of PK collection days, patients could have a light snack (i.e., crackers, toast, juice, and water). On days when dosing was administered at home, patients were not required to take their study treatment under fasting conditions.”

Reviewer’s Comment: The effect of food was not evaluated. The current dosing appears to be consistent with future clinical practice; therefore it appears to be acceptable.

4.2.6.4 ECG and PK Assessments

“A single ECG was taken at screening for safety purposes and to meet the inclusion criteria for the study. The first (baseline) set of five triplicate ECGs (i.e., the time-matched baseline) were taken on any day (preferably in the morning) between Days -28 and -1. These baseline ECGs were not taken on the same day as the other screening procedures, and all five ECGs were collected on the same day. The first ECG was labeled “0,” the next four ECGs were taken every 2 hours and labeled accordingly (i.e., “2 hours,” “4 hours,” “6 hours,” and “8 hours”). ECGs taken on Days 1 and 15, were taken at 0 (AM; pre-dose), and 2, 4, 6, and 8 hours post-dose, and time-matched as closely as possible with the baseline ECGs. Additional triplicate ECGs taken 2 minutes apart were collected on Day 1 of Cycles 2, 4, 6, and 10 at pre-dose (AM) and 4 hours post-dose. These ECGs were matched to the baseline 0 and 4 hour ECGs. Starting after Cycle 10, triplicate ECGs were collected pre-dose (AM) on Day 1 of every other 3-week cycle (every 6 weeks, i.e., Cycle 12, 14, 16, etc.).”

“Plasma PK samples were obtained on Days 1 and 15 of Cycle 1 at pre-dose (AM) and 2, 4, 6 and 8 hours post-dose, and on Day 1 of Cycles 2, 3, 4, 6, 8 and 10 at pre-dose (AM) and 4 hours post-dose. In addition, samples were obtained at disease progression when study treatment was stopped indefinitely and when the biopsy sample from the progressing lesion was taken. Starting after Cycle 10, samples were collected pre-dose (AM) on Day 1 of every other 3-week cycle (every 6 weeks, i.e., Cycle 12, 14, 16, etc.).”

Phase ▶	Screen	Study Treatment Visits ^{1,25}						Post Treatment			Follow up after Study Treatment	
		Cycle 1		Cycle 2	Cycle 3	Cycles 4-9	Cycles 10-1	Day of last study dose ²	Day of biopsy of progressing lesions ³	Final visit	28 days post dose	Every 12 weeks
Day ▶	-28 to -1	(baseline) 1	15 ¹	22	43	Day 1	Day 1					
Informed consent	X											
Medical history	X											
Physical exam (including height and weight) & vital signs ³	X	X		X	X	X	X			X		
ECOG performance status ³	X	X		X	X	X	X			X		
Head and neck SCC evaluation ⁴	X					X	X					X ²⁶
Chest CT for SCC evaluation ⁵	X					X	X					X ²⁶
Dermatology evaluation ⁶	X			X		X	X					X ²⁶
Serum for HIV, HBV, & HCV	X											
Hematology, biochemistry, & urinalysis ⁵	X	X		X	X	X	X			X		
LDH ³	X	X		X	X	X	X			X		
Serum pregnancy test ⁷	X											
Tumor assessment (CT/MRI/Bone Scans) ⁸	X				X	X	X			X		
ECG ⁹	X	X	X	X		X	X					
Plasma PK sampling ¹⁰		X	X	X	X	X	X	X ²	X ²			

Reviewer's Comment: The sampling time points are acceptable. PK and ECG measurements were collected to cover median T_{max} (4 hour) and up to 8 hours post-dose at steady state (Day 15). The PK and ECG profiles on Day 15 are anticipated to be flat because (1) the effective half-life is 53 hours, and (2) the drug is given twice daily.

4.2.6.5 Baseline

The sponsor used time-matched baseline in the primary analysis.

4.2.7 ECG Collection

“The ECG will include a 12-lead examination. Patients must be in a supine position for 5 minutes prior to the ECG. Rate, rhythm, interval durations, interval appearances and axis will be noted for each ECG. ECG will be obtained in triplicate 2 minutes apart using digital equipment provide by Sponsor. Abnormal findings will be noted for clinical significance. ECG results obtained in this study will be submitted and read centrally by (b) (4) ”

Source: Study Protocol

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

132 patients with metastatic melanoma were enrolled across a total of 15 centers. The median duration of follow-up was 6.87 months (range, 0.59 to 11.27 months). At the cutoff date, 48 patients (36%) had discontinued the study for the following reasons: 40 (30%) died (see section 3.5.2.3), 7 (5%) had progression of underlying disease, and 1 (1%) withdrew consent.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Central Tendency Analysis

“In the central tendency analysis, the largest mean QTcP prolongation (dQTcP) after the first RO5185426 dose on Day 1 was 3.3 ms (upper 95% CI: 5.0 ms), constituting a small QTc effect below the threshold of clinical significance. However, mean QTc prolongation increased with repeated RO5185426 dosing toward the expected steady-state on Day 15, which corresponded to the accumulation of RO5185426 concentration in plasma.

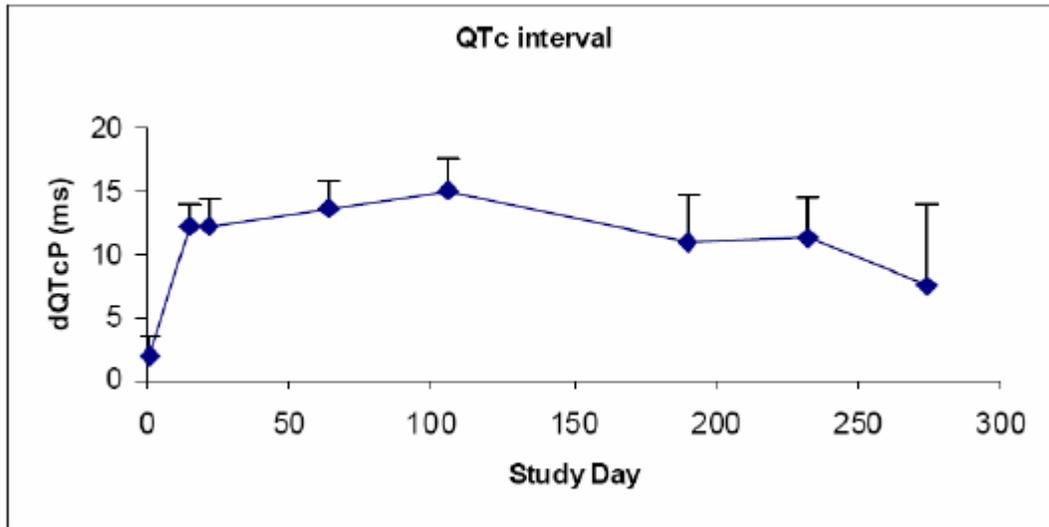
“The largest dQTcP on Day 15 was 12.8 ms (upper 95% CI: 14.9 ms), and appeared to remain sustained at a similar level in subsequent cycles. With the exception of Cycle 16, for which there were too few samples for interpretation (n=3), the largest dQTcP value in the study was 15.1 ms (upper 95% CI: 17.7 ms) on Day 1, Cycle 6 (n= 85 patients). This result may be more representative of the largest mean QTc prolongation potentially induced by RO5185426 at any time point after dosing in this study.” Table 7 and Figure 1 display the results from the sponsor’s analyses.

Table 7: Summary of Mean QTcP time-matched change from baseline with one-sided 95% CI (ECG evaluable population).

QTc Interval	RO5185426 (N=128) Mean One-side Upper 95% CI
Time-matched change from baseline	
Day1	
0 hr	NA
2 hr (n = 121)	2.8 (4.4)
4 hr (n = 113)	3.3 (5.0)
6 hr (n = 112)	2.5 (4.4)
8 hr (n = 111)	1.9 (3.6)
Day15	
0 hr (n = 106)	12.3 (14.1)
2 hr (n = 109)	12.8 (14.9)
4 hr (n = 103)	11.4 (13.6)
6 hr (n = 102)	11.4 (14.0)
8 hr (n = 102)	9.8 (12.1)
Cycle 2	
0 hr (n = 111)	12.3 (14.5)
2 hr	
4 hr (n = 108)	11.3 (13.3)
6 hr	
8 hr	
Cycle 4	
0 hr (n = 108)	13.7 (15.8)
2 hr	
4 hr (n = 105)	12.4 (14.4)
6 hr	
8 hr	
Cycle 6	

Source: the sponsor’s report, page 523

Figure 1: Mean Δ QTcP (+95% Upper CI) vs. Study Day.



Reviewer's Comments: We will provide our independent analysis results in section 5.2.

4.2.8.2.2 Categorical Analysis

Categorical analysis was used to summarize for the categories of QTc >450 ms, >480 ms and >500 ms, and changes from baseline QTc >30 ms and >60 ms. Two patients showed QTcP >500 ms, and 44 and 4 patients developed QTcP >450 ms and >480 ms, respectively. Table 8 summarized the results from the sponsor's categorical analysis.

Table 8: Number of Patients with Certain ECG Findings (ECG Evaluable Population)

ECG Findings	RO5185426 (N=128) n (%)
Absolute QT value at any post-baseline	
> 450 ms	14 (10.9)
> 480 ms	2 (1.6)
> 500 ms	0 (0.0)
Absolute QTc (QTcP) value at any post-baseline	
> 450 ms	44 (34.4)
> 480 ms	4 (3.1)
> 500 ms	2 (1.6)
Maximum individual changes from baseline in QTc interval	
> 30 ms	58 (45.3)
> 60 ms	1 (0.8)
PR changes from baseline \geq 50% if absolute baseline value < 200ms	0 (0.0)
PR changes from baseline \geq 25% if absolute baseline value > 200ms	0 (0.0)
QRS changes from baseline \geq 50% if absolute baseline value < 100ms	0 (0.0)
QRS changes from baseline \geq 25% if absolute baseline value > 100ms	0 (0.0)
New incidence of abnormal U wave	0 (0.0)
New incidence of abnormal T wave	19 (14.8)

4.2.8.3 Safety Analysis

Discussed with pooled safety population in section 3.4.

The sponsor reports that of the patients with QTcP >480 ms, QTcP >500 ms, and QTcP change from baseline >60 ms. There were no reported AEs that could be potentially associated with either QT prolongation or arrhythmia.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

Mean plasma concentration-time profiles of RO5185426 are presented in Figure 2 with summary statistics of the pharmacokinetics of RO5185426 in Table 9.

Figure 2: Mean RO5185426 Concentration vs. Time on Day 1 and 15 (Log Scale).

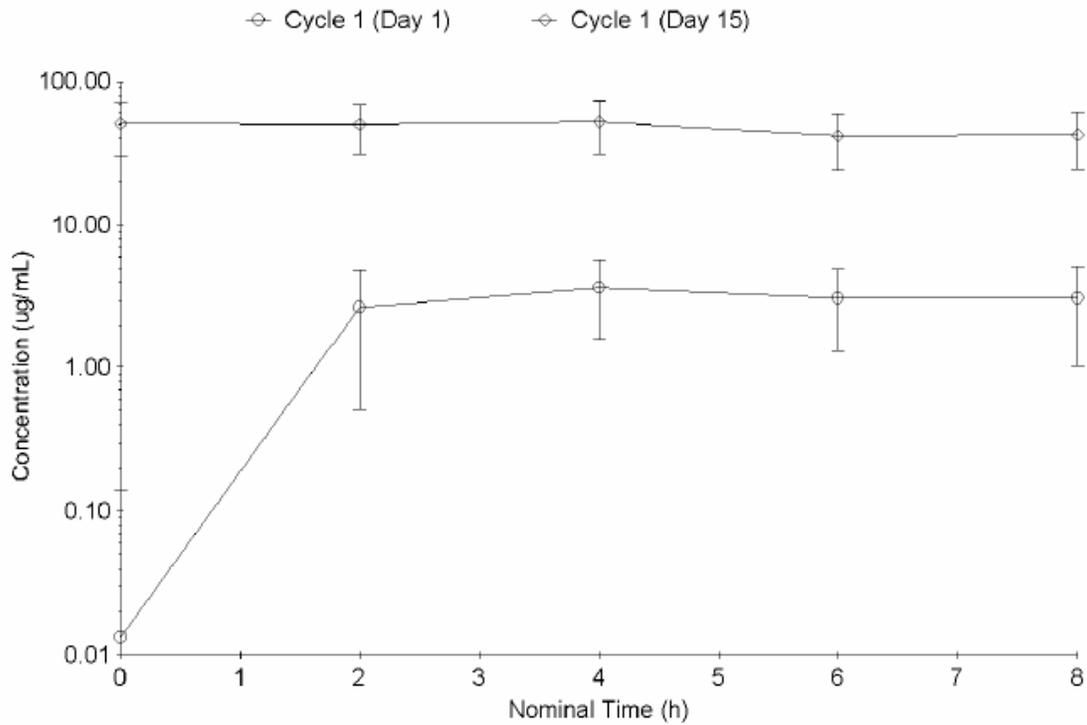


Table 9: Summary of RO5185426 PK Parameters on Day 1 and 15

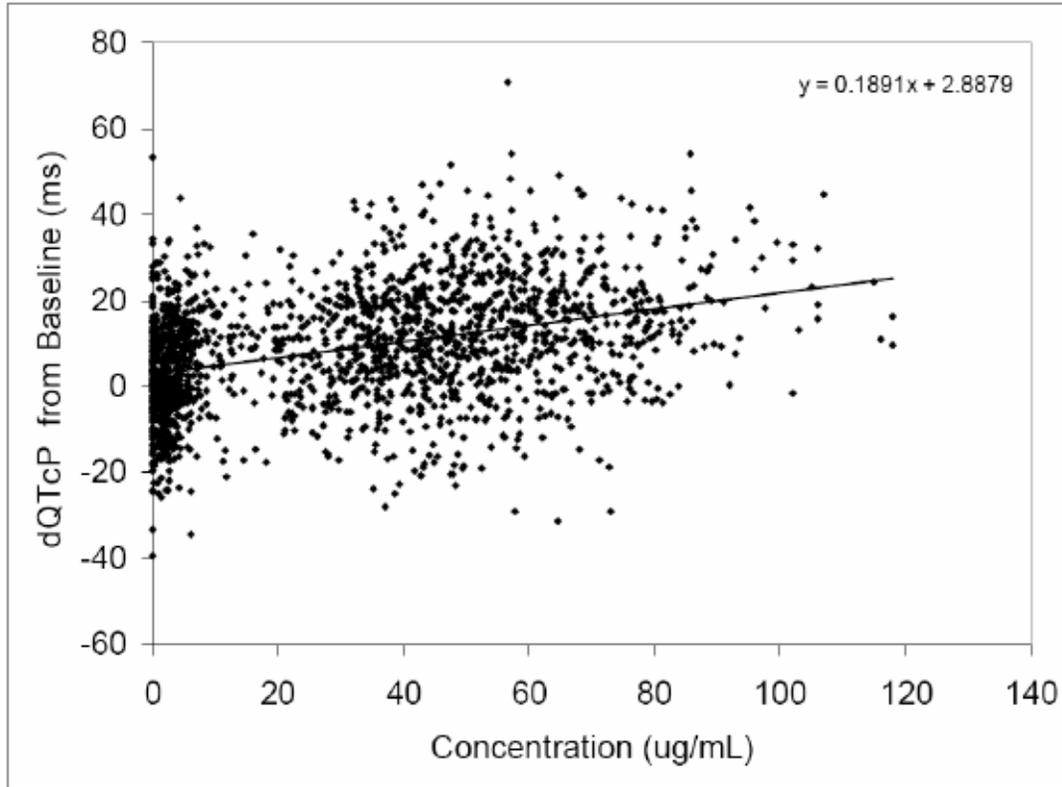
Parameter	N	Mean	SD	Median	Range (min-max)	CV%
AUC _{0-8h} -D1C1 (µg·h/mL)	88	22.07	12.71	19.28	(3.52-56.42)	57.58
AUC _{0-8h} -D15C1 (µg·h/mL)	87	380.16	143.56	369.19	(66.22-903.93)	37.76
C _{max} -D1C1 (µg/mL)	88	4.14	2.34	3.63	(0.64-11.80)	56.58
C _{max} -D15C1 (µg/mL)	87	56.73	21.76	56.00	(10.20-118.00)	38.36
T _{max} -D1C1 (h)	88	NA	NA	4.00	(1.77-8.08)	NA
T _{max} -D15C1 (h)	87	NA	NA	2.00	(0.00-8.92)	NA

Note: D1C1=Day 1 Cycle 1; D15C1=Day 15 Cycle 1

4.2.8.4.2 Exposure-Response Analysis

The preliminary concentration- Δ QTcP analysis shows that Δ QTcP increases with increasing RO5185426 concentration (Figure 3).

Figure 3: Individual QTcP Change from the Time-Matched Baseline vs. RO5185426 Concentration at All Time Points.



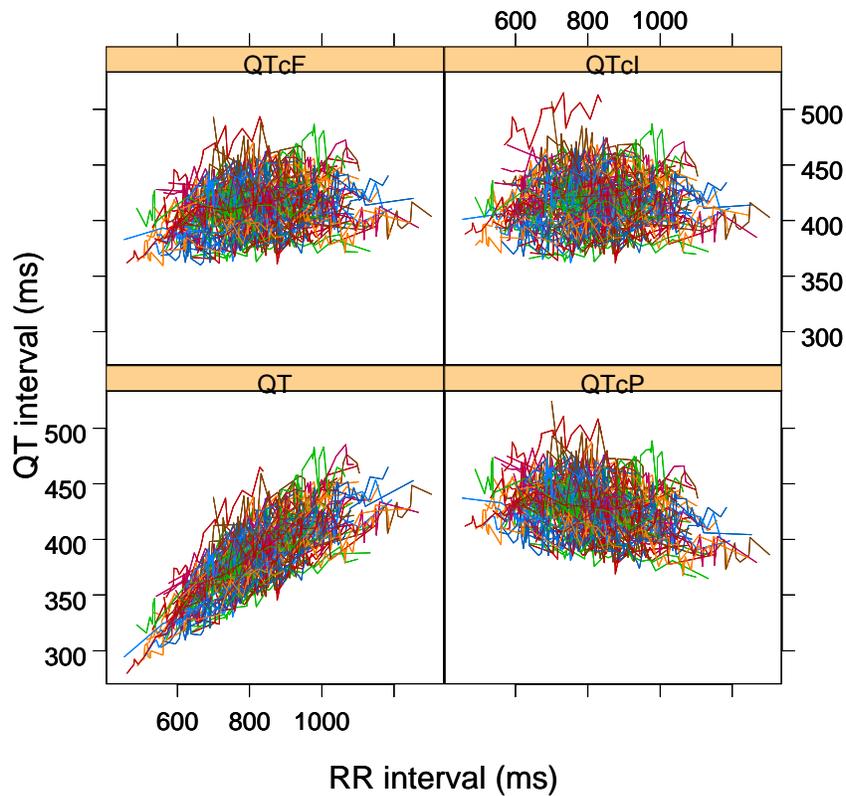
Reviewer's Analysis: We performed our independent analyses which are discussed in section 5.3.1

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods. The QT-RR interval relationship is presented Figure 4 together with the population (QTcP), Fridericia (QTcF), and individual correction (QTcI). Both QTcP and QTcF look similar in correcting RR effect. The sponsor used QTcP for the analysis which seems to be reasonable. To be consistent, the FDA reviewer also used QTcP for further analysis.

Figure 4: QT, QTcP, QTcF, and QTcI 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 RO5185426

The reviewer used mixed model to analyze the Δ QTcP effect. The analysis results are listed in Table 10. The largest upper bound of the two-sided 90% CI for Δ QTcP is 14.8 ms. There was no moxifloxacin arm in the study so the assay sensitivity can not be established.

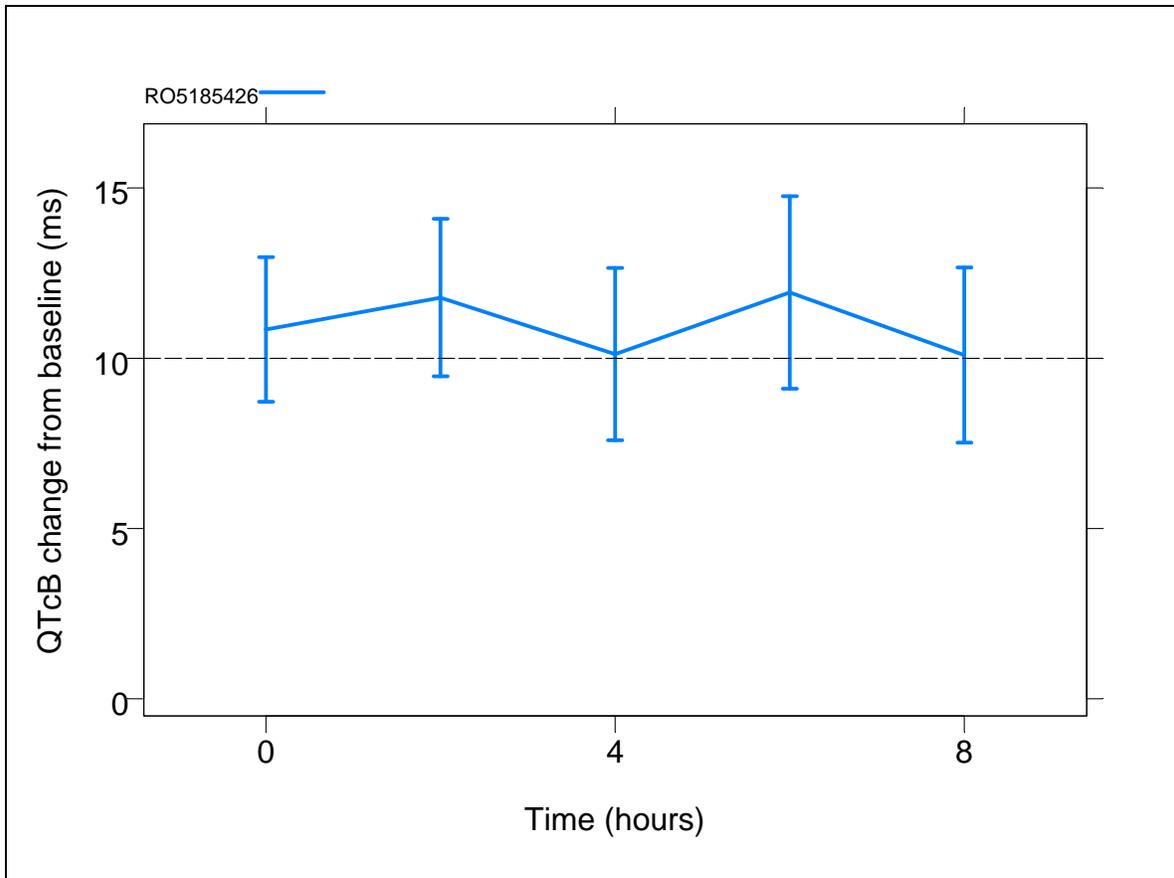
Table 10: Analysis Results of Δ QTcP for RO5185426 900 mg BID on Day 15.

Time(hr)	Δ QTcP		
	N	Mean	90% CI
0	113	10.8	(8.7, 13.0)
2	114	11.8	(9.5, 14.1)
4	112	10.1	(7.6, 12.6)
6	112	11.9	(9.1, 14.8)
8	112	10.1	(7.5, 12.7)

5.2.1.2 Graph of Δ QTcF Over Time

Figure 5 displays the time profile of Δ QTcP for RO5185426.

Figure 5: Mean and 90% CI Δ QTcP Time Course on Day 15.



5.2.1.3 Categorical Analysis

Table 11 lists the number of subjects as well as the number of observations whose QTcP values are ≤ 450 ms, between 450 ms and 480 ms. There were 5 subjects (3.8%) above 480 ms. There were 2 patients who experienced QTcP >500 ms after treatment.

Table 11: Categorical Analysis for QTcP

Treatment Group	Total N		Value \leq 450 ms		450 ms<Value \leq 480 ms	
	# Subj.	# Obs.	# Subj. (%)	# Obs. (%)	# Subj. (%)	# Obs. (%)
RO5185426	132	2587	86 (65.2%)	2353 (910%)	41 (31.1%)	216 (8.3%)

Table 12 lists the categorical analysis results for Δ QTcP. There were 3 subjects (2.3%) who had Δ QTcP above 60 ms.

Table 12: Categorical Analysis of Δ QTcP

Treatment Group	Total N		Value \leq 30 ms		30 ms<Value \leq 60 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
RO5185426	128	1853	64 (50.0%)	1711 (92.3%)	61 (47.7%)	139 (7.5%)

CLINICAL PHARMACOLOGY ASSESSMENTS

The relationship between Δ QTcP and RO5185426 concentrations was investigated by linear mixed effects modeling; linear model with intercept (Model 1), linear model with intercept fixed to zero (Model 2) and linear model with no intercept. The concentration- Δ QTcP relationship for RO5185426 is shown in Figure 6 which indicates clear positive relationship between Δ QTcP and RO5185426 concentrations.

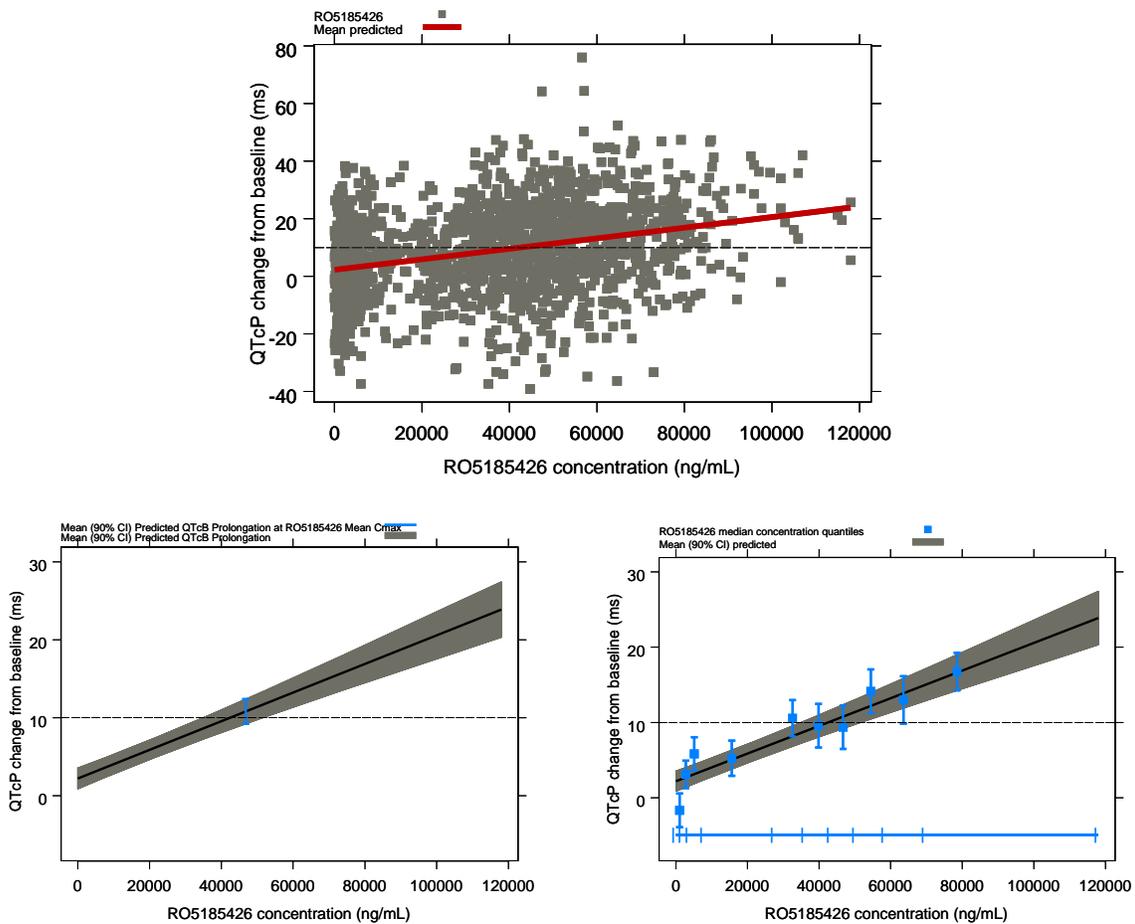
Table 13 summarizes the results for RO5185426 concentration- Δ QTcP analysis from three different models. The slope of exposure-response relationship shows positive trend with statistically significant p-value for all three models, implying that Δ QTcP would increase with increasing RO5185426 concentrations.

Table 13: Exposure-Response Analysis of RO5185426.

	Estimate	P-value
Model 1: Δ QTcP=Intercept + Slope * RO5185426 Concentration		
Intercept (ms)	2.2 (0.87, 3.54)	0.0072
Slope (ms per ng/mL)	0.000184 (0.000151, 0.000216)	<0.0001
Model 2: Δ QTcP=Intercept + Slope * RO5185426 Concentration (Fixed intercept)		
Intercept (ms)	0	

Slope (ms per ng/mL)	0.000205 (0.000174, 0.000235)	<0.0001
Model 3: $\Delta\text{QTcP} = \text{Slope} * \text{RO5185426 Concentration}$ (No intercept)		
Slope (ms per ng/mL)	0.000234 (0.0002, 0.000268)	<0.0001

Figure 6: ΔQTcP vs. RO5185426 Concentration



In addition, we also performed exposure-response analyses by gender. Table 14 shows parameter estimates of exposure-response analysis using Model 1 by different gender, which indicates 30% increase in slope estimate in female patients. However, given the large variability in slope estimates, the gender effect, if exists, is not considered as practically meaningful.

Table 14: Exposure-Response Analysis of RO5185426 by Gender using Model 1

	Parameter estimates	
	Female	Male
Intercept	1.39	2.69
Slope	0.000213 (0.000175, 0.000252)	0.000164 (0.000117, 0.000211)

5.3 CLINICAL ASSESSMENTS

5.3.1 Safety assessments

Events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death have been discussed in sections 3.4 & 4.2.8.3.

5.3.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. On review of a subset of waveforms in the warehouse, typically annotations were in lead II for QT and PR and lead V2 for QRS. Less than 0.7% of ECGs were reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.3.3 PR and QRS Interval

There were no clinically relevant effects on the PR and QRS intervals. On review of the datasets for categorical values, subjects with a post-treatment PR interval over 200 ms or a post-treatment QRS interval over 110 ms had a change from baseline that was less than 25%.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Highlights of Clinical Pharmacology (RO5185426 / PLX4032)

Therapeutic dose	Include maximum proposed clinical dosing regimen. 960 mg BID	
Maximum tolerated dose	Include if studied or NOAEL dose 960 mg BID	
Principal adverse events	<p>Include most common adverse events; dose limiting adverse events</p> <p>Most Common AEs: Photosensitivity, rash, fatigue, and arthralgia</p> <p>Dose Limiting AEs: At the 1120 mg bid dose, 4 of the 6 patients developed protocol-defined, non-life threatening DLTs (including Grade 3 rash with pruritus, fatigue, arthralgia) that resolved with temporary drug interruption. This dose was considered not tolerated.</p> <p>One DLT, pancytopenia (Grade 4), was observed at 720 mg bid.</p> <p>Serious AEs of cutaneous squamous cell carcinoma (SCC) were recently reported for 6 patients treated with PLX4032, all of which have been considered by the investigators to be possibly or probably related to study treatment.</p>	
Maximum dose tested	Single Dose	Specify dose 160 mg in MBP formulation
	Multiple Dose	Specify dosing interval and duration 1120 mg bid in MBP formulation with the longest treatment duration of 88 days
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) C _{max} and AUC (160 mg): Mean C _{max} : 3.6 ± 1.7 μM (48.2%) Mean AUC _{0-∞} : 85.8 ± 51.9 μM*hr (60.6%)
	Multiple Dose	Mean (%CV) C _{max} and AUC (1120 mg bid) Mean C _{max} : 172.2 ± 48.2 μM (28.0%) Mean AUC _{0-24h} : 2837.3 ± 741.2 μM*hr (26.1%)
Range of linear PK	Specify dosing regimen Dose proportional AUC and C _{max} demonstrated between 240 mg bid and 960 mg bid	
Accumulation at steady state	Mean (%CV); specify dosing regimen Mean: 6.8 ± 1.7 (30%) in the dose range 240 mg bid to 960 mg bid	
Metabolites	Include listing of all metabolites and activity None identified	
Absorption	Absolute/Relative Bioavailability	Mean (%CV) Absolute relative bioavailability not determined Relative bioavailability estimated to be ~40%
	T _{max}	<ul style="list-style-type: none"> Median (range) for parent Median T _{max} : 4.0 (range 4.0 to 6.0 hr) in single dose 160 mg (MBP formulation) HV study

		<ul style="list-style-type: none"> • Median (range) for metabolites Unknown
Distribution	Vd/F or Vd	<ul style="list-style-type: none"> • Mean (%CV) Vd/F: 57.9 ± 30.7 (L) from single dose 160 mg (MBP formulation) healthy volunteer study
	% bound	<ul style="list-style-type: none"> • Mean (%CV) Protein binding is 99.86 ± 0.06 (0.1%)
Elimination	Route	<ul style="list-style-type: none"> • Primary route; percent dose eliminated Primary route in humans is unknown Preclinical studies indicate excretion in bile <ul style="list-style-type: none"> • Other routes Unknown
	Terminal t _{1/2}	<ul style="list-style-type: none"> • Mean (%CV) for parent From single 160 mg dose in healthy volunteers, terminal half life is 17 h to 19 h (35%) In patients, the effective half life based on accumulation index is ~53 ± 15 h (28%) <ul style="list-style-type: none"> • Mean (%CV) for metabolites Unknown
	CL/F or CL	<ul style="list-style-type: none"> • Mean (%CV) From single 160 mg dose in healthy volunteers, clearance (CL/F) is 2.6 to 2.9 (68%) L/h
Intrinsic Factors	Age	<ul style="list-style-type: none"> • Specify mean changes in C_{max} and AUC Unknown
	Sex	<ul style="list-style-type: none"> • Specify mean changes in C_{max} and AUC Unknown
	Race	<ul style="list-style-type: none"> • Specify mean changes in C_{max} and AUC Unknown
	Hepatic & Renal Impairment	<ul style="list-style-type: none"> • Specify mean changes in C_{max} and AUC Unknown
Extrinsic Factors	Drug interactions	<ul style="list-style-type: none"> • Include listing of studied DDI studies with mean changes in C_{max} and AUC Not conducted
	Food Effects	<ul style="list-style-type: none"> • Specify mean changes in C_{max} and AUC and meal type (i.e., high-fat, standard, low-fat) Unknown
Expected High Clinical Exposure Scenario	<p>Describe worst case scenario and expected fold-change in C_{max} and AUC. The increase in exposure should be covered by the supra-therapeutic dose.</p> <p>Occasionally, in some patients, C_{max} and AUC that are ~60% higher than the mean exposure in a given dose cohort have been seen. At this time, this type of exposure variability is not well understood</p>	

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/s/

JOO YEON LEE
06/02/2011

HAO ZHU
06/02/2011

SUCHITRA M BALAKRISHNAN
06/02/2011

NORMAN L STOCKBRIDGE
06/02/2011

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

Date: May 26, 2011

Application Type/Number: NDA 202429

To: Robert Justice, Director
Division of Drug Oncology Products

Through: Melina Griffis, RPh, Team Leader
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Lubna Merchant, M.S., Pharm.D, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name and Strengths: Zelboraf (Vemurafenib) Tablets, 240 mg

Applicant/sponsor: Hoffmann-La Roche Inc.

OSE RCM #: 2011-1377

CONTENTS

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4. CONCLUSION AND RECOMMENDATIONS.....	3
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1. INTRODUCTION

This review evaluates the proposed labels and labeling for Zelboraf (Vemurafenib) Tablets (NDA 202429) for areas of vulnerabilities that could lead to medication errors. The proposed proprietary name is evaluated under separate review (OSE # 2011-1375).

2. METHODS AND MATERIALS

Using Failure Mode and Effects Analysis (FMEA)¹, the Division of Medication Error Prevention and Analysis (DMEPA) evaluates the container labels, carton labeling and insert labeling. This review focuses on labels and labeling submitted as part of the April 28, 2011 original NDA submission. See Appendix A-B for images of the proposed container labels and carton labeling.

3. RESULTS

The following section describes the results of our label and labeling review.

3.1 LABELS AND LABELING

Our evaluation of the proposed label and labeling noted the following deficiencies:

- Add the ‘Do not Crush or Chew Tablets’ statement on the labels.
- The oval graphic on the bottom of the carton labeling should be replaced with tablet image.

We provide labeling recommendations in section 4 to address these deficiencies.

4. CONCLUSION AND RECOMMENDATIONS

Our evaluation of the proposed labels and labeling identified areas of needed improvement in order to minimize the potential for medication errors. We provide recommendations in Section 4.1. Comments to the Applicant for the container labels and carton labeling. We request the recommendations in Section 4.1 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact the OSE Regulatory Project Manager, Sarah Simon at 301-796-5205.

4.1 COMMENTS TO THE APPLICANT:

A. General comments

We remind the Applicant of their requirement to comply with 21 CFR 208.24. We acknowledge the use of a Medication Guide statement. Please ensure that sufficient numbers of Medication Guides are provided with the product such that a dispenser can provide one Medication Guide with each new or refilled prescription. We recommend that each packaging configuration contain enough Medication Guides so that one is provided for each “usual” or average dose.

B. Proposed Container Label

1. Since the tablets are available in unit of use containers (15 days supply) and may be dispensed directly to patients, we recommend the addition of a statement “Do not crush or chew tablet” above the Rx only statement.
2. Relocate the “Each tablet contains...” statement to the side panel in order to decrease the clutter on the principal display panel.
3. The company symbol  Daiichi-Sankyo may be misinterpreted as the tablet image and should be deleted or relocated to the side panel.

C. Proposed Carton Labeling

1. See comment A1, A2 and A3.
2. Relocate the medication guide statement to appear below the Rx only statement as presented on the container label.
3. It is unclear what the oval graphic below the net quantity statement represents. The graphic should be deleted or replaced with the actual image of the tablet.

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

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/s/

LUBNA A MERCHANT
05/26/2011

MELINA N GRIFFIS
05/27/2011

CAROL A HOLQUIST
05/27/2011

DSI CONSULT: Request for Clinical Inspections

Date: 5/2/2011

To: Tejashri Purohit-Sheth, M.D., Branch Chief, GCP 2
Jean M. Mulinde, M.D., Acting Team Leader, GCP 2
Robert Young, M.D., GCP2
Division of Scientific Investigations
Office of Compliance/CDER

Through: Y. Max Ning, MD, PhD, Clinical Reviewer, DDOP
John Johnson, MD, Clinical Leader, DDOP
Robert Justice, MD, Division Director, DDOP

From: Theresa Ferrara, MPH, Regulatory Project Manager, DDOP

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 202429
Hoffmann-La Roche Inc.
340 Kingsland Street
Nutley, New Jersey 07110-1199
(Regulatory Contact: Linda J. Burdette, Ph.D.)
Phone: (973) 235-4578
Email: linda.burdette@roche.com

Drug Proprietary Name: ZELBORAF (proposed for vemurafenib)
NME or Original BLA (Yes/No): Yes
Review Priority (Standard or Priority): Priority

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication: *“for the treatment of BRAF^{V600} mutation-positive unresectable or metastatic melanoma”*

Letter Date: 04/27/2011 (for clinical submission)
PDUFA: 10/28/2011
Action Goal Date: ??/2011 (to be determined)
Inspection Summary Goal Date: 7/22/2011

DSI Consult
version: 5/08/2008

II. Protocol/Site Identification

Protocol: BRIM 3: A Randomized, Open-label, Controlled, Multicenter, Phase III Study in Previously Untreated Patients With Unresectable Stage IIIC or Stage IV Melanoma with V600E BRAF Mutation Receiving RO5185426 or Dacarbazine (DTIC)

Site # (Name,Address, Phone number, email, fax#)	Number of Enrolled Subjects	Number of Evaluable for Response	Number of Subjects with Best Response	Number of SAEs
Site #201192 Dr. Alessandro Testori, IEO Istituto Europeo di 14 4 0 Oncologia. Via Ripamonti, 435 , Milano, MI, 20141, 39-02-57489459, ITALY	14	11	5 (all with IND treatment)	0
Site #201202 Dr. Carmen Loquai, Universitaetsklinikum Mainz, Mainz, RP, 55131, 49-0-6131-17 ext 0, GERMANY	12	8	5 (all with IND treatment)	3
Site #200991 Dr. Jeffrey Sosman, Vanderbilt University Medical 9 6 4 Center, Nashville, TN, 37232, 1- 615-343-6653, USA	9	8	6 (5 with IND treatment; 1 with DTIC)	4
Site #200997 Dr. Kim Margolin, University of Washington, Seattle, WA, 98109, 1-206-288-7341, USA	7	7	4 (3 with IND treatment; 1 with DTIC)	2

The sites listed in the above table were selected based on the following applicant's reported information about the study BRIM3 that provides key support for this NDA.

A total of 675 patients were recruited from 104 study sites internationally, 337 patients assigned to receive RO5185426 and 338 patients assigned to receive dacarbazine. Regardless of treatment assignment, 60% of patients were in Western Europe, 25% in North America, 11% in Australia/New Zealand, 3% in Israel. Numbers of enrollment by study center ranged from 1 to 30. Approximately 65% of patients were considered evaluable for best response, defined as having scans performed at least 14 weeks prior to the time of planned interim analysis (January 2011) of the primary endpoint overall survival in all randomized patients.

A total of 118 deaths of the 675 patients had occurred at the time of the interim survival analysis: 43 in the RO5185426 group and 75 in the dacarbazine group. The analysis demonstrated a statistically significant improvement in overall survival in favor of the RO5185426 group ($p < 0.0001$, log-rank test). The observed median survival time was 9.2

months in the RO5185426 group compared with 7.8 months in the dacarbazine group. Since there were <20% of deaths with the analysis, these median survival times were not mature and may be subject to changes at the final survival analysis.

The reported response rate in the RO5185426 group was 48.4% (106/219; 95% CI: 41.6%, 55.2%) compared to 5.5% (12/220; 95% CI: 2.8%, 9.3%) in the dacarbazine group.

III. Site Selection/Rationale

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (Site# 201202; Site # 200991)
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify): Most of the enrollments were from Europe.

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Significant primary efficacy results pertinent to decision-making
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify): highly varied response results observed

Note: International inspection requests or requests for five or more inspections require sign-off by the OND Division Director and forwarding through the Director, DSI.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact DDOP at 301-796-2320.

Concurrence: (as needed)

Dr. Johnson, Medical Team Leader

Dr. Ning, Medical Reviewer for IND73620

Dr. Justice, Division Director (for foreign inspection requests)

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/s/

THERESA A FERRARA
05/03/2011

ROBERT L JUSTICE
05/03/2011