CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203388Orig1s000

OTHER REVIEW(S)

Attachment B: Sample 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: Drug Drug Interaction Trial

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	01/31/2013
	Study/Clinical trial Completion Date:	08/31/2014
	Final Report Submission Date:	02/28/2015
	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

The solubility of vismodegib is pH dependent as the solubility in (b) (4) at pH 7 is 0.1 µg/mL and is 0.99 mg/mL at pH 1. comedications that alter the pH of the upper GI tract may alter the solubility of vismodegib and reduce its bioavailability.

Based on the in vitro data, a clinical assessment of vismodegib's drug-drug interaction potential with gastric pH elevating agents (i.e., a proton-pump inhibitor, an H2-receptor antagonist, and/or an antacid) is necessary.

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

The goal of the clinical trial is to evaluate the effect of gastric pH elevating agents on vismodegib bioavailability. The gastric pH elevating agents (proton-pump inhibitors, H2-receptor antagonists, and/or antacids) are likely concomitantly taken with vismodegib by some patients in the indicated population.

Given the fact that vismodegib has a pH-dependent solubility, concomitant use of gastric pH elevating agents may reduce the absorption of vismodegib leading to a decrease in its systemic exposure and requiring appropriate dose adjustment. The applicant should conduct clinical studies to evaluate the effect of antacids and H2 blockers/proton pump inhibitors on the pharmacokinetics of vismodegib. The goal of this study is to determine how to dose vismodegib with regard to gastric pH elevating agents (i.e., a proton-pump inhibitor, an H2-receptor antagonist, and/or an antacid).

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.

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

The timetable you submitted on January 18, 2012 states that you will conduct this trial according to the following schedule:

Final Protocol Submission Date: January 2013

Trial Completion Date: August 2014

Final Report Submission: February 2015

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☒ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☒ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
dedicated drug-drug interaction study (see box 1)
☐ 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/

JIAN WANG
01/19/2012

NAM ATIQUR RAHMAN
01/25/2012

JEFFERY L SUMMERS
01/25/2012

eCTD NDA 203388/0
vismodegib (ERIVEDGE)
Labeling Meeting
1-18-12

Memorandum

Date: January 18, 2012

From: Mona Patel, DOP2/OHOP/CDER

Subject: Labeling Meeting: NDA 203388

Original Application: NDA 203388

Product: vismodegib [Proper Name- ERIVEDGE]
Submission Date: September 8, 2011
Received Date: September 8, 2011
Sponsor: Genentech, Incorporated
Proposed Indication: For the treatment of adult patients with basal cell carcinoma that has recurred following surgery or who are not candidates for surgery and [redacted] (b) (4) who are not candidates for radiation

Attendees:
Patricia Keegan
Mona Patel
Michael Axelson
Jeff Summers
Todd Palmby
Dubravaka Kufrin
Tammie Brent Howard
Carole Broadnax
Karen Munoz
Sharon Mills
Janet Xiaoping Jiang
Liang Zhou
Richard Abate
Jian Wang

FDA reviewed Genentech's January 13, 2012 response to FDA's proposed changes sent to Genentech for the USPI on January 11, 2012 and Genentech's January 17, 2012 response to FDA proposed changes sent to Genentech for the Medication Guide on January 9, 2012. At the conclusion of this meeting, it was decided that team would review their relevant sections offline and resolve a few outstanding issues (presentation of manufacturing information and language in section 7.1), and then RPM would send the final draft FDA responses to Dr. Keegan for final review and concurrence before sending back to GNE.

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/s/

MONA G PATEL
01/19/2012

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

METHODS VALIDATION CONSULT REQUEST FORM

TO: **FDA**
Division of Pharmaceutical Analysis
Attn: Benjamin (Nick) Westenberger
Suite 1002
1114 Market Street
St. Louis, MO 63101

FROM: Zedong Dong, CMC Reviewer
Liang Zhou, CMC Lead
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: zedong.dong@fda.hhs.gov
Phone: (301)-796-3885
Fax.: (301)-796-9745

Through: Liang Zhou
Phone: (301)-796-1781
and
Jeannie David, ONDQA Methods Validation Project Manager
Phone: 301-796-4247

SUBJECT: Methods Validation Request

Application Number: NDA 203388

Name of Product: vismodegib

Applicant: Genentech

Applicant's Contact Person: Mary Sliwkowski

Address: 1 DNA Way MS#241B, South San Francisco, CA 94080-4990

Telephone: 650-225-1558 Fax: 650-467-3198

Date NDA Received by CDER: **9/8/2011**

Submission Classification/Chemical Class: Type 1 (NME)

Date of Amendment(s) containing the MVP: **N/A**

Special Handling Required: No

DATE of Request: **January 12, 2012**

DEA Class: N/A

Requested Completion Date: **03/12/2012**

Format of Methods Validation Package (MVP)

PDUFA User Fee Goal Date: **3/8/2012**

☐ Paper ☒ Electronic ☐ Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

ATTACHMENT(S): *Methods Validation Request Sheet*, NDA Methods Validation Package (if not available in the EDR).

MVP Reference #	**METHODS VALIDATION REQUEST**	NDA # 203388

⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT

ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION
N/A		

⇒ ITEM 2: **Contents of Attached Methods Validation Package**	Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)	3.2.P.1
Specifications/Methods for New Drug Substance(s)	3.2.S.4
Specifications/Methods for Finished Dosage Form(s)	3.2.P.5
Supporting Data for Accuracy, Specificity, etc.	3.2.P.5
Applicant's Test Results on NDS and Dosage Forms	3.2.P.5
Other:	

⇒ ITEM 3: **REQUESTED DETERMINATIONS**
Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.

Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
(b) (4)	Identification, assay and degradation products	3.2.P.5	**0**	

Additional Comments:

Methods Validation Request Criteria

MV Request Category	Description
0	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)
4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method
6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a "for cause" reason

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/s/

ZEDONG DONG
01/18/2012

SARAH P MIKSINSKI
01/20/2012

JEANNIE C DAVID
01/20/2012
ONDQA Methods Validation Project Manager

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

Internal Consult

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

To: Mona Patel, Regulatory Project Manager
Division of Oncology Products 2 (DOP 2)
Office of Hematology Oncology Products

From: Carole C. Broadnax, Regulatory Review Officer
Division of Professional Promotion (DPP)
Office of Prescription Drug Promotion (OPDP)

Through: Andrew Haffer, Professional Group Leader, DPP, OPDP

CC: Karen Munoz, Regulatory Review Officer
Division of Direct-to-Consumer Promotion, OPDP

Date: January 12, 2012

Re: **Erivedge (vismodegib) capsule**
NDA 203388
Comments on a draft (b) (4)

In response to DOP 2's January 6, 2012, consult request, OPDP has reviewed Genentech's proposed (b) (4) for Erivedge. During the review (b) (4), OPDP used the most recent version of the revised draft Prescribing Information (PI), Genentech's response to the Agency's requested changes to the PI, forwarded by DOP 2 to OPDP via electronic mail on January 4, 2012. Genentech submitted a proposed (b) (4) .

OPDP's comments are provided below.

GENERAL COMMENTS

(b) (4)

Mailing of Important Information about Drugs

2. Please remind the sponsor to refer to 21 CFR § 200.5 (Mailing of important information about drugs) regarding the format for recommended mailing of important information regarding drug warnings. We recommend that the distinctive box described in 21 CFR § 200.5 appear in the letter as well as on the envelope.

Prescribing Information (PI)

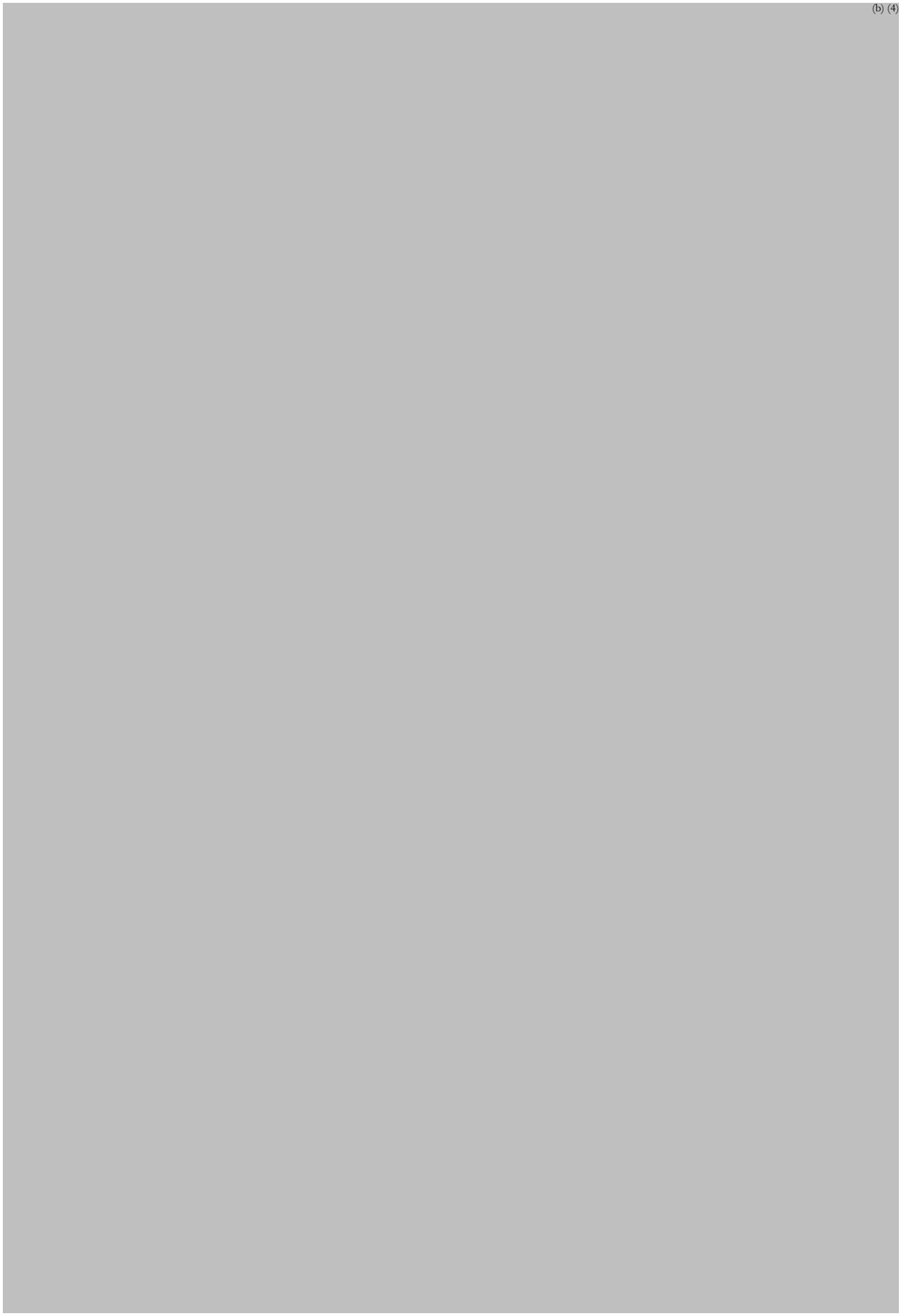
3. OPDP's comments are based on a draft PI. Please ensure that all information in this proposed (b) (4) is revised to be consistent with the PI once an approved version is available.

SPECIFIC COMMENTS

4. OPDP recommends that the proposed (b) (4) be updated in accordance with the draft guidance (b) (4) dated November 2010.

   The proposed (b) (4) for Erivedge is intended (b) (4) (b) (4)

(b) (4)


(b) (4)

OPDP appreciates the opportunity to provide comments (b) (4). If you have any questions, please contact me at 301-796-0575 or Carole.Broadnax@fda.hhs.gov.

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/s/

CAROLE C BROADNAX
01/12/2012

eCTD NDA 203388/0
vismodegib (ERIVEDGE)
Labeling Meeting
1-11-12

Memorandum

Date: January 11, 2012

From: Mona Patel, DOP2/OHOP/CDER

Subject: Labeling Meeting: NDA 203388

Original Application: NDA 203388

Product: vismodegib [Proper Name- ERIVEDGE]
Submission Date: September 8, 2011
Received Date: September 8, 2011
Sponsor: Genentech, Incorporated
Proposed Indication: For the treatment of adult patients with basal cell carcinoma that has recurred following surgery or who are not candidates for surgery (b) (4) or who are not candidates for radiation

Attendees:
Patricia Keegan
Mona Patel
Zedong Dong
Michael Axelson
Todd Palmby
Dubravaka Kufrin
Melissa Tassinari
Carole Broadnax
Karen Munoz
Sharon Mills
Janet Xiaoping Jiang

FDA reviewed Genentech's December 21, 2011 response to FDA's proposed changes sent to Genentech for the USPI on December 14, 2011. At the conclusion of this meeting, it was decided to send the USPI back to GNE to try and reach final agreement after 2 issues in section 11 and section 14 were resolved offline.

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/s/

MONA G PATEL
01/19/2012

Attachment B: Sample 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: A Dedicated Clinical Trial Assessing Hepatic Function on Vismodegib Systemic Exposure

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	01/31/2012
	Study/Clinical trial Completion Date:	09/30/2014
	Final Report Submission Date:	03/31/2015
	Other: Draft Protocol Submission Date	10/03/2011

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 clinical trial did not enroll sufficient number of patients with varying degree of hepatic dysfunction to allow for assessment of the effect of organ dysfunction on systemic exposure of vismodegib.

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

The goal of the clinical trial is to assess the need to further reduce the initial starting dose or recommend avoidance of vismodegib for patients with hepatic impairment.

Vismodegib and its metabolites are eliminated primarily by the hepatic route. Therefore, hepatic impairment may impact vismodegib disposition. Although the renal elimination only accounts for 4.4% of the total vismodegib dose, there have been examples where renal impairment has a substantial impact on systemic exposure even when the drugs are minimally eliminated by the kidney. Therefore, a full hepatic impairment study and a reduced renal impairment study are necessary to assess the effect of organ dysfunction on pharmacokinetics of vismodegib and address the need for dose adjustment in patients with hepatic or renal 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.

To conduct a clinical trial according to "FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function -Study Design, Data Analysis and Impact on Dosing and Labeling" The patient population may include patients with advanced or metastatic solid tumors that failed current standard of care. The number of patients enrolled in the study should be sufficient to detect PK differences that would warrant dosage adjustment recommendations in the label. The frequency and duration of plasma sampling should be sufficient to accurately estimate relevant PK parameters for the parent drug. A data analysis plan must be included in the protocol.

The timetable you submitted on 17 October 2011 states that you will conduct this trial according to the following schedule:

Draft Protocol Submitted to the FDA: 3 October 2011, Serial Number 0248
Final Protocol Submission Date: 31 January 2012
Trial Completion Date: 30 September 2014
Final Report Submission: 31 March 2015

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies
Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☒ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☒ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
dedicated hepatic fucntion study (see box 1)
☐ 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/

JIAN WANG
01/10/2012

HONG ZHAO
01/10/2012
I concur.

JEFFERY L SUMMERS
01/11/2012

Attachment B: Sample 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: A Dedicated Clinical Trial Assessing Renal Function on Vismodegib Systemic Exposure

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	01/31/2012
	Study/Clinical trial Completion Date:	09/30/2014
	Final Report Submission Date:	03/31/2015
	Other: Draft Protocol Submission Date	10/03/2011

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 clinical trial did not enroll sufficient number of patients with severe impairment to allow for assessment of the effect of organ dysfunction on systemic exposure of vismodegib.

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

The goal of the clinical trial is to assess the need to further reduce the initial starting dose or recommend avoidance of vismodegib for patients with renal impairment.

Although the renal elimination only accounts for 4.4% of the total vismodegib dose, there have been examples where renal impairment has a substantial impact on systemic exposure even when the drugs are minimally eliminated by the kidney. Therefore, a full hepatic impairment study and a reduced renal impairment study are necessary to assess the effect of organ dysfunction on pharmacokinetics of vismodegib and address the need for dose adjustment in patients with hepatic or renal 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)**

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     ☐ 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.

To conduct a clinical trial according to "FDA Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis and Impact on Dosing and Labeling". A "reduced" renal impairment study could be proposed to include subjects with normal renal function and subjects with severe renal impairment. The patient population may include patients with advanced or metastatic solid tumors that failed current standard of care. The number of patients enrolled in the study should be sufficient to detect PK differences that would warrant dosage adjustment recommendations in the label. The frequency and duration of plasma sampling should be sufficient to accurately estimate relevant PK parameters for the parent drug. A data analysis plan must be included in the protocol.

The timetable you submitted on 17 October 2011 states that you will conduct this trial according to the following schedule:

Draft Protocol Submitted to the FDA: 3 October 2011, Serial Number 0248
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Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☒ Pharmacokinetic studies or clinical trials
☒ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☒ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
dedicated renal fucntion study (see box 1)
☐ 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.*

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(signature line for BLAs)

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/s/

JIAN WANG
01/10/2012

HONG ZHAO
01/10/2012
I concur.

JEFFERY L SUMMERS
01/11/2012

Attachment B: Sample 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: Conduct a Pregnancy Pharmacovigilance Program to evaluate pregnancy outcomes and infant outcomes following exposure to vismodegib. This program will include a mechanism to collect, classify and analyze data on direct exposures (women exposed to vismodegib as treatment) and indirect exposures, (women exposed to vismodegib through the seminal fluid of a male partner. The Pregnancy Pharmacovigilance program will, at a minimum, include the following key elements (see the Guidance for Industry Establishing Pregnancy Exposure Registries for a detailed description of these elements):

• Specific program objectives
• Data collection of prospective and retrospective data points, adequate to produce informative, reliable data outcomes.
• Data analysis utilizing descriptive statistics for summarizing data that will fully capture outcomes of concern. Data collected prospectively analyzed separate from data collected retrospectively
• Description of patient contact and follow up efforts
• Description of plan to communicate program existence (Patient and HCPs) and description of plan to evaluate the effectiveness of the program
• Description of plan for discontinuation of the program
• Submission of a stand-alone report of cumulative program outcomes data to the Agency

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	03/31/2012
	Study/Clinical trial Completion Date:	Applicant to provide date
	Final Report Submission Date:	Applicancat to provide date
	Other:	

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

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

Advanced basal cell carcinoma is a rare condition that the applicant estimates at 2,300 cases per year in the United States with approximately 10% of cases occuring in women of child bearing potential. Vismodegib is a teratogen, with the potential to interfere with essential developmental pathways in the embryo. The clinical trial did not contain any cases of expsoure of vismodegib to pregnant women and fetal toxicity is a primary risk of vismodegib use. The rarity of the disease in women of childbearing potiential and standard pregnancy precautions make fetal exposure a rare event not likely to be captured in a standard premarketing safety database.

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

The goal of the pregnancy pharmacovigilance program is to assess the outcomes of developing embryos and pregnancy after exposure to vismodegib. Vismodegib is a Hh pathway inhibitor and is expected to be teratogenic in developing human fetuses based on its mechanism of action and observations in preclinical toxicology studies.

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.

A pharmacovigilance study should be conducted in accordances with "FDA Guidance for Industry: E2E Pharmacovigilance Planning."

A pregnancy pharmacovigilance program is not a formal pregnancy registry, however, should at a minimum include many key elements outlined in the Guidance for Industry Establishing Pregnancy Exposure Registries. The program should include a plan for collection of prospective and retrospective data, analysis of collected data, patient contact and follow up efforts, plan to communicate program existence and plan to evaluate the effectiveness of the program. The program may not have a comparison group, as would be found in a formal registry. Collected data points should be adequate to produce reliable data outcomes.

Submit the final report for the pharmacoviligence study in pregnant women exposed to vismodegib following the agreed upon milestone timelines:

- Draft Protocol Submitted to the FDA: March 31, 2012
- Final Protocol Submission Date: March 31, 2012
- Trial Completion Date: March 31, 2022
- Final Report Submission: March 31, 2023

Required

☒ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

☐ Primary safety study or clinical trial
☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
☐ Thorough Q-T clinical trial
☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
☐ Pharmacokinetic studies or clinical trials
☐ Drug interaction or bioavailability studies or clinical trials
☐ Dosing trials
☐ 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.*

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/s/

MICHAEL AXELSON
01/11/2012

JEFFERY L SUMMERS
01/11/2012

PMR/PMC Development Template

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

NDA #/Product Name:	NDA# 203388/Vismodegib
PMR/PMC Description:	To evaluate the potential for carcinogenicity, conduct a rodent carcinogenicity study in the mouse. Submit the carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

PMR/PMC Schedule Milestones:	Special Protocol Assessment Submission:	10/01/2012
	Final Protocol Submission:	07/31/2013
	Study/Trial Completion:	01/15/2016
	Final Report Submission:	10/16/2017
	Other:	

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

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

The proposed indication for vismodegib in NDA 203388 is for the treatment of adults with basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, [redacted] (b) (4) or who are not candidates for radiation. There are no approved therapies for this patient population. Although this is a serious and life threatening disease, some patients may have a life expectancy exceeding 2 years. The overall prognosis for some patients in the indicated population may be relatively prolonged. The median time of exposure to vismodegib was ~10 months while the range of treatment was 0.7 to 18.7 months in study SHH4476g, indicating that patients will be chronically exposed to the drug for relatively long periods of time. Carcinogenicity studies may be concluded post-approval for therapeutics intended to treat patients with certain serious diseases. Therefore, carcinogenicity studies were not requested or required for marketing for this indication.

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."

Results of the clinical trial used to support marketing (Study SHH4476g) indicate that the median time of exposure to vismodegib was ~10 months and that patients will be chronically exposed to the drug for relatively long periods of time. Carcinogenicity is a safety concern with chronic drug exposure. Vismodegib is in a pharmacologic class with no other approved drugs so the carcinogenic potential is unknown. There is a concern that chronic exposure to vismodegib could cause additional cancers in patients treated with vismodegib. To address this concern a carcinogenicity study in the mouse is being required to assess the potential for vismodegib to cause carcinogenicity.

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.

A carcinogenicity study in the mouse.

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/

DENALI D KUFRIN
01/11/2012

TODD R PALMBY
01/11/2012

JEFFERY L SUMMERS
01/11/2012

PMR/PMC Development Template

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

NDA #/Product Name:	NDA# 203388/Vismodegib
PMR/PMC Description:	To evaluate the potential for carcinogenicity, conduct a long-term rodent carcinogenicity study in the rat. Submit the carcinogenicity protocol for a Special Protocol Assessment (SPA) prior to initiating the study.

PMR/PMC Schedule Milestones:		
	Special Protocol Assessment Submission:	10/01/2012
	Final Protocol Submission:	07/31/2013
	Study Completion:	01/15/2016
	Final Report Submission:	10/16/2017
	Other:	

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

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

The proposed indication for vismodegib in NDA 203388 is for the treatment of adults with basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, [redacted] (b) (4) or who are not candidates for radiation. There are no approved therapies for this patient population. Although this is a serious and life threatening disease, some patients may have a life expectancy exceeding 2 years. The overall prognosis for some patients in the indicated population may be relatively prolonged. The median time of exposure to vismodegib was ~10 months while the range of treatment was 0.7 to 18.7 months in study SHH4476g, indicating that patients will be chronically exposed to the drug for relatively long periods of time. Carcinogenicity studies may be concluded post-approval for therapeutics intended to treat patients with certain serious diseases. Therefore, carcinogenicity studies were not requested or required for marketing for this indication.

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."

Results of the clinical trial used to support marketing (Study SHH4476g) indicate that the median time of exposure to vismodegib was ~10 months and that patients will be chronically exposed to the drug for relatively long periods of time. Carcinogenicity is a safety concern with chronic drug exposure. Vismodegib is in a pharmacologic class with no other approved drugs so the carcinogenic potential is unknown. There is a concern that chronic exposure to vismodegib could cause additional cancers in patients treated with vismodegib. To address this concern a long-term carcinogenicity study in the rat is being required to assess the potential for vismodegib to cause carcinogenicity.

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.

A long-term carcinogenicity study in the rat.

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.*

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(signature line for BLAs)

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/s/

DENALI D KUFRIN
01/11/2012

TODD R PALMBY
01/11/2012

JEFFERY L SUMMERS
01/11/2012

Attachment B: Sample 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: Drug Drug Interaction Trial

PMR/PMC Schedule Milestones:		
	Final protocol Submission Date:	07/09/2010
	Study/Clinical trial Completion Date:	03/30/2012
	Final Report Submission Date:	03/31/2012
	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

Vismodegib has a potential for inhibiting CYP2C8 based on in vitro studies with human liver microsomes. Since the [I]/Ki ratio is (b) (4) much greater than the cut-off threshold of 0.1, a clinical assessment of vismodegib's drug-drug interaction potential is necessary.

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

The goal of the clinical trial is to evaluate the effect of vismodegib on the pharmacokinetics of a sensitive CYP2C8 substrate (i.e., rosiglitazone) and on the pharmacokinetics of oral contraceptive components (i.e., ethinyl estradiol and norethindrone).

Females of reproductive potential are required to have an acceptable contraception during vismodegib therapy and for 7 months after discontinuing treatment because vismodegib can cause fetal harm. Oral contraceptives could be used concomitantly in female patients with child-bearing potential and receiving vismodegib therapy.

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.

To submit a final report from the ongoing drug interaction trial (Protocol SHH4593g) designed to evaluate the effect of vismodegib on the pharmacokinetics of a sensitive CYP2C8 substrate (rosiglitazone) and on the pharmacokinetics of oral contraceptive components (ethinyl estradiol and norethindrone) following the agreed upon milestone timelines: Trial Completion Date: March 30, 2012 Final Report Submission: March 31, 2012

Required

☐ Observational pharmacoepidemiologic study
☐ Registry studies

Continuation of Question 4

- ☐ Primary safety study or clinical trial
- ☐ Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- ☐ Thorough Q-T clinical trial
- ☐ Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- ☐ Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- ☒ Pharmacokinetic studies or clinical trials
- ☒ Drug interaction or bioavailability studies or clinical trials
- ☐ Dosing trials
- ☒ Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
  dedicated drug-drug interaction study (see box 1)
- ☐ 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/

JIAN WANG
01/10/2012

HONG ZHAO
01/10/2012
I concur.

JEFFERY L SUMMERS
01/11/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9858

Maternal Health Team Review

Date: January 6, 2012 **Date Consulted:** September 21, 2011

From: Tammie Howard, RN, MSN
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff

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

Lisa Mathis, MD
Associate Director, Office of New Drugs
Pediatric and Maternal Health Staff

To: Division of Oncology Products 2 (DOP2)

Drug: Erivedge (vismodegib) NDA 203388

Subject: NME Original Application

Sponsor: Genentech, Inc.

Materials Reviewed: Erivedge (vismodegib) product labeling and Risk Management Proposal

Consult Question: Genentech submitted an original NDA (NME) for vismodegib (Erivedge) for treatment of adult patients with advanced basal cell carcinoma (b) (4)
Genentech submitted a Med Guide and PI. We are requesting reviewer presence/input throughout application review process, and request meeting attendance.

INTRODUCTION

On September 8, 2011, Genentech, Inc. submitted NDA 203388 for vismodegib (Erivedge) to the Division of Oncology Drug Products (now Division of Oncology Products 2 (DOP2)). Vismodegib, a Hedgehog (Hh) pathway inhibitor, is a first-in-class New Molecular Entity (NME) with a proposed indication for treatment of adults with basal cell carcinoma that has recurred following surgery or who are not candidates for surgery, (b) (4) or who are not candidates for radiation. The sponsor was granted a priority review status with a PDUFA goal date of February 3, 2012. On September 21, 2011, the Pediatric and Maternal Health Staff - Maternal Health Team (PMHS-MHT) was consulted by DOP2 for input throughout the application review process. MHT has participated in internal and sponsor team meetings, labeling meetings and a regulatory briefing.

BACKGROUND

Vismodegib (Erivedge) is a Hedgehog (Hh) pathway inhibitor that binds to and inhibits the transmembrane protein, Smoothened, that is involved in Hh signal transduction. Dysregulation of this pathway may lead to abnormal cell proliferation and abnormal activation of the pathway has been implicated in the development of basal cell carcinoma and other cancers[1,2,3]. Vismodegib blocks signaling of this pathway and has shown clinical efficacy for BCC patients.

During embryonic development, Smoothened mediates normal Hh pathway signaling[4] which is essential for normal embryonic development. Vismodegib inhibits normal signaling of this developmental pathway, indicating great potential teratogenic risk for the embryo or fetus exposed to vismodegib. The teratogenic risk for Hh pathway inhibitors is well established and the anticipated teratogenic risk for vismodegib was confirmed in embryo-fetal development rat studies. (b) (4)

(b) (4)

[1] NDA 203388 Marketing Application: Vismodegib-Genetech, Inc., 3/Nonclinical Summaries (Advanced Basal Cell Carcinoma): 2-6-6.doc.
[2] Chen JK, Taipale J, Young KE, Maiti T and Beachy PA. Small molecule modulation of Smoothened activity. Proc. Natl. Acad. Sci. U.S.A. 2002;**99** (22): 14071–6.
[3] Xie J, Murone M, Luoh SM, Ryan A, Gu Q, Zhang C, Bonifas JM, Lam CW, Hynes M, Goddard A et al. Activating Smoothened mutations in sporadic basal-cell carcinoma. Nature. 1998;**391** (6662): 90–2.
[4] Chen JK, Taipale J, Young KE, Maiti T and Beachy PA. Small molecule modulation of Smoothened activity. Proc. Natl. Acad. Sci. U.S.A. 2002;**99** (22): 14071–6.

[redacted] (b) (4)

On October 19, 2011, the review team met with the sponsor to discuss the measures needed to ensure the safe use of the drug and the sponsor agreed to submit a revised risk management proposal. The sponsor submitted a revised proposal [redacted] (b) (4) on November 4, 2011. The revised proposal included updated product labeling (pregnancy category D proposed), medication guide, voluntary communication plan and an enhanced pharmacovigilance plan to investigate pregnancy vismodegib exposures. Distribution of vismodegib would occur via specialty pharmacy.

The Maternal Health Team participated in a Regulatory Briefing held on December 9, 2011 to determine the Office of New Drug's (OND) approach to management of teratogenic risk with vismodegib and other similar teratogenic oncologic drugs. The specific discussion focused on whether a REMS would be required for vismodegib or whether pregnancy labeling tools could adequately communicate and mitigate risk. The briefing concluded with overall recommendations that a REMS is not required and that labeling tools should be adequate to communicate risks for vismodegib. In addition, the Division proposed the following:

- The product be labeled pregnancy category D, to allow access to drug due to lack of alternative therapies
- The Division work closely with the sponsor on the voluntary communication plan for HCPs to ensure that the essential elements of risk for vismodegib are communicated adequately
- A post-marketing requirement to establish a pregnancy pharmacovigilance plan to ensure collection of outcomes data regarding vismodegib pregnancy exposures

The review team adopted this plan of action, however determined that the sponsor did not provide adequate detail regarding their enhanced pregnancy pharmacovigilance plan. The review team met with the sponsor on December 13, 2011 to further discuss the revised risk management proposal and the Agency requested that the sponsor provide additional specific detail regarding the pregnancy pharmacovigilance plan. In addition, the Agency requested that the sponsor collect and analyze data to further assess human teratogenic risk as a Post-Marketing Requirement (PMR). On January 4, 2012, the sponsor submitted details of the pregnancy pharmacovigilance program and proposed PMR language.

This review provides MHT labeling recommendations, recommendations regarding the pregnancy pharmacovigilance program and the sponsor's proposed PMR language.

REVIEW OF SUBMITTED MATERIAL

Sponsor's Proposed Submitted Labeling

A series of labeling meetings were conducted during the review cycle. Each discipline was scheduled for a labeling meeting to focus on discipline specific sections of labeling. The MHT reviewed the sponsor's proposed labeling version prior to the December 9, 2011 labeling meeting and participated in a labeling meeting on December 12, 2011. [redacted] (b) (4)

Sponsor's Pregnancy Pharmacovigilance Plan

The sponsor's pregnancy pharmacovigilance plan is designed to collect prospective and retrospective reports of pregnancy exposures to vismodegib. The plan is not a formal pregnancy registry; however, the design is very similar and corresponds to key elements described in the current Guidance for Industry Establishing Pregnancy Exposure Registries. (b) (4)

Sponsor's Proposed PMR Language

The sponsor proposes to implement a Pregnancy Pharmacovigilance Program to evaluate pregnancy and infant outcomes following exposure to vismodegib that will be initiated at product launch. Interim cumulative annual reports will be submitted until one of the following: 10 years have elapsed (March 31 2022) or 25 pregnancies with informative outcomes. The sponsor estimates that there may be approximately two pregnancies per year globally, and plans to finalize aspects of the program by March 31, 2012.

DISCUSSION

The Proposed Pregnancy and Lactation Labeling Rule published in May 2008. While the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule while still complying with current regulations. (b) (4)

he goal of this restructuring is to make the pregnancy and lactation section of labeling a more effective communication tool for clinicians.

The MHT discussed labeling recommendations with the review team during a labeling meeting on December 12, 2011. A summary and a detailed discussion of PMHS-MHT labeling recommendations appear by label section below. PMHS-MHT labeling recommendations (label excerpts) follow. During the labeling meeting, MHT recommendations were edited per discussion with the review team. Generally, revisions were made to place language into active voice. Specific review team revisions are addressed in the MHT summary of labeling recommendations. The label, including MHT edited recommendations, was sent to the sponsor on December 14, 2011. (b) (4)

Further labeling revisions are pending final labeling discussions with the sponsor.

[5] NDA 203388 Amendment: Vismodegib (GDC-04994)-Genetech, Inc., Regional (Q&A Response) (Request for Information) (Advanced Basal Cell Carcinoma).

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[redacted] (b) (4)

MHT RECOMMENDATIONS

MHT has the following Labeling Recommendations:

1. Retain the boxed warning describing the teratogenic risk associated with vismodegib and actions to mitigate the risk, as the associated risk can lead to death or serious injury.

2. Revise the warnings and precautions section to provide an overall statement of teratoginic risk and mitigating action, and provide cross reference to the Female and Males of Reproductive Potential section for more detailed information.

3. Pregnancy category D is recommended for this product. There are no positive human data for vismodegib, however, the drug's mechanism of action targets a developmental pathway essential to embryonic development and embryo-fetal development studies in rats confirm anticipated teratogenicity. In addition, the benefit for use of vismodegib during pregnancy may outweigh the risk to the fetus, as there may be no other alternative treatment.

4. Restructure the Pregnancy and Nursing Mothers sections of labeling, as described in the discussion section of this review.

5. Add a Females and Males of Reproductive Potential section under the Use In Specific Populations section of labeling. This section of labeling provides an area to address the specific risk (teratogenicity) and instructions for mitigation of risk (pregnancy planning and prevention) for female and male patients.

6. Restructure the Patient Counseling section to display information in bulleted format with sub-headers to indicate specific subject matter.

7. Add appropriate regulatory language in Highlights, Warnings and Precautions and Use in Special Populations section.

MHT has the following recommendation regarding the pregnancy pharmacovigilance program and proposed PMR language:

8. Regarding question two of the patient guided questionnaire, request that the sponsor consider the deletion of the term [redacted] (b) (4) and replace with the term "vasectomy (male patients)". The term [redacted] (b) (4) may be misleading to the patient.

9. Request that the sponsor consider combining questions 2 and 3 of the patient guided questionnaire, and removing the terms [redacted] (b) (4) from the questions. These terms may lead patients to not answer or be untruthful in response, as these words could be anxiety producing if the patient was using a [redacted] (b) (4) method. The choices alone would allow for data collection of [redacted] (b) (4) contraception methods.

1 [redacted] (b) (4)

11. Request that the sponsor provide a data based rationale supporting their assumption that their plan for active pregnancy prevention education will lead to a reduction in the number of unintended pregnancies.

CONCLUSION

Vismodegib, a Hedgehog pathway inhibitor, has shown clinical efficacy for adults with basal cell carcinoma. The proposed indication is for adults with BCC that has recurred following surgery or who are not candidates for surgery, [redacted] (b) (4) or who are not candidates for radiation. However, vismodegib inhibits a pathway that is essential for normal embryonic development and has great potential risk for human teratogenicity. [redacted] (b) (4) it was determined by the review team, with advice from senior CDER staff at a regulatory briefing, that [redacted] (b) (4) product labeling, a medication guide and a PMR for a pregnancy pharmacovigilance program would be sufficient to communicate and mitigate risk.

The Maternal Health Team participated in the review process for the vismodegib application and provided input during the review process. This review summarizes MHT vismodegib application recommendations.

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/s/

TAMMIE B BRENT HOWARD
01/09/2012

MELISSA S TASSINARI
01/09/2012

LISA L MATHIS
01/09/2012
Concur

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

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

Date: December 23, 2011

To: Mona Patel, Regulatory Project Manager
Division of Oncology Products 2 (DOP2)
Office of Hematology & Oncology Products

From: Karen Munoz, Regulatory Review Officer
Division of Direct-to-Consumer Promotion (DDTCP)
Office of Prescription Drug Promotion (OPDP)

Through: Kathleen Klemm, Regulatory Review Officer
Division of Professional Promotion (DPP), OPDP

CC: Shefali Doshi, DTC Group Leader, DDTCP, OPDP
Carole Broadnax, Regulatory Review Officer, DPP, OPDP
Andrew Haffer, Professional Group Leader, DPP, OPDP

Subject: **NDA 203388 - ERIVEDGE (vismodegib) capsule**

OPDP Comments on draft product labeling – Medication Guide

In response to the Division of Oncology Products 2 (DOP 2) September 16, 2011, consult request, DDTCP has reviewed the proposed Medication Guide for ERIVEDGE (vismodegib) capsule.

Reference is made to the December 7, 2011, and December 19, 2011, reviews by Carole Broadnax, which provided comments on the draft carton and container labeling and draft Package Insert, respectively. Reference is also made to an email from Mona Patel to Carole Broadnax dated December 14, 2011, clarifying that there is no PPI to review.

OPDP's comments on the Medication Guide are based on the substantially complete version of the draft labeling, titled, "FDA Proposed Vismodegib (NDA 203388) Labeling (12 14 11).doc" sent via email to OPDP by Mona Patel on December 14, 2011. OPDP's comments on the Medication Guide are provided directly in the attached document. Please note that OPDP hid deletions and formatting changes so that OPDP comments would be easier to read.

Thank you for the opportunity to comment on these proposed materials.
If you have any questions, please contact Karen Munoz at (301) 796-3274 or karen.munoz@fda.hhs.gov.

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/s/

KATHLEEN KLEMM
12/23/2011
Signing on behalf of Karen Munoz

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

PATIENT LABELING REVIEW

Date:	December 20, 2011
To:	Patricia Keegan, MD, Director **Division of Oncology Products 2 (DOP 2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Team Leader, Patient Labeling Team **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling Team **Division of Medical Policy Programs**
From:	Sharon R. Mills, BSN, RN, CCRP Patient Labeling Reviewer **Division of Medical Policy Programs**
Subject:	DMPP Review of Patient Labeling (Medication Guide)
Drug Name (established name):	ERIVEDGE (vismodegib)
Dosage Form and Route:	capsules
Application Type/Number:	NDA 203-388
Applicant:	Genentech, Inc.
OSE RCM #:	2011-3452

1 INTRODUCTION

This review is written in response to a request by the Division of Oncology Products 2 (DOP 2) for the Division of Medical Policy Programs (DMPP) to review the Applicant's proposed Medication Guide (MG) for ERIVEDGE (vismodegib).

The purpose of the Applicant's submission is to seek approval of their original New Drug Application (NDA) 203-388. The proposed indication is for the treatment of adults with basal cell carcinoma that has recurred following surgery and who are not candidates for surgery and radiation. 3 pages of d ft

2 MATERIAL REVIEWED

- Draft ERIVEDGE (vismodegib) Medication Guide (MG) received on September 8, 2011 and further revised by the Applicant on November 28, 2011.
- Draft ERIVEDGE (vismodegib) Prescribing Information (PI) received September 8, 2011 and further revised by the Applicant on November 28, 2011, revised by the Review Division and provided to DMPP on December 14, 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 DISCUSSION

(b) (4)

PI sections (b) (4) include language to inform healthcare professionals and patients not to open or crush the capsules.

Based on communication with the DOP 2 Medical Officer and the Pharmacology reviewer on December 16, 2011, it is our understanding that the concern about direct contact of opened or crushed capsules with the skin or mucous membranes applies only to healthcare professionals because of the potential teratogenicity issues with ERIVEDGE, and does not apply to patients.

5 CONCLUSIONS

The MG is acceptable with our recommended changes.

6 RECOMMENDATIONS

- We recommend clarifying the language in PI sections (b) (4) to indicate that the concern about direct contact of opened or crushed capsules with the skin or mucous membranes applies only to healthcare professionals and not patients. Patients are currently told in PI section (b) (4) not to open or crush the capsules, but there is no mention that patients do not need to be concerned about direct contact, but rather only the ingestion of the product.
- Please send these comments to the Applicant and copy DMPP on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DMPP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHARON R MILLS
12/20/2011

BARBARA A FULLER
12/20/2011

LASHAWN M GRIFFITHS
12/20/2011

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

Internal Consult

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

To: Mona Patel, Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology Oncology Products

From: Carole C. Broadnax, R.Ph., Pharm.D., Regulatory Review Officer
Division of Professional Promotion
Office of Prescription Drug Promotion (OPDP)

Date: December 19, 2011

Re: **NDA 203388 - ERIVEDGE (vismodegib) capsule**
OPDP Comments on proposed labeling (Package Insert)

In response to the Division of Oncology Products 2 (DOP 2) September 16, 2011, consult request, OPDP has reviewed proposed labeling (package insert) for ERIVEDGE (vismodegib**)**.

OPDP's comments for the package insert (PI) are based on the draft labeling sent via electronic mail to OPDP from DOP 2 on December 14, 2011. OPDP's PI comments are provided directly in the attached document. Please note that for the PI, OPDP hid deletions and formatting changes so that OPDP comments are easier to read.

OPDP comments for the proposed carton/container labeling were sent to DOP 2 on December 7, 2011.

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

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/s/

CAROLE C BROADNAX
12/19/2011

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: December 12, 2011

TO: Mona Patel, Regulatory Project Manager
Michael Axelson, Medical Officer
Division of Oncology Products 2

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

THROUGH: Susan Leibenhaut, M.D.
Acting Team Leader, Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Tejashri Purohit-Sheth, M.D.
Acting Division Director
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 203388

APPLICANT: Genentech, Inc.

DRUG: Vismodegib (Erivedge) Capsules

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATION: Treatment of adult patients with advanced basal cell carcinoma (b) (4)
(b) (4)

CONSULTATION REQUEST DATE: 9/23/2011
DIVISION ACTION GOAL DATE: 2/3/2012
PDUFA DATE: 3/8/2012

I. BACKGROUND:

Genentech, Inc., seeks approval to market vismodegib for the treatment of advanced basal cell carcinoma (BCC). The application is supported primarily by data from a single pivotal study, Study SHH4476g, entitled, "A Pivotal Phase II, Multicenter, Single-Arm, Two-Cohort Trial Evaluating the Efficacy and Safety of GDC-0449 in Patients with Advanced Basal Cell Carcinoma", sponsored by Genentech, Inc. The study population consisted of subjects ≥ 18 years old with a histologically confirmed diagnosis of metastatic or locally advanced basal cell carcinoma (BCC). Study SHH4476g was conducted at 31 Centers in the U.S., France, Germany, Belgium, Australia, and U.K. Planned enrollment was approximately 100 subjects. A total of 104 subjects were actually enrolled (33 subjects with metastatic BCC and 71 subjects with locally advanced BCC).

The study primary objective was to determine the clinical benefit of the test article in this patient population as measured by tumor overall response rate (ORR). Tumor assessments included an evaluation of all sites of disease and were performed at screening and every 8 weeks thereafter.

ORR was assessed separately for subjects with metastatic BCC and locally advanced BCC. For subjects with metastatic BCC, Response Evaluation Criteria in Solid Tumors (RECIST) was used to evaluate tumor lesions on standard radiologic imaging modalities (computed tomography [CT] or magnetic resonance imaging [MRI]) in non-skin organs, such as metastatic disease in lymph node, soft tissue, lung or liver. For subjects with locally advanced BCC, a composite response endpoint was used that incorporates externally visible tumor dimension (the longest dimension at each tumor assessment) and tumor ulceration, as well as RECIST for lesions with a RECIST-measurable component. Externally visible tumor assessment was documented using standardized digital photography. If the border of the tumor was no longer visible but a scar was present, the dimensions of the scar were measured.

In addition to tumor assessments described above an independent pathology assessment was conducted to verify histopathologic determination that archival tissue collected from study subjects was consistent with a past diagnosis of basal cell carcinoma (BCC). For study subjects with locally advanced BCC, an independent pathology assessment provided a histopathologic evaluation of response in tumor biopsy tissue collected post treatment.

In and effort to address possible bias in the assessment of primary and secondary endpoints related to tumor and lesion measurements, the sponsor used Independent Review Facilities (IRFs) to determine objective response, date of objective response, and date of disease progression. (b) (4), functioned under Charter as the Independent Review Facility (IRF) for assessment of standard radiologic imaging modalities CT/MRI for this study. (b) (4) functioned under Charter as the Independent Review Facility (IRF) for photographic images for this study. An independent pathologist contracted from (b) (6) functioned under Charter to assess tumor biopsies/histology as the Independent Pathologist.

Two clinical sites, chosen on the basis of site-specific efficacy data, number and types of protocol deviations, and patient number enrolled at each site were inspected for this NDA. The two IRFs responsible for assessment of the radiographic images and photographic images, respectively, were also inspected. Because this is an NME, the sponsor was inspected and the responsibilities and conduct of the Independent Pathologist were assessed during the sponsor inspection.

II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol #: and # of Subjects:	Inspection Date	Final Classification
CI#1: Site #25955 Michael R. Migden, M.D. MD Anderson Cancer Center 6655 Travis Street, Suite 650 Houston, Texas 77030	Protocol: SHH4476g Site #: 25955 Number of Subjects: 11	(b) (4)	Pending Interim classification: VAI
CI#2: Site #23735 Anthony E. Oro, M.D. Stanford University Medical Center 269 Campus Drive CCSR, Room 2145 Stanford, California 94305	Protocol: SHH4476g Site #: 23735 Number of Subjects: 8		Pending Interim classification: VAI
(b) (4)			
Sponsor: Genentech, Inc. 1 DNA Way South San Francisco, California 94080	Protocol: SHH4476g <u>Site #/Subject Records Reviewed</u>: 25955/11 23735/8 24087/3 22118/5	(b) (4)	Pending Interim classification: VAI

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 and EIR has not been received from the field or complete review of EIR is pending and final classification letter has not issued.

1. **CI#1:** – Dr. Michael R. Migden,
(Site Number 25955)
MD Anderson Cancer Center
6655 Travis Street, Suite 650
Houston, Texas 77030

Note: Observations noted for this site are based on preliminary communications with the FDA investigator, and review of the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

a. **What was inspected**: The site screened 11 subjects and all were treated with test article. A total of 4 subjects have completed the study. The study records of all 11 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, efficacy endpoints, clinical laboratory results, adverse events, treatment regimens and reporting of AEs in accordance with the protocol. The FDA field investigator also assessed informed consent documents, test article accountability, 1572s, IRB committee correspondence, monitoring and safety reports, and financial disclosure forms.

b. **General observations/commentary**: Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data were generated by several different IRF (b) (4), (b) (6) The FDA field investigator verified that standard radiologic imaging modalities CT/MRI, standardized digital photography and tumor biopsy tissue were taken in accordance with the protocol for each subject, reviewed by the site and then sent for independent review to the IRF. The primary efficacy endpoint data for the subjects enrolled at this site were verified during the CRO inspections. There was no evidence of under-reporting of AEs. The FDA field investigator issued a Form FDA 483 for the following violations:

1. Three of the 4 SAEs experienced at this site were not reported to the sponsor within 24 hours as required by the protocol, but instead were reported from 3 to 31 days of the site becoming aware of the events.
2. Of the 11 consented subjects 1 was not appropriately re-consented with an updated version of the consent form.
3. Certain protocol required periodic assessments such as SF-36 Health Survey, pregnancy test, and vital signs were missed; however, these were isolated in nature.

4. There were several record keeping violations noted concerning recording of the number of capsules of medication. Each of these 3 observations was discrepant by a single capsule.

These were isolated observations, were not of a systemic nature, and did not significantly impact data generated by this site.

c. **Assessment of data integrity:** Not withstanding the observations noted above, the data for Dr. Migden's site, associated with Study SHH4476g submitted to the Agency in support of NDA 203388, appear reliable based on available information.

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

2. **CI#2: – Anthony E. Oro**
(Site Number 23735)
Stanford University Medical Center
269 Campus Drive
CCSR, Room 2145
Stanford, California 94305

Note: Observations noted for this site are based on preliminary communications with the FDA investigator, and review of the Form FDA 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

a. **What was inspected**: The site screened 9 subjects, and 8 subjects were treated with test article. One subject is still active in the study. The study records of all 9 subjects were audited in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to CRFs with particular attention paid to inclusion/exclusion criteria compliance, efficacy endpoints, clinical laboratory results, adverse events, treatment regimens and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, and monitoring and safety reports, and financial disclosure forms.

b. **General observations/commentary**: Generally, the investigator's execution of the protocol was found to be adequate. The primary efficacy endpoint data were generated by several different IRFs (b) (4), (b) (6) The FDA field investigator verified that standard radiologic imaging modalities CT/MRI, standardized digital photography and tumor biopsy tissue were taken in accordance with the protocol for each subject, reviewed by the site and then sent for independent review to the IRF. The primary efficacy endpoint data for the subjects enrolled at this site were verified during the CRO

inspections. There was no evidence of under-reporting of AEs. The FDA field investigator issued a Form FDA 483 for the following violations:

1. Four of the 9 enrolled subjects were consented with an Informed Consent Form that was not IRB-approved prior to use. This ICF included minor formatting changes, removing the name of one of the Research Staff who was no longer involved in the study and then changing the "Version" number from "6" to "7".
2. One SAE was not reported to the sponsor within 24 hours as required by the protocol, but instead was reported approximately one month after the site became aware of the event.
3. The protocol specifies that an SF-36 Health Survey is required at End of Treatment/Early Termination for all subjects as a secondary efficacy outcome measure of change from Day 1 in patient-reported outcomes, as measured on the Short Form 36 (SF-36) Health Survey. Two subjects, 20502 and 20505, failed to complete an End of Treatment SF-36 Health Survey. This observation was noted in 2 of the 9 subjects enrolled at this site and will not impact the primary efficacy endpoint measure of overall response rate based on tumor assessments.
4. There were several record keeping violations where several updates were made to subject source documents that were either not properly initialed or dated. Specifically, the Case History File for Subject 20506 showed that the Week 88 visit had an updated entry to ECOG data, however, the date the updated ECOG test was actually administered was not listed. The Case History File for Subject 20503 had a (b) (4) (b) (4) Protocol Inquiry Form that was initialed in the wrong place, and white-out was used in making the correction. These observations will not impact efficacy or safety data generated by the site.

These were isolated observations, were not of a systemic nature, and did not significantly impact data generated by this site.

c. Assessment of data integrity: Not withstanding the observations noted above, the data for Dr. Oro's site, associated with Study SHH4476g submitted to the Agency in support of NDA 203388, appear reliable based on available information.

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

(b) (4)

Note: Observations noted for this site are based on preliminary communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

a. What was inspected: The CRO was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The inspection included a review of the firm's organization and personnel, training and qualification records, transfer of responsibilities, "Independent Review Charter," financial disclosures, subject records and source documents, media (imaging) receipts, image qualifications and reading, handling and transferring data to the sponsor, and data assessment and validation for primary efficacy endpoint. All of the primary efficacy endpoints were reviewed for all applicable subjects at each of the (b) clinical sites noted in the Table above for the identified study inspected at this CRO site.

b. General observations/commentary: Records and procedures were clear, and generally well organized. The primary efficacy endpoint data generated by this IRF and submitted to NDA 203388 were verifiable for (b) clinical sites noted in the Table above specific for the inspection of this CRO, 2 of which were also audited by FDA. No Form FDA 483 was issued.

(b) (4) has performed multiple system analyses in an effort to implement corrective actions initiated in response to observations listed on a previously received Form FDA 483. The analyses encompassed assessments of the blinding, storing, and reading of radiographic image activities, and audit trail assessments. Read results appeared complete and accurate. Impact analyses and validation implementation was reviewed and appeared adequate.

c. Assessment of data integrity: The data generated at this site, as it pertains to Study SHH4476g were audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. The data from this CRO submitted to the agency in support of NDA 203388 appear reliable.

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

(b) (4)

Note: Observations noted for this site are based on preliminary communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

a. What was inspected: The CRO was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The inspection included a review of the firm's organization and personnel, training and qualification records, transfer of responsibilities, "Independent Panel Review of Photographs," financial disclosures, subject records and source documents, media

(imaging) receipts, image qualifications and reading, handling and transferring data to the sponsor, and data assessment and validation for primary efficacy endpoint. All of the primary efficacy endpoints were reviewed for all applicable subjects at (b) (4) clinical sites and (b) (4) applicable subjects for the identified study. This comprised a total of 1010 data points.

b. General observations/commentary: Records and procedures were clear, and generally well organized. The primary efficacy endpoint data generated by this IRF and submitted to NDA 203388 were verifiable at the CRO site for (b) (4) clinical sites and (b) (4) subjects. Training records, qualifications and certificates of completion of required training processes prior to performing independent reads were reviewed and maintained for all dermatologists involved in the study reviewed. CVs and financial disclosures were also current and available. No Form FDA 483 was issued.

c. Assessment of data integrity: The data generated at this site, as it pertains to Study SHH4476g were audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. The data from this CRO submitted to the agency in support of NDA 203388 appear reliable.

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

5. Sponsor: Genentech, Inc.
1 DNA Way
South San Francisco, California
94080

Note: Observations noted for this site are based on preliminary communications with the FDA investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

a. What was inspected: The sponsor, Genentech, was inspected in accordance with the Sponsor/Monitor/CRO data validation compliance program, CP 7348.810. The inspection covered adherence to Protocol, and review of the firm's SOPs, monitoring reports, actions related to monitoring deficiencies, Ethics Committee/IRB approvals, completed Form FDA 1572s, communications with the sites, drug accountability and review of data management from the clinical study sites to the submission of the NDA to the Agency. The inspection also audited the conduct of the Independent Pathologist, (b) (6), to assess the primary efficacy endpoint component generated in accordance with the Independent Pathology Review Charter. The FDA field investigator specifically audited subjects records from 4 clinical study sites; Site 25955 (Dr. Michael Migden, 11 subjects), Site 23735 (Dr. Anthony Oro; 8 subjects), Site 24087 (Dr. Joel Gelfand; 3 subjects), and Site 22118 (Dr. James Solomon; 5 Subjects), against the data listings submitted to NDA 203388. The FDA field investigator selected the 2 additional clinical sites randomly.

b. General observations/commentary: Records and procedures were clear, and generally well organized. There was nothing to indicate under-reporting of AEs/SAEs. The FDA field investigator audited all source notes generated by the independent pathologist (b) (4) (b) (6) and compared these with the data listings submitted in the NDA 203388 for the 4 sites noted in item a. above. No discrepancies were noted. There was no evidence of underreporting protocol violations. Overall site monitoring appeared adequate. Monitoring reports indicated that efforts were made by the sponsor/CRO to ensure site compliance with the protocol. The Sponsor appeared to maintain adequate oversight of the study.

In accordance with the Independent Pathology Review Charter, (b) (6) provided an independent histopathologic determination that archival tissue collected from study subjects was consistent with a past diagnosis of basal cell carcinoma (BCC). For study subjects with locally advanced BCC, (b) (4) provided a histopathologic evaluation of response in tumor biopsy tissue collected post treatment. The FDA field investigator issued a Form FDA 483 for the following violations:

1. Per the Independent Pathology Review Charter, Genentech contracted with an independent pathologist as an independent contractor to provide independent histopathologic review of archival tumor tissue and tumor biopsy tissue for all study subjects enrolled in the clinical study. The independent pathologist or Genentech did not always comply with the Charter.
   a. The inspection noted that controlled access to (b) (6) source records and her direct access to the Rave© electronic data capture system were not limited to (b) (6). The office where (b) (6) conducted her study-related work was in a Genentech controlled building to which other Genentech employees had access. At least 7 Genentech Employees, including a Genentech Pathologist, had access to her office and the file cabinet with restricted access where (b) (6) (b) (6) kept her source records including her Identifier Code and Unique password for access to the Rave© electronic data capture server. It is unknown whether or not any of the 7 Genentech Employees had used the Independent Pathologist's identifier code and unique password to enter the Rave© electronic data capture server and alter or change the Independent Pathologist's review of the study subject's tissue samples.
   b. The Charter states that, "Before the Pathologist conducts her first histopathologic review, an organizational meeting will be held between the Pathologist and the Genentech Medical Monitor, other Genentech Clinical Science representatives (as applicable), and the Genentech Research Pathologist. The purpose of this meeting will be to review the SHH4476g protocol and this Charter, and establish guidelines for the histopathologic review. This meeting may be via telephone or in person. A question and issue log will be initiated and appended to this charter, as necessary. Meeting minutes and a training record will be stored with the Pathologist's CV in the Trial Master File." The FDA field investigator was unable to verify that Genentech representatives and (b) (6) (b) (6) had such meetings as there were no meeting minutes taken. By not maintaining any meeting minutes between the Independent Pathologist and

Genentech, it is unknown exactly what was discussed regarding the clinical trial and the histopathologic review of archival tumor tissue and tumor biopsy tissue for study subjects enrolled in the clinical study.

c. The Independent Pathology Review Charter states, "Histopathologic review performed by the Pathologist is an independent function and not subject to input from Genentech, its designees, or any site involved in this clinical trial" and "The final histopathologic assessments by the Pathologist are not subject to input from Genentech, its designees, or any site involved in this clinical trial." However, there were instances where (b) (6) appears to have consulted with others. The following entries were found in the Independent Patholologist's log

By reviewing the clinical trial cases and slides with Genentech Doctors and/or Employees, it is unknown whether or not the Genentech Doctors and/or Employees influenced the Independent Pathologist's review and final histopathologic assessments of the clinical study patient samples.

OSI Reviewer's Note: These inspectional observations were discussed with DOP2 clinical reviewer, Dr. Michael Axelson on December 2, 2011, and presented at a Review Team meeting held on December 5, 2011. OSI confirmed that there were no inspectional observations that suggested any inappropriate manipulation of (b) (6) source records or any evidence that someone other than (b) (6) had logged into the electronic data capture system in her absence. (b) (6) functioned more like that of a Genentech Inc. employee instead of an independent CRO. OSI also informed Dr. Axelson that all the protocol-specific pathology slides interpreted by (b) (6) remain in archive at Genentech and may be reread at any time if the review division wishes to have a third party independent pathologist reread the tumor specimens. OSI reviewer Dr. Lauren Iacono-Connors and Dr. Michael Axelson agreed that while the circumstances related to the work environment of the Independent Pathologist/CRO were not ideal the data generated by (b) (6) may be considered reliable because there was no evidence of inappropriate manipulation of source records.

c. **Assessment of data integrity:** The data generated at this site, as it pertains to Study SHH4476g were audited in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. The findings are that the data from this Sponsor submitted to the agency in support of NDA 203388 appear reliable.

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

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for clinical investigators Dr. Oro, and Dr. Migden, study sponsor, Genentech Inc., (b) (6), (b) (4) the study data collected appear reliable.

The two clinical sites inspected, Dr. Migden (Site 25955) and Dr. Oro (Site 23735), and the study sponsor Genentech Inc. were issued a Form FDA 483 citing inspectional observations and preliminary classifications for each of these inspections are Voluntary Action Indicated (VAI). The preliminary classifications for the remaining inspections of (b) (4) the CROs responsible for generation key components of the primary efficacy endpoint data, are No Action Indicated (NAI).

The 2 clinical Sites audited revealed nothing to indicate under-reporting of AEs/SAEs. In addition, the primary efficacy endpoint data were verifiable for those sites audited via inspection of the CROs that generated key endpoint data. The inspection of Dr. Migden's site (25955) found that 3 of the 4 SAEs experienced at this site were not reported to the sponsor within 24 hours as required by the protocol, but instead were reported from 3 to 31 days of the of the site becoming aware of the event. Of the 11 consented subjects 1 was not appropriately re-consented with an updated version of the consent form. Also, certain protocol required periodic assessments were missed and there were several record keeping violations noted. The inspection of Dr. Oro's site (23735) found that the site used a site-modified informed consent form that was not IRB-approved to obtain consent from 4 of the 9 enrolled subjects. The changes included formatting issues, removing the name of one of the Research Staff and changing the "Version" number from "6" to "7". One SAE was not reported to the sponsor within 24 hours as required by the protocol, but instead was reported approximately 1 month after the site becoming aware of the event. Two subjects failed to complete an End of Treatment SF-36 Health Survey, as specified in the protocol. Also, the field investigator noted that there were several updates made to subject source documents that were either not properly initialed or dated. None of these observations were of a systemic nature and should not significantly impact data generated by this site.

The inspection of the sponsor, Genentech, Inc., found that they adequately controlled the study. The inspection also audited the conduct of the Independent Pathologist (b) (6) (b) (6) to assess the integrity of the primary efficacy endpoint component generated in accordance with the Independent Pathology Review Charter. It was found that the sponsor failed to follow their investigational plan and Independent Pathology Review Charter. Specifically, (b) (6) was to function independently and without potential outside influences. In addition, access to her source records and her entries into the eCRFs were to be restricted to (b) (6). According to the FDA field investigator

Genentech employees, including a Genentech pathologist, had access to [redacted] password which would have allowed them access to the electronic database where [redacted] had entered her assessments of the tissue samples. Therefore, [redacted] functioned more like that of a Genentech Inc. employee instead of an independent CRO. The FDA field investigator audited all source notes generated by [redacted] and compared these with the data listings submitted in the NDA 203388. No discrepancies were noted, and no obvious signs of inappropriate manipulation of source records were noted.

A limited review of the impact of these inspectional observations and further discussions with the review division medical Officer Michael Axelson and review team in December 2011 conclude that these observations would not impact data reliability or study endpoints.

Although regulatory violations were noted as described above, for Sites 25955 and 23735, they are unlikely to significantly impact primary safety and efficacy analyses. The overall data in support of this application may be considered reliable based on available information.

Note: 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.

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Susan Leibenhaut, M.D.
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Tejashri Purohit-Sheth, M.D.
Acting Division Director
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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/s/

LAUREN C IACONO-CONNORS
12/12/2011

SUSAN LEIBENHAUT
12/12/2011

TEJASHRI S PUROHIT-SHETH
12/12/2011

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

Internal Consult

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

To: Mona Patel, Regulatory Project Manager
Division of Oncology Products 2
Office of Hematology Oncology Products

From: Carole C. Broadnax, R.Ph., Pharm.D., Regulatory Review Officer
Division of Professional Promotion
Office of Prescription Drug Promotion (OPDP)

Date: December 7, 2011

Re: **NDA 203388 - ERIVEDGE (vismodegib) injection for intravenous infusion**
OPDP Comments on proposed carton and container labeling

In response to the Division of Oncology Products 2 (DOP 2) September 16, 2011, consult request, OPDP has reviewed proposed labeling (carton and container) for ERIVEDGE (vismodegib**)**.

The carton and container labeling used in this review can be found in the original application (folder 0000) at: \\CDSESUB5\EVSPROD\NDA203388\203388.enx.

OPDP does not have comments for the carton and container labeling at this time.

OPDP comments for the proposed package insert will be sent under separate cover.

Thank you for your consult. If you have any questions regarding the carton/container labeling, please contact Carole Broadnax at 301-796-0575 or Carole.Broadnax@fda.hhs.gov.

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/s/

CAROLE C BROADNAX
12/07/2011

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

Label and Labeling Review

Date:	December 6, 2011
Reviewer(s):	Richard Abate, RPh, MS, Safety Evaluator Division of Medication Error Prevention and Analysis
Team Leader	Carlos Mena-Grillasca, RPh, Team Leader Division of Medication Error Prevention and Analysis
Division Director	Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
Drug Name(s) and Strength:	Erivedge (Vismodegib) Tablets, 150 mg
Application Type/Number:	NDA 203388
Applicant:	Genentech, Inc.
OSE RCM #:	2011-3484

1 INTRODUCTION

This review summarizes the Division of Medication Error Prevention and Analysis's (DMEPA's) evaluation of the proposed labels and labeling for Erivedge (vismodegib) for NDA 203388 for vulnerabilities that could lead to medication errors.

1.1 REGULATORY HISTORY

The Application (NDA 203388) was submitted September 8, 2011 and granted Priority Review Designation on November 4, 2011.

1.2 PRODUCT INFORMATION

Erivedge (vismodegib) is a hedgehog pathway inhibitor indicated for the treatment of adult patients with advanced basal cell carcinoma (b) (4) Erivedge is an oral capsule available in a single, 150 mg, strength presentation. The dose is one capsule (150 mg) once daily. Erivedge is packaged in unit of use HDPE bottles with a child-resistant screw cap (b) (4) containing 28 capsules. Each bottle is packaged individually in a carton and stored at 68° F to 77° F (20° C to 25° C) with excursions permitted to 59° F to 86° F (15° C to 30° C).

Erivedge is proposed (b) (4) However, hospitals, physician clinics, and closed systems (b) (4) will be able to obtain Erivedge from the manufacturer without a contract. A medication guide will be included in each carton.

2 METHODS AND MATERIALS REVIEWED

Using Failure Mode and Effects Analysis[1], the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:

- Container Labels submitted September 8, 2011
- Carton Labeling submitted September 8, 2011
- Insert Labeling submitted November 18, 2011

3 RESULTS AND DISCUSSION

Our evaluation identified the following deficiencies and concerns:

3.1 CONTAINER LABELS

- The container label lacks a medication guide statement as required per 21 CFR 208.24 (d).
- The container label lacks a usual dose statement as required per 21 CFR 201.55.

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

Although both of these statements can be found on carton labeling, the unit of use bottles may be removed from the carton prior to dispensing which would remove this needed information. Additionally, the placement of the medication guide statement on the container label communicates to the pharmacist the need to dispense the medication guide included in the carton to the patient if the bottle of Erivedge is removed from the carton and placed back on the pharmacy shelf.

3.2 CARTON LABELING

- The medication guide statement appears on the side panel of the carton and lacks the prominence as required by 21 CFR 208.24 (d).
- [redacted] (b) (4) should be replaced with an image of the actual capsule which is pink and gray.

3.3 INSERT LABELING

- The first sentence of Section 2 Dosage and Administration of the Full Prescribing Information should be consistent with the corresponding section in the Highlights and include the route of administration and the dose in terms of dosage form (one capsule). [redacted] (b) (4)

  These concerns were addressed and resolved with the Division of Oncology Products 2 at the initial labeling meeting for Erivedge.

4 CONCLUSIONS AND RECOMMENDATIONS

DMEPA concludes that the proposed container label and carton labeling introduce vulnerability that can lead to medication errors because the container labels lack required statements and the container labeling includes information that may be missed. We recommend the following:

A. Container Label

1. Add a medication guide statement similar to the one included on the carton labeling to the principal display panel. The medication guide statement is required per 21 CFR 208.24(d).
2. To make space, delete [redacted] (b) (4) or relocate this warning to the side panel adjacent to the manufacturer information.
3. Include a usual dosage statement, "Usual Dosage: See prescribing information." on the side panel as required per 21 CFR 201.55. Place the statement underneath the "each capsule contains" statement above the storage instructions, if space permits.

B. Carton Labeling

1. Relocate the medication guide statement to the principal display panel as it lacks prominence as required per 21 CFR 208.24(d).
2. To make adequate space, the "Avoid pregnancy…" warning should be relocated to the current position of the medication guide statement.

3. Delete [redacted] (b) (4) or replace it with an image of the actual Erivedge capsule.

If the Division has further questions or need clarifications, please contact Sue Kang, project manager, at 301-796-4216.

1 page of draft labeling has been withheld in full as B(4)CCI/TS immediatley following this page

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/s/

RICHARD A ABATE
12/06/2011

CARLOS M MENA-GRILLASCA
12/06/2011

CAROL A HOLQUIST
12/06/2011

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

NDA	203388
Generic Name	Vismodegib (Erivedge, GDC-0449)
Sponsor	Genentech, Inc.
Indication	Advanced basal cell carcinoma
Dosage Form	Capsule
Drug Class	Hedgehog (Hh) signal pathway inhibitor
Therapeutic Dosing Regimen	150 mg q.d.
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	Not determined
Submission Number and Date	SDN 001, 8 Sep 2011
Review Division	DOP 2

1 SUMMARY

1.1 OVERALL SUMMARY OF FINDINGS

No significant QTc prolongation effect of vismodegib 150 mg was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between vismodegib 150 mg and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated in Figure 3, indicating that assay sensitivity was established.

In this randomized, blinded, mixture of parallel and crossover study, 60 healthy females received vismodegib 150 mg, placebo, and a single oral dose of moxifloxacin 400 mg. Overall summary of findings is presented in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Vismodegib 150 mg and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
Vismodegib 150 mg	12	3.9	(-0.8, 8.6)
Moxifloxacin 400 mg*	3	18.3	(13.7, 22.9)

* Multiple endpoint adjustment of three time points was applied.

Supratherapeutic doses were not studied in this thorough QT trial. Steady-state C_{max} values for the 270 and 540 mg doses were similar to that for the therapeutic dose (150 mg) due to saturable absorption and protein binding. It is important to note that the

exposures observed in the thorough QT study with 150 mg q.d. (mean C_{max}=15 μM) were lower than those observed at the same dose (150 mg) in the Phase I study (mean C_{max}=23 μM). Further, no exposure-response for ΔΔQTcF was observed with vismodegib concentrations. Vismodegib is primarily eliminated via the hepatic route. Based on the population PK analysis, the PK of patients with mild or moderate renal impairment is similar to those with normal renal function. The effect of hepatic impairment on the vismodegib pharmacokinetics is unknown since the study is ongoing.

2 PROPOSED LABEL

2.1 THE SPONSOR PROPOSED LABEL

The sponsor proposed the following language in the package insert:

(b) (4)

2.2 QT-IRT PROPOSED LABEL

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

(b) (4)

3 BACKGROUND

3.1 PRODUCT INFORMATION

Vismodegib (GDC-0449) is a small-molecule inhibitor of the Hh signal pathway. The Hedgehog (Hh) signaling pathway presents a novel and potentially beneficial target for cancer therapy. Hh signaling regulates epithelial and mesenchymal interactions in a variety of tissues during mammalian embryogenesis.

3.2 MARKET APPROVAL STATUS

Vismodegib is not approved for marketing in any country.

3.3 PRECLINICAL INFORMATION

From eCTD 2.6

"The in vitro effects of vismodegib on the hERG channel mediated ion current (IKr; rapidly activating, delayed rectifier cardiac potassium current) were evaluated in voltage-clamped HEK293 cells that stably express hERG potassium channels. At concentrations of 3 μM, 10 μM, 30 μM, and 80 μM, vismodegib inhibited hERG potassium current by (mean ± SEM) 4.9 ± 0.5%, 14.4 ± 0.3%, 40 ± 0.4%, and 77 ± 0.8%, respectively, compared to 0.2 ± 0.1% in vehicle-treated controls. The IC50 for the effect of vismodegib on hERG potassium current was 37.2 μM, which is approximately 340-fold greater than typical free plasma drug concentration in patients at steady state (0.11 μM based on a typical total drug plasma concentration of 22.3 μM).

"The purpose of this study was to assess the potential of vismodegib to affect the cardiovascular system when given by a single dose via PO gavage to conscious beagle dogs. Four male and 4 female non-naïve purebred beagles with telemetry instrument implants were used on this study. The study was separated into two dosing phases, during which the animals were assigned to two groups (control and high-dose or control and mid-dose groups). A descending dose design was used to establish a no-observable-effect level. Animals were given a single PO dose of either vehicle (0.5% hydroxypropyl methylcellulose and 0.2% polysorbate 80 in reverse osmosis water, pH 3 ± 0.2) or vismodegib at 600 or 2000 mg/kg.

"Collection of ECG, blood pressure measurements, and body temperature assessments began at least 60 minutes prior to dosing on each dosing day and continued for at least 6 hours based on the last animal's dose time and for at least 15 minutes each 30 minutes through 96 hours (± 1 hour) postdose. Administration of vismodegib at 600 or 2000 mg/kg had no toxicologically relevant effects on ECG results (RR interval, QT interval, or QT interval corrected for variations in heart rate), blood pressure measurements including heart rate, systolic, diastolic and mean arterial pressure and pulse pressure (systolic-diastolic), or on body temperatures. A complete scan of the lead II ECG waveforms after dose administration revealed no abnormalities."

Reviewer's comments: vismodegib inhibits hERG currents with low affinity.

3.4 PREVIOUS CLINICAL EXPERIENCE

From eCTD 2.7.4

"As of March 2011, more than 750 patients and healthy volunteers have been treated with vismodegib in Genentech-sponsored and NCI CTEP-sponsored clinical studies. Treatment-emergent adverse events have been seen across all studies that included patients with advanced and metastatic BCC, advanced ovarian cancer, metastatic CRC, and other refractory malignancies. In general, the overall safety profile for vismodegib was consistent across all monotherapy studies. The majority of adverse events were mild to moderate in severity.

"A total of 26.1% of patients in the pooled safety population experienced a treatment-emergent serious adverse event. The serious adverse events that occurred in 2 or more patients were death (n = 3), pneumonia (n = 3), cardiac failure (n = 2), gastrointestinal hemorrhage (n = 2), pulmonary embolism (n = 2), deep vein thrombosis (n = 2), and hemorrhage (n = 2). The expanded pooled safety population had a slightly lower incidence of serious adverse events, with 22% of vismodegib-treated patients experiencing serious adverse events.

"A total of 17 deaths (12.3%) occurred in the pooled safety population. Seven deaths were attributed to progressive disease. Eight deaths in the pooled safety population were attributed by the investigators to treatment-emergent adverse events. This number of deaths remained unchanged when the ovarian cancer patients were added to the expanded pooled safety population analysis. An analysis of the deaths does not suggest a definite pattern of events or a causal relationship to vismodegib; all the patients had significant co-morbidities and preexisting risk factors."

"Exposure–response analyses were conducted to assess the relationship between plasma concentrations of vismodegib and common adverse events in cancer patients (see Section 3.3.3 of the SCP). No clinically relevant exposure-response relationship was observed for the adverse events of weight loss, alopecia, dysgeusia, fatigue, muscle spasms, or nausea on the basis of the combined safety data from Studies SHH4476g and SHH3925g. Furthermore, there was no evidence of an effect of vismodegib plasma concentration on QTc interval prolongation.

"Study SHH3925g (Solid Tumors). No pattern of clinically significant change was identified in vital signs for any cohort (see Tables 14.2/33, 14.2/34, 14.2/35, and 14.2/36 of the SHH3925g CSR). Analyses and review of the ECG safety data collected during the study suggest that vismodegib is associated with a relatively low risk for delayed ventricular repolarization, prolongation of the QT interval, and unstable arrhythmias. The clinical observations to date are in agreement with the nonclinical data (i.e., a human ether-à-go-go–related gene, or hERG, and cardiovascular safety study in dogs), which suggested no apparent relationship between plasma vismodegib concentrations and prolongation of the QT interval (see the SHH3925g CSR Addendum).

"Study SHH4683g. Individual data of vital signs assessments, including baseline-adjusted values, were collected. There were no clinical significant changes in supine systolic and diastolic blood pressures, pulse rate, and oral body temperature. There were no findings of clinical relevance for clinical laboratories, vital signs, ECGs, or physical examinations (see Section 11.5 of the SHH4683g CSR). All ECGs were interpreted as normal or, if abnormal, as not clinically significant. No changes or trends of clinical significance were seen for the heart rate, PR interval, QRS duration, QT interval, QTcB interval, and QTcF interval. During the study, QTcB intervals and QTcF intervals > 450 msec were observed in 5 subjects and 1 subject, respectively.

"Further, QTcB intervals and QTcF intervals with a change from baseline > 30 msec were observed in 8 subjects and 0 subjects, respectively during the study.

"Study SHH4871g. No pattern of clinically significant change in vital signs was identified for any treatment group. Physical examinations of all subjects yielded normal results at all assessment visits with two exceptions: 1) 1 subject in Arm B had a clinically

significant abnormal physical finding of Grade 2 bilateral sciatica on Day 4 and 2) 1 subject in Arm C reported Grade 2 right sciatica on Day 4 (see Section 9.5 of the SHH4871g CSR). Results suggest that when vismodegib was dosed to steady state, there was no meaningful change in corrected QT interval compared with baseline. ECG safety data collected during the study support the observation that vismodegib is associated with a relatively low risk for delayed ventricular repolarization, prolongation of the QT interval, and unstable arrhythmias.

"Study SHH4433g. While the sample size was too small to draw strong conclusions, individual and mean systolic and diastolic vital signs evaluations trended downward at 4 to 8 hours post-dose but remained within normal limits. Results of all 12-lead ECGs were either normal or clinically insignificant abnormalities. Although the sample size was too small to draw strong conclusions, there appeared to be no trends in the mean 12-lead ECG results over time (see Section 8.5 of the SHH4433g CSR)."

Reviewer's comments: No sudden cardiac death or ventricular arrhythmias were reported in vismodegib's clinical program. No clinically relevant ECG changes were reported.

3.5 CLINICAL PHARMACOLOGY

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

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND (b) (4). The sponsor submitted the study report SHH4871g for vismodegib, including electronic datasets and waveforms to the ECG warehouse.

4.2 TQT STUDY

4.2.1 Title

A Multiple-dose, Randomized, Double-blind, Placebo-controlled, active-comparator, parallel-group study to investigate the effect of vismodegib on the QT/QTc interval in healthy female subjects

4.2.2 Protocol Number

SHH4871g

4.2.3 Study Dates

25 August 2010 -- 18 March 2011

4.2.4 Objectives

Primary

To evaluate whether vismodegib has a threshold pharmacological effect on cardiac repolarization, as detected by changes in electrocardiogram (ECG) QT

intervals corrected for heart rate by Fridericia's correction method (QTcF) in healthy female subjects

Secondary

- To investigate the effect of vismodegib on the following ECG parameters: PR, RR, QRS, QT, QTcB, and T-wave morphology
- To investigate the safety and tolerability of vismodegib
- To further characterize the pharmacokinetics of vismodegib
- To characterize the exposure-effect relationship (if any) between vismodegib plasma concentrations and ECG interval changes

4.2.5 Study Description

4.2.5.1 Design

This is a Phase I, single-center, three-arm, randomized, double-blind, active- and placebo-controlled study to investigate the effect of vismodegib on the QT/QTc Interval in healthy female subjects of non-childbearing potential.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

All treatment arms were administered blinded using a double dummy approach. Moxifloxacin tablets were overencapsulated.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

"This was a Phase I, single-center, three-arm, randomized, double-blind, active- and placebo-controlled study to investigate the effect of vismodegib on the QT/QTc interval in healthy female subjects of non−childbearing potential. Up to 72 subjects were to be randomized in parallel, up to 24 in each of the following three arms to ensure 20 evaluable subjects per arm:

- **Arm A:** 22 female subjects will receive 1 × 400 mg moxifloxacin and 1 × 150 mg VISMODEGIB-placebo on Day 1 followed by 1 × 400 mg moxifloxacin-placebo and 1 × 150 mg vismodegib -placebo daily from Day 2 to Day 8 inclusive.
- **Arm B:** 22 female subjects will receive 1 × 400 mg moxifloxacin-placebo and 1 × 150 mg vismodegib -placebo daily from Day 1 to Day 7 inclusive followed by 1 × 400 mg moxifloxacin and 1 × 150 mg vismodegib -placebo on Day 8.
- **Arm C:** 22 female subjects will receive 1 × 400 mg moxifloxacin-placebo daily from Day 1 to Day 8 included, 1 × 150 mg vismodegib daily from Day 1 to Day 7 inclusive, and VISMODEGIB-placebo on Day 8."

4.2.6.2 Sponsor's Justification for Doses

"In the Phase I dose-escalation study (SHH3925g), vismodegib was administered daily at doses of 150, 270, or 540 mg. The 150 mg/day vismodegib dose has been

associated with a favorable safety profile in subjects. In Study SHH3925g, 12 Grade 3 or 4 adverse events were considered related to vismodegib therapy. No Grade 5 adverse events were attributed to vismodegib. In lieu of dosing at a lower daily dose, alternative less frequent dosing was evaluated in a separate phase 1 study (SHH4610g). In that study, less frequent dosing at 150 mg led to lower plasma concentration levels, with the potential for lower efficacy. Therefore, 150 mg/day was chosen as the recommended dose for future clinical studies, including label-enabling studies, in all indications.

"Higher doses of vismodegib were administered in the Phase I trial in an attempt to identify a maximum tolerated dose. Following a single dose of 270 or 540 mg with a 7-day observation period, vismodegib plasma exposure was greater than with the 150-mg dose. However, upon continued daily dosing in the same subjects, steady-state concentrations were equivalent for the three dose levels. No additional dose escalations were performed because of a lack of an increase in exposure with increasing dose and because of the absence of DLTs at the 270- and 540-mg dose levels.

"Because of the lack of a dose-dependent increase in vismodegib steady-state exposure, it was not possible to achieve supratherapeutic plasma concentrations with increasing the dose of this drug. Therefore, the selected dose for this QT study was 150 mg, which is the dose that was used in the pivotal trial in advanced BCC (SHH4476g)."

(Source: Sponsor's Clinical Study Report, section 6.4.4, page 25)

Reviewer's Comment: The studied dose appears reasonable as higher doses did not increase steady-state exposure of vismodegib due to saturable absorption and protein binding. Steady-state C_{max} values for the 270 and 540 mg doses were 0.94- and 0.97-fold that of the C_{max} for the therapeutic dose (150 mg). It is important to note that the exposures observed in the thorough QT study with 150 mg q.d. (mean C_{max}=15 µM) were lower than those observed at the same dose (150 mg) in the Phase I study (mean C_{max}=23 µM). Vismodegib is primarily eliminated via the hepatic route. Based on the population PK analysis, the PK of patients with mild or moderate renal impairment is similar to those with normal renal function. The effect of hepatic impairment on the vismodegib pharmacokinetics is unknown since the study is ongoing.

4.2.6.3 Instructions with Regard to Meals

Subjects received 150 mg vismodegib or vismodegib-placebo and 400 mg moxifloxacin or moxifloxacin-placebo daily by mouth for 8 days (from Day 1 to Day 8 inclusive) with approximately 8 ounces (i.e., about 240 mL) of water in a fasted state (approximately a 10-hour fast).

Reviewer's Comment: No change in steady-state vismodegib concentrations was observed in the PK food-effect study. Therefore, timing of dosing with regards is not expected to affect vismodegib exposure.

4.2.6.4 ECG and PK Assessments

ECG Assessments:

> "Continuous cardiac recording started on Day −1 approximately 25 hours before the Day 1 dosing time (i.e., the first dose) and continued until 24 hours after the first dose (i.e., on Day 2), then started 1 hour before the dosing time on Day 7 until 24 hours after the last dose on Day 8. Subjects were in a supine position for at least 10 minutes before recordings and remained resting and supine during the recordings on Day −1 (time-matched to Day 1 pre-dose and 1, 2, 3, 8, and 12 hours post-dose); Day 1 (pre-dose and 1, 2, 3, 8, 12, and 24 hours post-dose); Day 7 (pre-dose and 1, 2, 3, 8, and 12 hours post-dose); and Day 8 (pre-dose and 1, 2, 3, 8, 12, and 24 hours post-dose)."
>
> *(Source: Sponsor's Clinical Study Report, page 28)*

PK Assessments:

Blood was sampled for PK on Day 1, Day 7, and Day 8: pre-dose and 1, 2, 3, 8, 12, and 24 h post-dose; on Days 2 to Day 6: pre-dose only; and on Day 9: 24 h after the Day 8 dose.

Reviewer's Comment: The timing of PK samples and ECGs is acceptable. The early time points capture the rise in concentrations. Because of the long half life, samples at 8 and 24 h describe the elimination after a single dose and steady-state concentrations after multiple doses.

4.2.6.5 Baseline

"For the comparison between vismodegib and placebo, baseline was defined as the average of the triplicate ECG measurements obtained from the scheduled timepoints on Day − 1 in each arm. The change from baseline was calculated by subtracting the baseline from the average of triplicate post-dose assessments at each scheduled timepoint on Day 7.

For the moxifloxacin arms, baseline was Day 8 for Arm A and Day 1 for Arm B."

4.2.7 ECG Collection

Twelve-lead ECGs (25 mm/second) were digitally recorded by Holter monitor. The digital ECGs files were stored. ECGs were reviewed by a central ECG laboratory in a validated ECG management system. Triplicate ECGs were extracted at the specified timepoints over a 10-minute period and within approximately 5 minutes of the specified timepoint. The subject was at rest and in a supine position 10 minutes before the extraction period and 10 minutes during the extraction period. Additional timepoints could be used to establish the individual QT/RR relationship.

Safety Twelve-lead ECGs (25 mm/sec for 10 seconds) were collected in triplicate. The timepoints selected for safety ECGs were pre-dose and 1, 2, 4, and 10 hours post-dose on Days −1, 1, 7, and 8; 4 hours on Days 2−6; and 24 hours after the last dose on Day 8 (i.e., on Day 9).

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

A total of 61 subjects were screened and enrolled in this study. Twenty subjects were enrolled in Arm A, 20 subjects in Arm B, and 21 subjects in Arm C. One subject (25042) in Arm C discontinued the study prematurely because of an adverse event (Grade 1 tachycardia).

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Table 11.1/4
Demographic and Baseline Characteristics
All Randomized Subjects

	Treatment Arm A (N=20)	Treatment Arm B (N=20)	Treatment Arm C (N=21)	All Subjects (N=61)
Age (yr)				
n	20	20	21	61
Mean (SD)	59.8 (6.1)	59.0 (4.6)	58.2 (4.9)	59.0 (5.2)
Median	60.5	58.5	59.0	59.0
Range	47 - 71	51 - 70	46 - 69	46 - 71
Sex				
Female	20 (100.0%)	20 (100.0%)	21 (100.0%)	61 (100.0%)
Race				
White	19 (95.0%)	20 (100.0%)	21 (100.0%)	60 (98.4%)
Black	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
American Indian or Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Not Available	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ethnicity				
Hispanic or Latino	1 (5.0%)	0 (0.0%)	0 (0.0%)	1 (1.6%)
Not Hispanic or Latino	19 (95.0%)	20 (100.0%)	21 (100.0%)	60 (98.4%)
Not Available	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Height (cm)				
n	20	20	21	61
Mean (SD)	160.0 (5.5)	160.7 (5.0)	161.4 (5.5)	160.7 (5.3)
Median	159.5	161.6	163.0	161.2
Range	150.0 - 168.0	150.0 - 168.3	153.0 - 174.0	150.0 - 174.0
Weight (kg)				
n	20	20	21	61
Mean (SD)	61.9 (9.5)	62.9 (8.0)	63.7 (7.6)	62.8 (8.3)
Median	61.7	61.9	62.6	62.6
Range	46.8 - 80.7	51.6 - 75.4	50.0 - 79.8	46.8 - 80.7

Arm A subjects receive Moxifloxacin on Day 1 and Placebo on Days 2 to 8; Arm B subjects receive Placebo on Days 1 to 7 and Moxifloxacin on Day 8; Arm C subjects receive GDC-0449 on Days 1 to 7 and Placebo on Day 8.
The percentages are based on the number of randomized subjects as given in the column headings.
Age is calculated using subject enrolled date and imputed birth date. Only the month and year of birth are collected due to French regulatory requirements. The mid day of the month is used as the imputed day of birth.
Source Listing: L13.2/3 and L13.2/19.

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4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

"The primary variable for the PD analysis was the QTcF (QT interval corrected by Fridericia's correction method) at timepoints on Day − 1, 1, 7, and 8 (0, 1, 2, 3, 8, 12, and 24 hours).

"To evaluate the appropriateness of the QTcF heart-rate correction, each subject's average of the triplicate QTcF intervals was plotted against the time-matched heart rate and RR interval. Visually, no apparent relationship was evident between QTcF interval and heart rate or RR interval, indicating that the Fridericia's method of correction adequately removed the dependence of the baseline QT interval on heart rate for this dataset.

"For the comparison between vismodegib and placebo, the baseline was Day -1. The baseline-adjusted QTcF interval (ΔQTcF) was calculated by subtracting Day -1 QTcF from Day 7 time-matched QTcF for all subjects. Subjects in Arms A and B were

combined for the placebo group. Per protocol, the effect of vismodegib on QTcF was considered as non-inferior to that of placebo if the upper limit of the 90% CI for the difference in mean ΔQTcF between vismodegib and placebo was ≤ 20 ms at all timepoints evaluated. The maximum upper bound of 90% CI was 10.0 ms at the 12-hour timepoint and was less than 20 ms at all timepoints evaluated as in following table."

Table 2: Analysis of Change from Baseline in QTcF at Steady-State: Vismodegib and Placebo Comparison (Sponsor's Results)

Change from baseline in QTcF	Vismodegib vs. Placebo LS Mean Difference (90% CI)
1 hour post-baseline	-1.3 (-5.0, 2.3)
2 hours post-baseline	1.0 (-2.9, 4.8)
3 hours post-baseline	-0.4 (-4.6, 3.8)
8 hours post-baseline	0.9 (-3.4, 5.3)
12 hours post-baseline	5.3 (0.5, 10.0)
24 hours post-baseline	-0.9 (-4.8, 2.9)

CI = confidence interval; LS = least squares.

Source: Sponsor's report Table 4

Reviewer's Comments: The reviewer used linear regression model instead of mixed model since this part of study is parallel. The results are similar to the sponsor's. See reviewer's analysis in section 5.2.

4.2.8.2.2 Assay Sensitivity

"For the comparison between moxifloxacin and placebo, the change from baseline for moxifloxacin and placebo was calculated for subjects in Arms A and B. For all timepoints, the 90% two-sided CI was calculated for the difference in QTcF between moxifloxacin and placebo. Per protocol, moxifloxacin had an effect on QTcF if the lower limit of the 90% CI was ≥ 5 ms for at least one timepoint. The lower limit of the 90% CI was greater than 5 ms at all timepoints evaluated with the exception of 24 hours (see following table).

"For the comparison between moxifloxacin and placebo at time t,

ΔΔQTcF = Average of the following two equations:

{QTcF [Day 1] − QTcF[Day 8]} − {QTcF[Day 7] − QTcF [Day − 1]} from Arm A and

{QTcF[Day 8] − QTcF[Day 1]} − {QTcF[Day − 1] − QTcF [Day 7]} from Arm B"

Table 3: Analysis of Change from Baseline in QTcF at Steady-State: Moxifloxacin and Placebo Comparison (Sponsor's Results)

Change from baseline in QTcF	Moxifloxacin vs. Placebo LS Mean Difference (90% CI)
1 hour post-baseline	14.1 (9.8, 18.4)
2 hours post-baseline	17.4 (12.8, 21.9)
3 hours post-baseline	19.0 (15.1, 22.8)
8 hours post-baseline	15.2 (11.1, 19.2)
12 hours post-baseline	12.6 (9.3, 16.0)
24 hours post-baseline	7.0 (3.6, 10.4)

CI = confidence interval; LS = Least Square

Source: Sponsor's report Table 7

Reviewer's Comments: The reviewer's results are similar to the sponsor's. See reviewer's analysis in section 5.2.

4.2.8.2.3 Categorical Analysis

"No subjects in the vismodegib arm (Arm C) had QTcF ≥ 450 ms. No subject who received vismodegib (Arm C) had QTcF change from baseline (Day - 1) ≥ 30 ms. Four subjects in Arms A and B had QTcF change from the baseline ≥ 30 ms. 8 subjects in the moxifloxacin group, and 1 subject in the placebo group reported QTcF change from baseline ≥ 30 ms."

4.2.8.3 Safety Analysis

The most frequently reported adverse events (> 5%) in subjects in Arm C (vismodegib) were application site erythema (due to ECG lead patches and/or medical dressing at the catheter site) (14.3%) and headache (9.5%). Most events of > 5% incidence were reported in the control Arms A and B, and only the incidence of application site erythema was higher in the vismodegib arm.

Most adverse events were Grade 1 or 2 in severity. Only 4 subjects reported Grade 3 adverse events (all four events were presyncope); none of these events were considered to be related to the study drug by the investigator.

No Grade ≥ 4 event was reported in this study.

No serious adverse event or death was reported in this study.

One adverse event (Grade 1 tachycardia) that led to study drug discontinuation was reported in 1 subject in the vismodegib arm.

4.2.8.4 Clinical Pharmacology

4.2.8.4.1 Pharmacokinetic Analysis

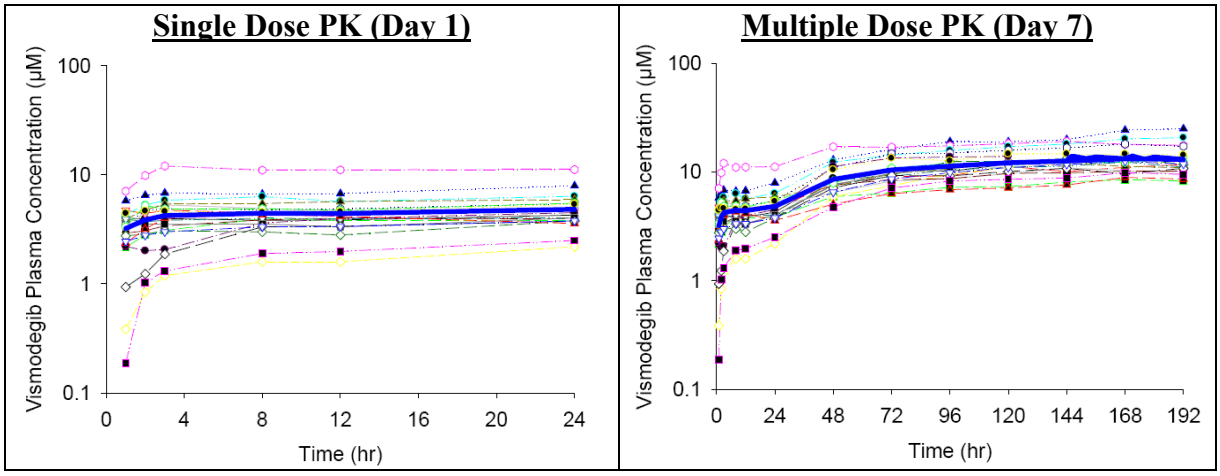
Vismodegib PK results are presented in Table 4,
Figure 1, and in Appendix 6.1. Phase 1 data indicates that at steady-state, C_{max} and AUC values from the therapeutic dose in the thorough QT study were similar to those observed with the 270 and 540 mg doses (Appendix 6.1). The fact that no increase was observed in exposure has been attributed to saturable absorption and protein binding. Table 4 shows that exposures observed in the thorough QT study were lower than those observed at the same dose (150 mg) in the Phase I study (Appendix 6.1).

Table 4: Vismodegib Single- and Multiple-dose PK Parameters

PK Parameters	Day 1	Day 7
Cmax (uM)		
N	21	20
Mean (SD)	4.93 (2.06)	14.45 (4.00)
Median	4.30	13.30
Range	2.18 - 12.00	9.54 - 24.90
Tmax (hr)		
N	21	20
Mean (SD)	18.79 (8.53)	5.95 (4.42)
Median	23.90	3.00
Range	1.27 - 23.90	1.00 - 12.00
AUC0-24 (uM*hr)		
N	21	20
Mean (SD)	102.69 (45.23)	324.24 (87.91)
Median	91.80	301.79
Range	37.20 - 255.00	217.05 - 546.24

(Source: Sponsor's Clinical Study Report, Table 11.2/17)

Figure 1: Pharmacokinetic Time Course of Vismodegib Concentrations. Profiles for individuals are shown by dashed lines and the solid blue line depicts the population mean



(Source: Sponsor's Clinical Study Report, Figures 4 & 5)

4.2.8.4.2 Exposure-Response Analysis

The sponsor did not report an exposure-response analysis for ΔΔQTcF. See Section 5.3 for the reviewer's analysis.

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the appropriateness of the correction methods the sponsor submitted (QTcF and QTcB). Baseline values were excluded in the validation. Ideally, a good correction QTc would result in no relationship of QTc and RR intervals.

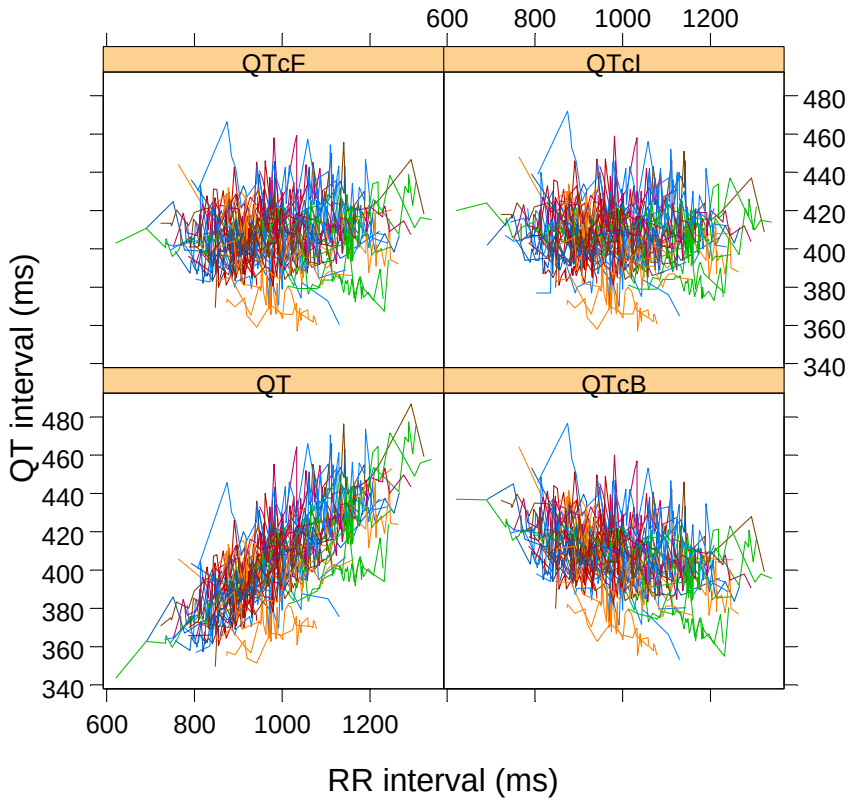
We also used the criterion of Mean Sum of Squared Slopes (MSSS) from individual regressions of QTc versus RR to evaluate the linear relationships between different correction methods and RR. The smaller this value is, the better the correction. Based on the results listed in Table 5, it also appears that QTcF is the best correction method. Therefore, this statistical reviewer used QTcF for the primary statistical analysis. This is consistent with the sponsor's choice of QTcF for their primary analysis.

Table 5: Average of Sum of Squared Slopes for Different QT-RR Correction Methods

	Treatment							
	Moxifloxacin 400 mg		Placebo		Vismodegib 150 mg		Overall	
Method	N	MSSS	N	MSSS	N	MSSS	N	MSSS
QTcB	40	0.0113	60	0.0061	21	0.0083	61	0.0085
QTcF	40	0.0074	60	0.0023	21	0.0028	61	0.0028

The relationship between different correction methods and RR is presented in Figure 2.

Figure 2: QT, QTcB, 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 Vismodegib

The statistical reviewer used linear regression model to analyze the ΔQTcF effect. Baseline values are also included in the model as a covariate. The analysis results are listed in the following tables.

Table 6: Analysis Results of ΔQTcF and ΔΔQTcF for Treatment Group = Vismodegib 150 mg

	Vismodegib 150 mg	Placebo	ΔΔQTcF	
Time/(hr)	Mean	Mean	Diff LS Mean	90% CI
0	-8.7	-8.1	-0.6	(-4.4, 3.2)
1	-8.8	-6.9	-1.9	(-5.4, 1.5)
2	-6.4	-6.6	0.2	(-3.2, 3.6)
3	-4.9	-4.1	-0.9	(-4.9, 3.2)
8	-3.0	-3.3	0.4	(-4.0, 4.7)
12	2.3	-1.6	3.9	(-0.8, 8.6)
24	-1.0	0.6	-1.6	(-5.4, 2.1)

The largest upper bound of the 2-sided 90% CI for the mean difference between vismodegib 150 mg and placebo was 8.6 ms at 12 hours after dose.

5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 7. The largest 90% lower confidence interval is 13.7 ms by considering Bonferroni multiple endpoint adjustment of 3 time points at 3 hours after dose, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

Table 7: Analysis Results of ΔQTcF and ΔΔQTcF for Moxifloxacin

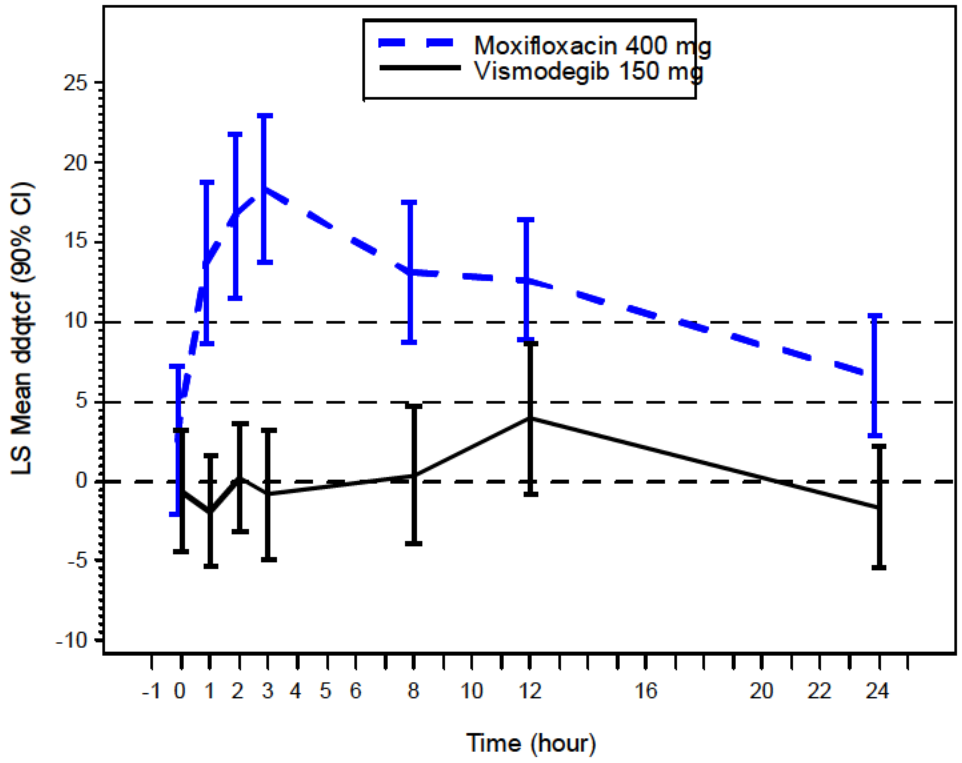
	Moxifloxacin 400 mg	Placebo	ΔΔQTcF	
Time/(hr)	Mean	Mean	Diff LS Mean	90% CI
0	0.3	-2.3	2.6	(-2.1, 7.3)
1	13.5	-0.1	13.7	(8.6, 18.7)
2	15.2	-1.5	16.7	(11.5, 21.8)
3	17.4	-0.9	18.3	(13.7, 22.9)
8	12.8	-0.3	13.1	(8.7, 17.5)
12	11.5	-1.1	12.6	(8.8, 16.4)
24	6.1	-0.6	6.6	(2.9, 10.4)

* Bonferroni method was applied for multiple endpoint adjustment for 3 time points.

5.2.1.3 Graph of ΔΔQTcF Over Time

The following figure displays the time profile of ΔΔQTcF for different treatment groups.

Figure 3: Mean and 90% CI ΔΔQTcF Timecourse



5.2.1.4 Categorical Analysis

Table 8 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 8: Categorical Analysis for QTcF

	Total N		Value<=450 ms		450 ms<Value<=480 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Baseline	61	305	61 (100%)	305 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	40	240	36 (90.0%)	232 (96.7%)	4 (10.0%)	8 (3.3%)
Placebo	60	360	60 (100%)	360 (100%)	0 (0.0%)	0 (0.0%)
Vismodegib 150 mg	21	126	21 (100%)	126 (100%)	0 (0.0%)	0 (0.0%)

Table 9 lists the categorical analysis results for ΔQTcF. No subject's change from baseline was above 60 ms.

Table 9: Categorical Analysis of ΔQTcF

	Total N		Value<=30 ms		30 ms<Value<=60 ms	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Moxifloxacin 400 mg	40	239	36 (90.0%)	233 (97.5%)	4 (10.0%)	6 (2.5%)
Placebo	40	238	40 (100%)	238 (100%)	0 (0.0%)	0 (0.0%)
Vismodegib 150 mg	20	119	20 (100%)	119 (100%)	0 (0.0%)	0 (0.0%)

5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 10. The largest upper limits of 90% CI for the HR mean differences between vismodegib 150 mg and placebo is 4.6 bpm.

Table 10: Analysis Results of ΔHR and ΔΔHR for Treatment Group = Vismodegib 150 mg

	Vismodegib 150 mg	Placebo	ΔΔHR	
Time/(hr)	Mean	Mean	Diff LS Mean	90% CI
0	1.2	2.0	-0.8	(-2.7, 1.2)
1	-0.4	1.6	-2.0	(-4.2, 0.2)
2	0.7	0.7	0.1	(-1.8, 1.9)
3	0.4	0.3	0.1	(-1.8, 2.0)
8	1.0	0.2	0.8	(-1.7, 3.3)
12	1.7	-0.9	2.6	(0.6, 4.6)
24	-1.3	-0.7	-0.6	(-2.6, 1.4)

5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 11. The largest upper limits of 90% CI for the PR mean differences between vismodegib 150 mg and placebo is 3.2 ms.

Table 11: Analysis Results of ΔPR and ΔΔPR for Treatment Group = Vismodegib 150 mg

	Vismodegib 150 mg	Placebo	ΔΔPR	
Time/(hr)	Mean	Mean	Diff LS Mean	90% CI
1	3.4	3.9	-0.5	(-4.2, 3.2)
2	1.8	3.9	-2.1	(-5.7, 1.4)
3	2.7	4.2	-1.5	(-5.3, 2.3)
8	0.2	3.7	-3.5	(-7.2, 0.2)
12	-0.4	5.1	-5.6	(-9.2, -2.0)
24	3.5	4.7	-1.2	(-5.2, 2.8)

5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 12. The largest upper limits of 90% CI for the QRS mean differences between vismodegib 150 mg and placebo is 3.5 ms.

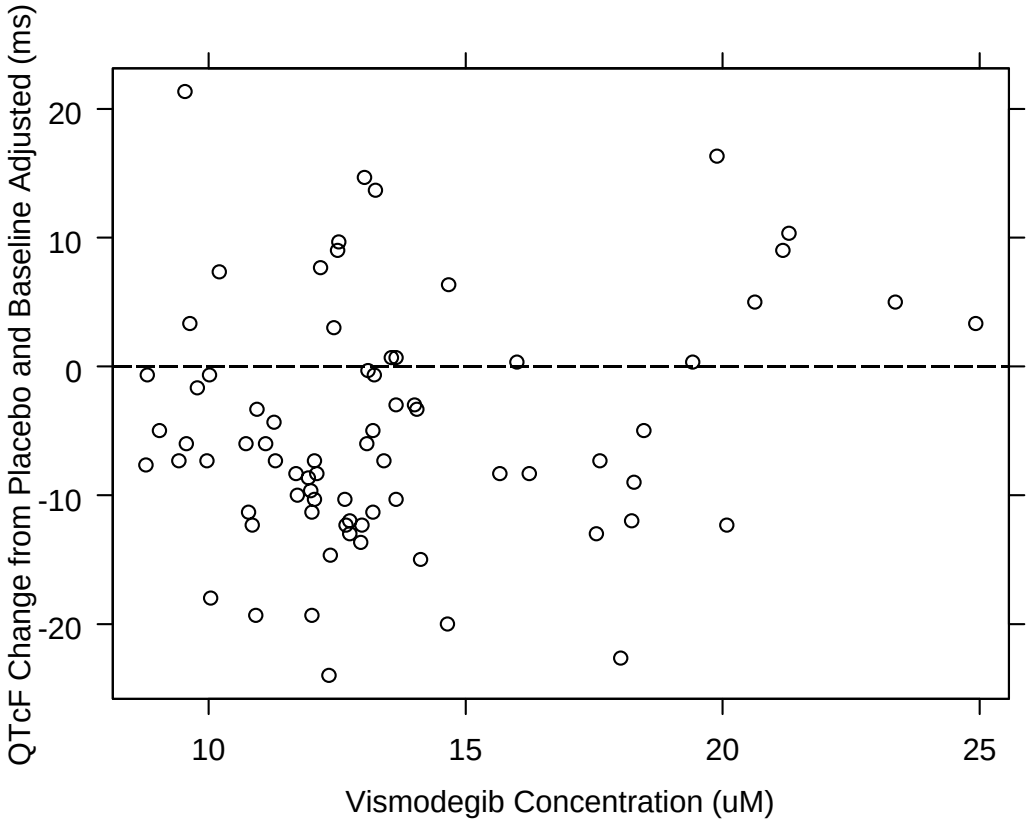
Table 12: Analysis Results of ΔQRS and ΔΔQRS for Treatment Group = Vismodegib 150 mg

	Vismodegib 150 mg	Placebo	ΔΔQRS	
Time/(hr)	Mean	Mean	Diff LS Mean	90% CI
0	-0.9	-1.4	0.5	(-0.9, 1.9)
1	-0.5	-0.7	0.2	(-1.4, 1.9)
2	1.1	-0.9	2.0	(0.6, 3.3)
3	0.1	-1.0	1.1	(-0.3, 2.4)
8	0.4	-1.3	1.8	(0.4, 3.1)
12	0.4	-1.8	2.2	(0.9, 3.5)
24	-0.2	-1.1	0.9	(-0.9, 2.6)

5.3 Clinical Pharmacology Assessments

The relationship between ΔΔQTcF and drug concentrations is visualized in Figure 4 with no evident exposure-response relationship.

Figure 4: ΔΔ QTcF vs. Vismodegib Concentration



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG assessments

Waveforms from the ECG warehouse were reviewed. According to ECG warehouse statistics 96% of the ECGs were annotated in the primary lead II, with less than 0.5% of ECGs reported to have significant QT bias, according to the automated algorithm. Overall ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS Interval

Three subjects had a PR > 200 ms at baseline and no post-baseline increases were reported.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic Dose	Include maximum proposed clinical dosing regimen 150 mg QD	
Maximum Tolerated Dose	Include if studied or NOAEL dose 150, 270 and 540 mg dose levels were evaluated. MTD was not reached.	
Principal Adverse Events	Include most common adverse events; dose limiting adverse events AEs seen in ≥30% of patients (pooled safety population): muscle spasm, alopecia, dysgeusia, weight loss, fatigue, and nausea.	
Maximum Dose Tested	Single Dose	Specify dose: 540 mg
	Multiple Dose	Specify dosing interval and duration QD continuous
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) Cmax and AUC 150 mg: C_{max}=3.58 µM (37%) AUC_{0-24}=53.2 µM*hr (44%) 270 mg: C_{max}=6.33 µM (54%) AUC_{0-24}=102 µM*hr (46%) 540 mg: C_{max}=6.81 µM (39%) AUC_{0-24}=115 µM*hr (46%)
	Multiple Dose	Mean (%CV) Cmax and AUC 150 mg: C_{ss}=22.6 µM (48%); $^{+}AUC_{0-24}$=359 µM*hr (52%) 270 mg: C_{max}=21.3 µM (52%) 540 mg: C_{max}=22.0 µM (36%)
Range of Linear PK	Specify dosing regimen PK is nonlinear due to saturable absorption and protein binding.	
$^{+}$Accumulation at Steady State	Mean (%CV); specify dosing regimen 150 mg QD: 6.64 (36%)	
Metabolites	Include listing of all metabolites and activity Parent compound was predominant (98%) in human plasma. Seven minor metabolites from pooled human plasma, urine, and feces: oxidative (M1, M3, and M14), glucuronides (M4 and M5), and pyridine ring cleavage (M13 and M18).	
Absorption	Absolute/Relative Bioavailability	Mean (%CV) 31.8 (14%)
	Tmax	•Median (range) for parent: 24 hours (1–48 hours) •Median (range) for metabolites N/A

Distribution	Vd/F or Vd	Mean (%CV) Single Dose: 16.4 L (11%) Steady State: 26.8 L (22%)
	% bound	Mean (%CV) Single Dose: 99.7 (60%) Steady State: 99.3 (44%)
Elimination	Route	•Primary route; percent dose eliminated Hepatic; 82.2% recovery in feces •Other routes Renal is minimal with only 4.43% recovery in urine.
	Terminal t½	•Mean (%CV) for parent Single Dose: 12 days (18%) Steady State: 4 days •Mean (%CV) for metabolites N/A
	CL/F or CL	Mean (%CV) Single Dose: 0.0434 L/hr (31%) Steady State: 0.0785 L/hr (21%)
Intrinsic Factors	Age	Specify mean changes in Cmax and AUC In the Population PK analysis, age was identified as statistically significant covariate ($p < 0.01$) for vismodegib $CL_{unbound}$, but sensitivity analysis suggested that it had no clinically significant impact on Css. (≤5% on total vismodegib, ≤17% on unbound vismodegib).
	Sex	Specify mean changes in Cmax and AUC Based on Population PK analysis, sex did not appear to affect the concentration of vismodegib.
	Race	Specify mean changes in Cmax and AUC Not evaluated.
	Hepatic & Renal Impairment	Specify mean changes in Cmax and AUC Hepatic/renal PK study (GP27839) ongoing. No impact of CrCL or hepatic function (ALT, AST, total protein, and bilirubin) on PK of vismodegib based on population PK analysis.

<table>
<tr><td>Extrinsic Factors</td><td>Drug Interactions</td><td>Include listing of studied DDI studies with mean changes in Cmax and AUC
SHH4593g study ongoing.</td></tr>
<tr><td></td><td>Food Effects</td><td>Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)
<table>
<tr><th colspan="2" rowspan="2">Group</th><th colspan="2">Mean change compared to fasted group</th></tr>
<tr><th>C_{max}</th><th>$AUC_{0\text{-}168}$</th></tr>
<tr><td rowspan="2">Single dose</td><td>Low-fat</td><td>1.13 fold</td><td>1.11 fold</td></tr>
<tr><td>High-fat</td><td>1.38 fold</td><td>1.32 fold</td></tr>
<tr><td>Multiple dose</td><td>Fed</td><td>No change*</td><td>No change*</td></tr>
</table>
* The GMRs were within the pre-defined 90% CI of (67%, 150%) as specified by the protocol.</td></tr>
<tr><td>Expected High Clinical Exposure Scenario</td><td colspan="2">Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.
Given the strong correlation between AAG and steady state concentrations of vismodegib (total concentrations), high clinical exposures can be expected in patients with high AAG levels. High drug concentrations may also reached in patients with severe hepatic impairment as vismodegib is primarily eliminated via the hepatic route.</td></tr>
</table>

+Calculated based on data from 3 subjects with extensive PK sampling on D15 in the phase I study.

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/s/

QIANYU DANG
11/23/2011

JOANNE ZHANG
11/28/2011

JUSTIN C EARP
11/29/2011

NITIN MEHROTRA
11/29/2011

MONICA L FISZMAN
11/29/2011

NORMAN L STOCKBRIDGE
11/30/2011

REGULATORY PROJECT MANAGER
PLR FORMAT LABELING REVIEW

Application: NDA 203388

Name of Drug: Erivedge (vismodegib) 150 mg oral capsule

Applicant: Genentech, Inc.

Labeling Reviewed

Submission Date: September 8, 2011

Receipt Date: September 8, 2011

Background and Summary Description

This application is for a New Molecular Entity to treat adult patients with advanced basal cell carcinoma (b) (4) This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidances(s), and FDA recommendations to provide for labeling quality and consistency across review divisions.

Review

The submitted labeling was reviewed in accordance with the labeling requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" section of this review. Labeling deficiencies are identified in this section with an "X" in the checkbox next to the labeling requirement.

In addition, the following labeling issues were identified:

General Comments

1. Command language is not used throughout labeling.

Highlights

2. The drug proper name located following the tradename in the Highlights heading should be in parentheses and not brackets, e.g. Tradename (vismodegib).
3. Each summarized statement under the appropriate Highlights heading must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information. The DOSAGE AND ADMINISTRATION statement should reference section 2 of FPI.

4. White spacing is not consistent.
5. All headings should be presented in the center of a horizontal line.

(b) (4)

8. Contact information (name, telephone number, and web address) needs to be added for reporting suspected adverse reactions.
9. The revision date at the end of Highlights replaces the (b) (4) date at the end of the full prescribing information and should not appear in both places. (b) (4)

Table of Contents

10. The same title for the boxed warning should appear in the HL, FPI and TOC.
11. The statement (b) (4) should read as "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information

12. Identifying numbers should be presented in bold print and should precede the heading or subheading by at least two squares of the size of the letter "m" in 8 point type. Specifically, spacing needs to be adjusted for section and subheadings under section 12 and 13.

(b) (4)

15. In the Boxed Warning, subsection 5.1 is not cross-referenced. Clarification should be requested from the applicant.
16. A bullet should be used for each contraindication rather than subsections.

(b) (4)

18. In section 6.1, paragraph 1, line 3, please add the word "clinical" before the word "practice."

19. If requirements do not support a pediatric indication, the following statement: “Safety and effectiveness have not been established in pediatric patients” needs to be added in subsection 8.4.
20. In section 16, the units in which the dosage form is ordinarily available for prescribing by practitioners should be stated (e.g., bottles of #) is not included.
21. The statement “See FDA-approved patient labeling (Medication Guide)” should appear at the beginning of Section 17 to give it prominence.
22. The manufacturer name and address information is not identical between FPI and MG. Request that applicant clarify why they are different.

Conclusions/Recommendations

The applicant should address the identified deficiencies and resubmit labeling no later than November 23, 2011. The resubmitted labeling will be used for further labeling discussions.

Regulatory Project Manager Date

Chief, Project Management Staff Date

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**

☐ HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.

☐ HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.

☐ There is no redundancy of information.

☐ If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)

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

☒ All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.

☒ Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.

☐ Section headings are presented in the following order:

• **Highlights Limitation Statement** (required statement)
• **Drug names, dosage form, route of administration, and controlled substance symbol, if applicable** (required information)
• **Initial U.S. Approval** (required information)
• **Boxed Warning** (if applicable)
• **Recent Major Changes** (for a supplement)
• **Indications and Usage** (required information)
• **Dosage and Administration** (required information)
• **Dosage Forms and Strengths** (required information)
• **Contraindications** (required heading – if no contraindications are known, it must state “None”)
• **Warnings and Precautions** (required information)
• **Adverse Reactions** (required AR contact reporting statement)
• **Drug Interactions** (optional heading)
• **Use in Specific Populations** (optional heading)
• **Patient Counseling Information Statement** (required statement)
• **Revision Date** (required information)

- **Highlights Limitation Statement**
  - ☐ Must be placed at the beginning of HL, **bolded,** and read as follows: "**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE)**."

- **Product Title**
  - ☐ Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol.

- **Initial U.S. Approval**
  - ☐ The verbatim statement "Initial U.S. Approval" followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.

- **Boxed Warning**
  - ☐ All text in the boxed warning is **bolded**.
  - ☐ Summary of the warning must not exceed a length of 20 lines.
  - ☐ Requires a heading in UPPER-CASE, **bolded** letters containing the word "**WARNING**" and other words to identify the subject of the warning (e.g.,"**WARNING: LIFE-THREATENING ADVERSE REACTIONS**").
  - ☐ Must have the verbatim statement "***See full prescribing information for complete boxed warning***." If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.

- **Recent Major Changes (RMC)**
  - ☐ Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
  - ☐ The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, "Dosage and Administration, Coronary Stenting (2.2) --- 2/2010."
  - ☐ For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line ("margin mark") on the left edge.
  - ☐ A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
  - ☐ Removal of a section or subsection should be noted. For example, "Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010."

- **Indications and Usage**

  ☐ If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)].” Identify the established pharmacologic class for the drug at:

  http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm.

- **Contraindications**

  ☐ This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”

  ☐ All contraindications listed in the FPI must also be listed in HL.

  ☐ List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.

  ☒ For drugs with a pregnancy Category (b)(4) state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

  ☐ Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).

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

- **Patient Counseling Information Statement**

  ☐ Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**.

- **Revision Date**

  ☐ A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval.

Contents: Table of Contents (TOC)

☐ The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.

☒ The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.

☐ All section headings must be in **bold** type, and subsection headings must be indented and not bolded.

☐ When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:

8.1 Pregnancy

8.3 Nursing Mothers (not 8.2)

8.4 Pediatric Use (not 8.3)

8.5 Geriatric Use (not 8.4)

☐ If a section or subsection is omitted from the FPI and TOC, the heading "**Full Prescribing Information: Contents**" must be followed by an asterisk and the following statement must appear at the end of TOC: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI)

- **General Format**

☐ A horizontal line must separate the TOC and FPI.

☐ The heading – **FULL PRESCRIBING INFORMATION** – must appear at the beginning in UPPER CASE and **bold** type.

☐ The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

- **Boxed Warning**

☐ Must have a heading, in UPPER CASE, **bold** type, containing the word "**WARNING**" and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.

☒ Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

- **Contraindications**

☒ For Pregnancy Category (b)(4) drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

  ☐ Only "adverse reactions" as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as "adverse events" or "treatment-emergent adverse events," should be avoided.

  ☒ For the "Clinical Trials Experience" subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

  ☐ For the "Postmarketing Experience" subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

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

- **Use in Specific Populations**

  ☐ Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

  ☐ This section is required and cannot be omitted.

  ☒ Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement "See FDA-approved patient labeling (insert type of patient labeling)." should appear at the beginning of Section 17 for prominence. For example:

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

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/s/

MONA G PATEL
11/14/2011

KAREN D JONES
11/15/2011

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 # 203388 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Erivedge Established/Proper Name: vismodegib Dosage Form: capsule Strengths: 150mg		
Applicant: Genentech, Inc. Agent for Applicant (if applicable):		
Date of Application: September 8, 2011 Date of Receipt: September 8, 2011 Date clock started after UN: NA		
PDUFA Goal Date: March 8, 2012	Action Goal Date (if different): February 3, 2012	
Filing Date: November 7, 2011	Date of Filing Meeting: October 4, 2011	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1		
Proposed indication(s)/Proposed change(s): Advanced Basal Cell Carcinoma		

Type of Original NDA: AND (if applicable) Type of NDA Supplement: ***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.***	☒ 505(b)(1) ☐ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)
Review Classification: ***If the application includes a complete response to pediatric WR, review classification is Priority.*** ***If a tropical disease priority review voucher was submitted, review classification is Priority.***	☐ Standard ☒ Priority ☐ Tropical Disease Priority Review Voucher submitted
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system ☐ Pre-filled biologic delivery device/system ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Drug/Biologic ☐ Separate products requiring cross-labeling ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)
☐ Fast Track ☐ Rolling Review	☐ PMC response ☐ PMR response:

☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (*if OTC product*):

List referenced IND Number(s): 74573 & 103846

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA and Action Goal dates correct in tracking system? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? ***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.***	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)? ***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*** ***If no, ask the document room staff to make the appropriate entries.***	P			
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***		X		
If yes, explain in comment column.			X	
If affected by AIP, has OC/DMPQ been notified of the submission? **If yes,** date notified:			X	
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			

User Fee Status	Payment for this application:
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	☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required

and contact user fee staff.	
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.	Payment of other user fees: ☒ Not in arrears ☐ In arrears

505(b)(2) **(NDAs/NDA Efficacy Supplements only)**	**YES**	**NO**	**NA**	**Comment**
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X	
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)].**			X	
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)]?** ***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***			X	
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*** **If yes**, please list below:			X	

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

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.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
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***		X		

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)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***			X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? ***(NDAs/NDA efficacy supplements only)*** **If yes**, # years requested: 5 ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	X			Applicant cites 21 CFR 314.108(b)(2) for 5 years exclusivitiy
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (***NDAs only***)?		X		
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)? ***If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.***			X	

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

[1] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf

☒ legible ☒ English (or translated into English) ☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #			**X**	
Forms and Certifications				
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.*				
Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	X			
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	X			
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	X			
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	X			
Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature?	X			

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]. ***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…"*				
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***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)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***			X	The applicant did submit a field copy certification although not required for this electronic submission

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

Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC RPM (PeRC meeting is required)***[2] ***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.*	X			PerC notified and will go before Perc on 11.16.11.
If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?		X		Full waiver **requested** in original application; pediatric plan submitted in an

[2] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm

				amendment 9/30/11.
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? ***If no, request in 74-day letter***	X			See block above.
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)? ***If no, request in 74-day letter***	X			
<u>BPCA</u> (NDAs/NDA efficacy supplements only): Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)***[3]		X		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	X			
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ DCRMS via the DCRMSRMP mailbox***	X			Consult to OSE/DRISK submitted on 9.15.2011
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☒ Medication Guide (MedGuide) ☒ Carton labels ☒ Immediate container labels ☐ Diluent ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request in 74-day letter.***	X			
Is the PI submitted in PLR format?[4]	X			

[3] http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.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? ***If no waiver or deferral, request PLR format in 74-day letter.***			X	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			Consult Request sent on 9.16.11
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (*send WORD version if available*)	X			Consult Request sent on 9.15.11
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	X			
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted? ***If no, request in 74-day letter.***			X	
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***			X	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***			X	
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?			X	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	X			QT-IRT: Sent 9/21/2011,MHT: Sent 9/21/11
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):** ***If yes, distribute minutes before filing meeting***		X		

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm

Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 5/10/11 & 5/11/11 ***If yes, distribute minutes before filing meeting***	X			
Any Special Protocol Assessments (SPAs)? **Date(s):** 9/11/08 & 1/5/09 ***If yes, distribute letter and/or relevant minutes before filing meeting***	X			Applicant submitted SPA request twice; no agreement reached.

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 4, 2011

NDA #: 203388

PROPRIETARY NAME: Erivedge

ESTABLISHED/PROPER NAME: vismodegib

DOSAGE FORM/STRENGTH: Capsule, 150 mg

APPLICANT: Genentech, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Advanced basal cell carcinoma

BACKGROUND: Genentech, Incorporated has submitted a New Drug Application (NDA) for vismodegib, new molecular entity, on September 8, 2011, received by FDA on September 8, 2011. Vismodegib is indicated for the treatment of adult patients with advanced basal cell carcinoma (b) (4). Since October 2006, the clinical development of vismodegib has been conducted under Genentech's IND 74573 and NCI's IND 103846.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Mona Patel	Y
	CPMS/TL:	Karen Jones	Y
Cross-Discipline Team Leader (CDTL)	Ke Liu		Y
Clinical	Reviewer:	Michael Axelson	N
	TL:	Ke Liu	Y
Social Scientist Review (*for OTC products*)	Reviewer:		
	TL:		
OTC Labeling Review (*for OTC products*)	Reviewer:		
	TL:		
Clinical Microbiology (*for antimicrobial products*)	Reviewer:		

	TL:		
Clinical Pharmacology	Reviewer:	Jian Wang	Y
	TL:	Hong Zhao	Y
Biostatistics	Reviewer:	Xiaoping (Janet) Jiang	Y
	TL:	Kun He	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Dubravaka Kufrin	Y
	TL:	Todd Palmby	Y
Statistics (carcinogenicity)	Reviewer:	N/A	
	TL:	N/A	
Immunogenicity (assay/assay validation) *(for BLAs/BLA efficacy supplements)*	Reviewer:	N/A	
	TL:	N/A	
Product Quality (CMC)	Reviewer:	Anne MarieRussell; Zedong Dong	N N
	TL:	Liang Zhou	Y
Quality Microbiology *(for sterile products)*	Reviewer:	John Metcalfe	Y
	TL:	David Hussong	N
CMC Labeling Review	Reviewer:	N/A	
	TL:	N/A	
Facility Review/Inspection	Reviewer:	Mahesh Ramanadham	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Rick Abate	Y
	TL:	Lubna Merchant	N
OSE/DRISK (REMS)	Reviewer:	Amarilys Vega	Y
	TL:	Cynthia LaCivita	N
OC/DCRMS (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (DSI)	Reviewer:	Lauren Iacono-Connors	N
	TL:		
Controlled Substance Staff (CSS)	Reviewer:	N/A	
	TL:	N/A	
Other reviewers	Tammie B. Howard (MHT) Carole Broadnax (OPDP) Karen Munoz (OPDP) Christian Grimstein (DCPIII)		Y N N Y
Other attendees	Patricia Keegan Richard Pazdur Jeff Summers Deborah Mesmer Sarah P. Miksinski		Y Y Y Y Y

FILING MEETING DISCUSSION:

GENERAL • 505(b)(2) filing issues? **If yes,** list issues:	☒ Not Applicable ☐ YES ☐ NO
• Per reviewers, are all parts in English or English translation? **If no**, explain:	☒ YES ☐ NO
• Electronic Submission comments **List comments**:	☐ Not Applicable eCTD submission-no filing issues
CLINICAL **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• Clinical study site(s) inspections(s) needed? **If no,** explain:	☒ YES ☐ NO
• Advisory Committee Meeting needed? **Comments**:	☐ YES Date if known: ☒ NO ☐ To be determined

If no, for an original NME or BLA application, include the reason. For example: o ***this drug/biologic is not the first in its class*** o ***the clinical study design was acceptable*** o ***the application did not raise significant safety or efficacy issues*** o ***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***	Reason: ***the application did not raise significant safety or efficacy issues***
• Abuse Liability/Potential **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
• 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? **Comments**:	☒ Not Applicable ☐ YES ☐ NO
CLINICAL MICROBIOLOGY **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CLINICAL PHARMACOLOGY **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
• Clinical pharmacology study site(s) inspections(s) needed?	☐ YES ☒ NO
BIOSTATISTICS **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE

Comments:	☐ Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
PRODUCT QUALITY (CMC) **Comments**:	☐ Not Applicable ☒ FILE ☐ REFUSE TO FILE ☒ Review issues for 74-day letter
<u>Environmental Assessment</u> • Categorical exclusion for environmental assessment (EA) requested? **If no**, was a complete EA submitted? **If EA submitted**, consulted to EA officer (OPS)? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☐ YES ☐ NO ☒ YES ☐ NO
<u>Quality Microbiology</u> (for sterile products) • Was the Microbiology Team consulted for validation of sterilization? (**NDAs/NDA supplements only**) **Comments**: 1 comment to be issued with 74 day letter	☐ Not Applicable ☒ YES ☐ NO
<u>Facility Inspection</u> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? **Comments**:	☐ Not Applicable ☒ YES ☐ NO ☒ YES ☐ NO

Facility/Microbiology Review (BLAs only) **Comments**:	☒ Not Applicable ☐ FILE ☐ REFUSE TO FILE ☐ Review issues for 74-day letter
CMC Labeling Review **Comments**:	 ☐ Review issues for 74-day letter

REGULATORY PROJECT MANAGEMENT

Signatory Authority: Richard Pazdur

21st Century Review Milestones (see attached) (listing review milestones in this document is optional):

Comments:

REGULATORY CONCLUSIONS/DEFICIENCIES

☐	The application is unsuitable for filing. Explain why:
☒	The application, on its face, appears to be suitable for filing. Review Issues: ☐ No review issues have been identified for the 74-day letter. ☒ Review issues have been identified for the 74-day letter. List (optional): Review Classification: ☐ Standard Review ☒ Priority Review

ACTIONS ITEMS

☒	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).
☐	If RTF, notify everybody who already received a consult request, OSE PM, and Product Quality PM (to cancel EER/TBP-EER).
☐	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.

☐	BLA/BLA supplements: If filed, send 60-day filing letter
☒	If priority review: • 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)
☒	Send review issues/no review issues by day 74
☒	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
☐	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]
☐	Other

Mona G. Patel	11.3.2011
Regulatory Project Manager	Date
Karen D. Jones	11.4.2011
Chief, Project Management Staff	Date

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/s/

MONA G PATEL
11/04/2011

KAREN D JONES
11/04/2011

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

Memorandum

DATE: November 3, 2011

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

SUBJECT: Designation of NDA application review status
Sponsor: Genentech, Incorporated
Product: vismodegib (capsules)
Indication: Treatment of adult patients with advanced basal cell carcinoma [redacted] (b) (4)

TO: NDA 203388

The review status of this file submitted as a NDA application is designated to be:

☐ Standard (10 Months) ☒ Priority (6 Months)

Patricia Keegan, M.D.:_____

{See appended electronic signature page}

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/s/

MONA G PATEL
11/03/2011

PATRICIA KEEGAN
11/03/2011

DSI CONSULT: Request for Clinical Inspections

Date: September 21, 2011

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Lauren Iacono-Connor, M.D., Regulatory Director
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Michael Axelson, Medical Officer, OODP/DOP2
Ke Liu, Team Leader, OODP/DOP2
Patricia Keegan, M.D. Director, DOP2

From: Mona Patel, Regulatory Project Manager, OHOP/DOP2

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 203388/0
Applicant/ Applicant contact information (to include phone/email):
Genentech, Inc.
Contact: Sarah Wayson, Ph.D.
Scientist, Regulatory Affairs-Oncology.
1 DNA Way.
South San Francisco, CA 94080
Direct:650-225-7928
e-mail:wayson.sarah@gene.com

Drug Proprietary Name: [vismodegib (generic)]
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(s): Treatment of adult patients with advanced basal cell carcinoma (b) (4)

PDUFA date: March 8, 2012
Action Goal Date: February 3, 2012
Inspection Summary Goal Date: January 20, 2012

II. Protocol/Site Identification

The applicant conducted the pivotal trial (Pivotal Phase 2, Multicenter, Single-Arm, Two-Cohort Trial Evaluating the Efficacy and Safety of GDC-0449 in Patients with Advanced Basal Cell Carcinoma) at 31 sites in Australia, Belgium, France, Germany, the United Kingdom and the United States. The trial was an industry-sponsored study.

We request site inspections at the following sites (in descending order of priority). Note that protocol deviations below refer to major inclusion criteria protocol deviations:

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
S23735 – Anthony E. Oro, M.D., Ph.D. Stanford University Medical Center 269 Campus Drive CCSR, Room 2145 Stanford, CA 94305 USA oro@standford.edu 650-723-7843 (phone) 650-723-8762 (fax)	SHH4476g	8	3 protocol deviations
S25955 - Michael R. Migden, M.D. MD Anderson Cancer Center 6655 Travis Street, Suite 650 Houston, TX 77030 USA email 713-563-2772 (phone) 713-563-2771 (fax)	SHH4476g	11	Highest enrolling site.

III. Site Selection/Rationale

This DSI consult request is to assist in the evaluation of data integrity for a new drug application for a new molecular entity. The sites were chosen based upon an analysis of site-specific efficacy data, number and types of protocol deviations, and patient number enrolled at each site.

Domestic Inspections:

Reasons for inspections (please check all that apply):

__X__ Enrollment of large numbers of study subjects
___ High treatment responders (specify):
__X__ 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.
__X__ Other (specify): substantial protocol violations that may be pertinent to efficacy analysis

International Inspections:

Reasons for inspections (please check all that apply):

_____ There are insufficient domestic data
____ 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.
_____ Enrollment of large numbers of study subjects, site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study.

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): Not applicable.

Should you require any additional information, please contact Mona Patel at 301-796-4236 or Michael Axelson *at* 301-796-5225.

Concurrence: (as needed)

__Michael Axelson,_____ Medical Reviewer
__ Ke Liu _____ Medical Team Leader
_____ Division Director (for foreign inspection requests or requests for 5 or more sites only)

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

/s/

MONA G PATEL
09/23/2011

MICHAEL AXELSON
09/23/2011

KE LIU
09/23/2011