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RESEARCH**

APPLICATION NUMBER:

206192Orig1s000

SUMMARY REVIEW

Division Director Summary Review

Date	November 4, 2015
From	Patricia Keegan
Subject	Division Director Summary Review
NDA	NDA 206192
Applicant Name	Genentech
Date of Submission	December 11, 2014
Major Amendment Received	June 15, 2015
PDUFA Goal Date	November 11, 2015
Proprietary Name / Established (USAN) Name	Cotellic/ cobimetinib
Dosage Forms / Strength	Tablets for oral administration/ 20-mg
Proposed Indication(s)	indicated for use in combination with Zelboraf (vemurafenib) for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation.
Recommended Action for NME:	<i>Approval</i>

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Regulatory Project Manager Review	Meredith Libeg
Medical Officer Review	Ruthann Giusti
Statistical Review	Xiaoping (Janet) Jiang
Pharmacology Toxicology Review	Shawna L. Weis & M. Anwar Goheer
Quality Review	Olen Stephens (Technical Lead), Gaetan Ladouceur (Drug Substance), Donghao Lu (Drug Product), Zengfang Ge (Process, Microbiology), Sunita Iyer (Facility), Maziar Kakhi (Biopharmaceutics)
Clinical Pharmacology Review	Ruby Leong
OSI	Lauren Iacono-Connors
OSE/DMEPA	Otto Townsend
OSE/DRISK	Amarilys Vega
Ophthalmology Review	Wiley Chambers
QT IRT Consult Review	Dinko Rekić
Controlled Substances Staff Review	Katherine Bonson
DPMH Review	Miriam Dinatale

OND=Office of New Drugs
 OSI=Office of Scientific Investigations
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DRISK=Division of Risk Management
 QT IRT=QT Interdisciplinary Review Team
 DPHM=Division of Pediatric and Maternal Health

Division Director Summary Review

1. Introduction

Cobimetinib (Cotellic; Genentech Oncology) is a reversible, non-ATP-competitive inhibitor of the mitogen-activated protein kinase (MAPK)/extracellular signal regulated kinase 1 (MEK1) and MEK2. These proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes cellular proliferation. In patients with melanoma containing BRAF V600E or BRAF V600K mutations, the ERK pathway is constitutively activated, resulting in promotion of tumor growth, which can be inhibited in nonclinical studies with exposure to cobimetinib.

This approval is based on the results of a single, adequate and well-controlled, multicenter, international, randomized (1:1), open-label trial, Study GO28141. Key eligibility criteria were previously untreated, BRAF V600 mutation-positive unresectable or metastatic melanoma. The presence of BRAF V600 mutation was detected using the cobas® 4800 BRAF V600 mutation test. All patients received vemurafenib 960 mg orally twice daily on days 1-28 and were randomized (1:1) to receive cobimetinib 60 mg or matching placebo orally once daily on days 1-21 of an every 28-day cycle until disease progression or unacceptable toxicity. Randomization was stratified by geographic region (North America vs. Europe vs. Australia/New Zealand/others) and disease stage (unresectable Stage IIIc, M1a, or M1b vs. Stage M1c). Patients randomized to receive placebo were not allowed to receive cobimetinib at the time of progression. The primary endpoint of this trial was investigator-assessed progression-free survival (PFS) per RECIST v1.1; key secondary endpoints were investigator-assessed confirmed objective response rate (ORR), overall survival (OS), and PFS as assessed by blinded independent central review. Patients with available tumor samples were retrospectively tested using next generation sequencing to identify the BRAF mutation subtype (BRAF V600E or V600K). BRAF mutation subtype could be determined in 81% of the study population; 86% of these patients had BRAF V600E mutation-positive melanoma and 14% as had BRAF V600K mutation-positive melanoma.

The trial showed a statistically significant improvement in PFS [HR: 0.56 (95% CI: 0.45, 0.70), $p < 0.001$] for patients randomized to receive cobimetinib with vemurafenib compared to those randomized to receive placebo with vemurafenib. The estimated median PFS was 12.3 months (95% CI: 9.5, 13.4) for patients randomized to receive cobimetinib with vemurafenib and 7.2 months (95% CI: 5.6, 7.5) for the patients randomized to receive placebo with vemurafenib. In addition, the trial also showed a statistically significant improvement in OS [HR: 0.63 (95% CI: 0.47, 0.85); stratified log-rank p -value=0.0019 (nominal significance level of 0.019)] for patients randomized to receive cobimetinib with vemurafenib compared to those randomized to receive placebo with vemurafenib. The estimated median OS was not reached at the time of the analysis (NR) (95% CI: 20.7, NR) for patients randomized to receive cobimetinib with vemurafenib and 17.0 months (95% CI: 15.0, NR) for the patients randomized to receive placebo with vemurafenib. The ORR was 70% among patients randomized to receive cobimetinib with vemurafenib compared to 50% among patients

randomized to receive placebo with vemurafenib ($p < 0.001$). Complete responses were observed in 16% of patients randomized to receive cobimetinib with vemurafenib compared to 11% of patients randomized to receive placebo with vemurafenib. The median duration of response was 13.0 months (95% CI: 11.1, 16.6) among patients randomized to receive cobimetinib with vemurafenib and 9.2 months (95% CI: 7.5, 12.8) among patients randomized to receive placebo with vemurafenib.

The safety of cobimetinib was evaluated primarily in the 247 patients receiving cobimetinib in Study GPO14821; 66% of patients were exposed to cobimetinib for more than 6 months and 24% were exposed to cobimetinib for greater than 1 year. Patients with abnormal liver function tests, history of acute coronary syndrome within 6 months, or evidence of Class II or greater congestive heart failure (New York Heart Association) were not eligible for this trial. The most common adverse reactions in patients receiving cobimetinib and vemurafenib ($\geq 20\%$) were diarrhea, nausea, vomiting, rash, arthralgia, fatigue, photosensitivity reaction, and pyrexia. The most common Grade 3 or 4 laboratory abnormalities were elevations in creatine phosphokinase (13%), GGT (13%), ALT (11%), AST (9%). Fifteen percent of patients discontinued cobimetinib and 55% required dose reductions or interruptions for adverse reactions. The most common adverse reactions resulting in permanent discontinuation were elevation in liver enzymes, rash, pyrexia, and retinal detachment. Among the 247 patients receiving cobimetinib, adverse reactions led to dose interruption or reductions in 55%. The most common reasons for dose interruptions or reductions of cobimetinib were rash (11%), diarrhea (9%), chorioretinopathy, (7%), pyrexia (6%), vomiting (6%), nausea (5%), and increased creatine phosphokinase (CPK) (4.9%). The most serious adverse reactions of cobimetinib, occurring more commonly in the cobimetinib plus vemurafenib arm compared with vemurafenib alone, were an increased risk of second primary basal cell cancers, hemorrhagic events, cardiomyopathy as detected by clinically important decreases in left ventricular ejection fraction, severe skin toxicity, serous retinopathy, rhabdomyolysis, and severe photosensitivity reactions. In addition, the addition of cobimetinib to vemurafenib, decreases but does not eliminate the risk of an increased risk of second primary cutaneous (cutaneous squamous cell carcinoma, keratoacanthoma, and melanoma) and non-cutaneous primary cancers.

Specific issues considered during this review were:

- Evidence supporting efficacy in patients with BRAF V600K mutation-positive melanoma;
- Inclusion of the updated efficacy analyses, [REDACTED] (b) (4) [REDACTED] in the US product labeling; and
- Whether there was clinical evidence of opioid effects.

2. Background

Proposed Indication and Available Therapy

Genentech's proposed indication, as cited in the proposed physician package insert (USPI) in the original NDA is:

Cobimetinib is indicated [REDACTED] for the treatment of patients with unresectable or metastatic melanoma with BRAF [REDACTED] mutation.

Based on the Surveillance, Epidemiology, and End Results (SEER) Program, there will be an estimated 73,870 new cases and 9,940 deaths due to melanoma in the United States in 2015.¹ Of these new cases, 4% will be metastatic at diagnosis with a projected 5-year survival rate of 17%. Approximately half of the patients with metastatic melanoma will have detectable mutations in the BRAF V600 gene in tumor specimens. Based on review of published literature, the presence of BRAF V600 mutations may be a poor prognostic factor for survival².

Vemurafenib was approved on August 17, 2011, for the treatment of patients with unresectable or metastatic melanoma with BRAF-V600E mutation as detected by an FDA-approved test. Vemurafenib is not recommended for use in patients with wild-type BRAF melanoma. This approval was based on demonstration of a clinically important and statistically significant improvement in overall survival as compared to dacarbazine; based on updated results, the median overall survival was 13.6 months vs 10.3 months for vemurafenib and dacarbazine, respectively. This was supported by demonstration of improvements in progression-free survival (5.3 vs. 1.6 months) and overall response rates (48.4% vs. 5.5%).

Ipilimumab was approved on March 25, 2011, for the treatment of unresectable or metastatic melanoma. This approval was based on demonstration of a clinically important and statistically significant improvement in overall survival as compared to an investigational vaccine, with median survivals of 10 months for ipilimumab vs. 6 months for the investigational vaccine. These results were supported by demonstration of improved survival in a second trial comparing ipilimumab with dacarbazine.

Dabrafenib was approved on May 29, 2013 for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutations, as detected by an FDA-approved test. Dabrafenib is not indicated for the treatment of patients who have received prior BRAF-inhibitor therapy. This approval was based on demonstration of a clinically important improvement in progression-free survival as compared to dacarbazine, with a median PFS of 5.1 months and 2.7 months for dabrafenib and dacarbazine, respectively, and supported by improvement in overall response rates (52% vs. 17%).

¹ <http://seer.cancer.gov/statfacts/html/melan.html>. accessed on November 2, 2015

² Impact of BRAF mutation status in the prognosis of cutaneous melanoma: an area of ongoing research. Bhatia P, Friedlander P, Zakaria EA, Ann Transl Med. Feb; 3(2): 24, 2015.

Trametinib was approved on May 29, 2013 for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or BRAF V600K mutations, as detected by an FDA-approved test. Trametinib is not indicated for the treatment of patients who have received prior BRAF-inhibitor therapy. This approval was based on demonstration of a clinically important improvement in progression-free survival as compared to chemotherapy (dacarbazine or paclitaxel) with a median PFS of 4.8 months in the trametinib arm as compared to 1.5 months in the chemotherapy arm.

Other FDA-approved drugs: There are additional drugs which are approved for a broader population of patients with unresectable or metastatic melanoma (i.e., regardless of BRAF mutation status), which include pembrolizumab, nivolumab, aldesleukin, and dacarbazine. In addition, there are two drugs approved in combination for treatment of patients with BRAF mutation-positive melanoma. These other drugs are not considered “available therapy” for the following reasons:

- Dacarbazine is no longer relevant to the US standard of care for this patient population, since the approvals of vemurafenib, dabrafenib.
- Aldesleukin is indicated only for patients with excellent performance status and end-organ function; it is administered at high doses requiring intensive cardiopulmonary monitoring and support. Therefore its use is limited to the specialized medical centers and thus is not considered part of the US standard of care at most institutions.
- Pembrolizumab, as a single agent, and nivolumab, as a single agent, were approved under the provisions of 21 CFR 601 Subpart E (accelerated approval) based on demonstration of an effect on a surrogate endpoint (durable responses) and therefore are not considered available therapy.
- Dabrafenib and trametinib for use in combination were approved under the provisions of 21 CFR 314 Subpart H (accelerated approval) based on demonstration of an effect on a surrogate endpoint (durable responses) and therefore are not considered available therapy.

Pre-Submission Regulatory History

On December 20, 2006, IND (b)(4) was received; this IND evaluated the safety and preliminary activity of cobimetinib in solid tumors.

On September 30, 2010, IND 109307 for the investigation of cobimetinib was allowed to proceed. The initial trial, Study NO25395, was a dose-finding, safety and pharmacology trial evaluating the combination of cobimetinib and vemurafenib in Patients with BRAFV600E mutation-positive melanoma who had progressed after treatment with vemurafenib. This open-label, multicenter study had two stages, a dose-escalation stage and a cohort-expansion stage. All patients in the dose-escalation stage receive continuous, twice daily oral vemurafenib in combination with cobimetinib administered once daily by one of the following schedules: 14 consecutive days followed by a 14-day drug holiday (14/14), 21 consecutive days followed by a 7 day drug holiday (21/7), or as a continuous daily dose (28/0).

On June 17, 2012, an End-of-Phase 1 meeting was held to discuss the proposed development plan to support the use of cobimetinib in combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutations and specifically, the design of Study GO28141. Study GO28141, titled “A Phase III, double-blind, placebo-controlled study of vemurafenib versus vemurafenib plus GDC-0973 in previously untreated BRAFV600-mutation positive patients with unresectable locally advanced or metastatic melanoma,” (b) (4)

The trial was limited to patients with no prior treatment, considering the efficacy results in 28 patients enrolled in Study NO25395, where partial responses were observed in 8% (2/24) of patients previously treated with vemurafenib and 50% (2/4) of patients who had not received vemurafenib. Key discussions and agreements reached were:

- The proposed dose was acceptable, although based on limited clinical experience.
- The proposed study design was acceptable, however in addition to the investigator assessments of PFS as the primary endpoint, assessments of PFS should be also subjected to a blinded, independent review committee.
- Based on toxicities observed with this product and others directed against this target, Roche would develop more detailed case report forms to systematically collect information on ophthalmologic central serous retinopathy and retinal vein occlusion to include the findings, bases for recommendations, on dosing, dose modification and long term outcomes to better describe reversibility and potential risk factors; evaluations for cardiac toxicity (assessment of LVEF by echocardiogram or MUGA) at baseline and periodically during treatment; thorough head and neck examinations to detect second primaries.
- An NDA based primarily on the results of study GO28141 would require demonstration of a robust effect on PFS that is of sufficient magnitude to be direct evidence of clinical benefit and permit a positive risk-benefit determination—a determination that may also consider the treatment landscape for the proposed patient population at the time of a marketing application as described in 21 CFR 312.84.
- The trial be adequately powered (80%) to detect a clinically important effect on overall survival by increasing the sample size and number of death events at the time of final analyses. FDA will evaluate the interim OS data at the time of the NDA submission both for supportive evidence of efficacy and for assessment of safety.
- The NDA submission should contain a drug interaction study evaluating the effect of strong CYP3A4 inducers (e.g. rifampin) on cobimetinib pharmacokinetics and either dedicated hepatic and renal impairment trials for cobimetinib or justification for not conducting such studies based on the results from the planned mass balance study. The plan for collection of ECGs for assessment of effects on QTc appeared reasonable; whether a formal drug interaction study between cobimetinib and vemurafenib would be required was contingent on review of available PK data from Study NO25395.
- FDA stated that if a rat embryofetal toxicity study was positive for teratogenic effects, a rabbit study would not be required; if a dose-range finding study in pregnant rats is sufficiently designed, a definitive study may not be warranted. FDA agreed with the inclusion of a standard *in vitro* phototoxicity assay to address this risk.

On November 27, 2012, end-of-Phase 2 meeting to discuss the cobimetinib CMC data and to obtain FDA's feedback on proposals for the product manufacture and development of cobimetinib in preparation for the planned initial NDA submission for BRAF V600mutation positive, unresectable or metastatic melanoma. FDA provided general agreement with the proposed starting materials and provided detailed advice on the information to be included in the quality section of the planned NDA. FDA also agreed with the proposed dissolution method for quality control testing of the registration batches and commercial drug product for release and on stability and provided a detailed list of the information to be included in the NDA regarding this method and the results to be provided.

On April 22, 2013, issued Written Responses to a Type C meeting request to confirm the suitability of planned clinical pharmacology studies intended to support the use of cobimetinib in combination with vemurafenib. In response to the questions posed, FDA stated that:

- The conducted and planned clinical pharmacology studies appeared appropriate.
- The proposed study design for the CYP3A inhibition study using itraconazole as the probe inhibitor appeared acceptable.
- The proposal to stage the drug-drug interaction studies using PBPK modeling and simulation appeared acceptable.
- FDA did not agree that drug interaction studies for cobimetinib and vemurafenib were not required; a justification, supported by the PBPK studies would be required for not conducting such studies.
- The final study results of the hepatic impairment study should be included in the NDA; a post-marketing requirement (PMR) for the hepatic impairment study with proposed submission timeline could be considered if this study is not completed at the time of the NDA submission.
- A second food-effect study using the optimized tablets may not be necessary.
- The proposed Pop PK and exposure-response analysis plans, with more specific details, should be resubmitted to the IND for FDA review prior to initiation of Study GO28141.

On June 4, 2013, FDA issued the meeting minutes to the April 22, 2013, meeting with the following post-meeting addendum:

“As the results of mass balance and pharmacokinetic drug-interaction studies have not been presented, it is unclear whether specific aspects of intrinsic factors (hepatic or renal impairment) and extrinsic factors (drug interactions) could be further evaluated with collection of PK data in Study GO28141, using a population PK analysis. However, since this trial has been initiated, this makes FDA feedback regarding the planning of the phase 3 trial and data collection for specific PK analyses difficult. Ultimately the characterization of the effects of these intrinsic and extrinsic factors will be a review issue. FDA has no further comments on the analysis plan at this time.”

On November 29, 2013, FDA issued Written Responses in response to a Type C meeting request to discuss general content and format issues for a proposed NDA to support the

approval of vemurafenib in combination with cobimetinib for the treatment of patients with BRAF V600 mutation-positive, unresectable or metastatic melanoma. FDA noted the following:

- The primary analysis of overall response rate must be conducted in the intent-to-treat population, which consists of all randomized patients, and has been confirmed to be durable for at least 4 weeks.
- A complete Integrated Summary of Safety (ISS) must be provided in the NDA in order to ensure that it is a complete application.
- Adverse Events of Special Interest (AESI) should also include (b)(4) malignancies.
- An Integrated Summary of Efficacy (ISE) must be included in the NDA submission in Module 5, section 5.3.5.3, and include datasets and analyses of the pivotal trial and all supportive studies.
- The proposed approach for submission of clinical study reports, case narratives, case report forms, datasets in CDISC, and statistical analysis programs were acceptable. FDA requested that datasets be provided in STDM and that a reviewer's guide and define file be provided in the NDA.
- The planned format and content of the clinical pharmacology plan as described appeared generally acceptable. The NDA should also include an assessment of the potential pharmacokinetic (PK) interactions between cobimetinib and vemurafenib, the physiologically-based pharmacokinetic (PBPK) report intended to predict the effect of strong CYP3A inducers on cobimetinib pharmacokinetics, and the following PMR studies: hepatic impairment study and drug interaction study with itraconazole. FDA stated that additional clinical pharmacology studies (e.g., drug interaction study with a strong CYP3A inducer, dedicated drug interaction study of cobimetinib in combination with vemurafenib) may be requested after review of the NDA.

On February 11, 2014, FDA provided Written Responses to a request for clarification of the November 29, 2013, Written Responses, stating

- If Hoffman La-Roche determined that a study is supportive, the datasets for that study must be submitted in the NDA application for it to be a complete application per PDUFA V and that the dataset should be in CDISC format.
- Hoffman La-Roche agreed to include (b)(4) malignancies as an adverse event of special interest (AESI) and will provide their proposal for inclusion and analysis of AESI to be included in the Summary of Clinical Safety (CSC) to FDA prior to the NDA submission. FDA stated that this should be provided no later than the preNDA meeting package.
- FDA agreed with the proposal for approach for submission of data to assess effects on QTc.

On January 31, 2014, Orphan Drug Designation was granted for cobimetinib for Stages IIB, IIC, III and IV melanoma with BRAF V600 mutation.

On March 5, 2014, a CMC pre-NDA meeting was held to obtain the Agency's feedback on proposals for the development with regard to product characterization and manufacture of cobimetinib in preparation for the planned NDA for (b)(4) BRAF V600 mutation-positive, unresectable or metastatic melanoma. Key agreements regarding the content of the NDA were:

- In order to support approval of drug manufactured at an alternate drug packaging site (Segrate, Italy), FDA stated that the NDA should contain at least three batches (from the new site) with three months accelerated stability data in the NDA submission and up to three batches (from the new site) on long-term stability data reported in an annual report. The Agency stated that all stability update should be submitted within the first 60 days of the NDA submission.
 - The NDA should contain acceptance criteria for (b) (4) and a periodic evaluation strategy for microbiological tests.
 - The NDA should contain the complete multipoint dissolution profile data for the pivotal clinical and registration stability batches both at release and on storage to support setting the final acceptance criterion.
 - The NDA should provide a clear overview of any formulation changes throughout development and the effects of these changes on dissolution performance and bioavailability, where appropriate.



On August 15, 2014, FDA issued correspondence stating that FDA was designating as a Fast Track Development program, the investigation of cobimetinib and vemurafenib for the treatment of patients with BRAF V600E-mutation positive, unresectable or metastatic melanoma to demonstrate improved progression-free survival and overall survival.

On October 8, 2014, a pre-NDA meeting was held to discuss the data to support the proposed NDA for the following indication in unresectable or metastatic melanoma with BRAF V600 mutation. The NDA was to be supported by the efficacy results from Study GO28141 (coBRIM) providing the primary safety and efficacy data and Study NO25395 (BRIM7) providing supportive evidence of activity and safety data for the combination of cobimetinib and vemurafenib. Key agreements and discussions during this meeting were:

- Based on the high-level efficacy and safety results as presented in the meeting briefing document and previous meetings, the clinical, clinical pharmacology, and non-clinical data package appeared adequate to support an NDA filing for cobimetinib.
- Roche agreed to include analyses for Study NO25395 based on the subgroup of patients who had progressed on or after vemurafenib at the recommended dose and schedule.
- The proposed list of adverse events of special interest identified in the meeting briefing package was acceptable; FDA stated a communication would be sent following the meeting clarifying the data to be provided to characterize ocular toxicity with regard to whether data should be provided for all studies or only the efficacy trial and for asymptomatic as well as symptomatic patients (See letter issued November 10, 2014).

- Genentech stated their interest in amending the Statistical Analysis Plan (SAP) and protocol in order to conduct an earlier assessment of final OS, which would be provided as an efficacy supplement, post-approval. FDA stated that if the revised plan is found to be acceptable and the trial meets the specified threshold for significance as described under the revised SAP plan, OS results may be included in the label. Roche will submit the revised SAP for FDA review.
- Roche agreed to submit the formal request for the submission schedule of the planned rolling NDA. In addition, Roche agreed to hold an application orientation meeting within 30 days of submission of the last module submission.
- FDA stated that a plan for Risk Evaluation and Mitigation Strategies would not be required for the filing of the NDA.
- Based on the information, and provided there are no changes to the device specific to this combination use, FDA agreed that a PMA supplement will not be needed for the cobas® 4800 BRAF Mutation Test to support approval of cobimetinib in combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation, because the test is used in accordance with its label, (i.e., to select patients eligible for vemurafenib treatment).
- Genentech agreed to include additional data on (b) (4) throughout manufacturing and stability which supports the proposal to exclude (b) (4) testing. Data available and presented in the NDA clearly demonstrates that (b) (4) is not a critical quality attribute for the cobimetinib drug product. Genentech also agreed to provide a proposal and supporting rationale for the periodic evaluation strategy for microbiological tests.

On October 28, 2014, FDA issued a letter accepting the proposal for rolling NDA submission.

On November 10, 2014, FDA issued an Advice/Information Request letter, stating: “During the development of cobimetinib, ophthalmic examinations have not been performed in a uniform manner, and the terminology used to describe clinical findings has been inconsistent. It is therefore recommended that all ophthalmic scans that were performed on patients treated with cobimetinib be collected and submitted for all studies, pre- and post-treatment. In addition, to the extent that individual findings from ophthalmic examinations were collected, it is recommended that these individual findings from all ophthalmic exams for all patients involved in clinical trials of cobimetinib be submitted, preferably as Excel spreadsheets. If the ophthalmic clinical findings are submitted in this manner, individual patient summaries of patients having ophthalmic events are not needed.”

Regulatory History of the NDA

On October 30, 2014: First module of the NDA, containing non-clinical information, was submitted.

On December 11, 2014: All remaining components of the NDA submitted.

On March 10, 2015, a 90-day safety update was submitted.

On May 14, 2015, Genentech submitted an amendment to the NDA responding to FDA's information request regarding discrepancies between the original datasets and the 90-day safety update.

On May 15, 2014, a teleconference was held between FDA and Genentech to obtain clarify on the information submitted May 14, 2015.

On May 20, 2014, FDA issued an Information Request letter requesting additional data and clarification of the datasets.

On June 15, 2015, Genentech submitted an amendment to the NDA responding to FDA's May 20, 2014, information request.

On June 25, 2015, FDA issued a Major Amendment letter, extending the PDUFA goal date by 3 months, based on the June 15, 2015, amendment.

3. CMC/Biopharmaceutics

I concur with the conclusions reached by the chemistry, microbiology, biopharmaceutics, and facilities reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 30 months when stored at room temperature below 30°C (86°F). There are no outstanding issues precluding approval and no post-marketing commitments were identified by the Quality review team.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

The NDA contained nonclinical data which supported the proposed mechanism of action of reversible, non-ATP-competitive inhibitor of MEK1 and MEK2 signaling. In addition, binding of cobimetinib to the μ -opioid receptor was demonstrated. In murine xenografts, cobimetinib administration, alone or with vemurafenib, delayed tumor growth in animals bearing in BRAF V600E melanoma xenografts.

The results of 4-week and 13-week general toxicology studies identified skin and the GI tract as the major organs of toxicity in rats and dogs, respectively. Additional organs affected were liver, kidney, thyroid, adrenals, thymus, and lymph nodes. No dedicated fertility studies were conducted, however nonclinical toxicology studies in rats demonstrated effects on reproductive organs in rats (ovarian necrosis, decreases in corpora lutea, cysts and increased vaginal epithelial cell apoptosis), suggesting potential impairment in fertility.

Also noted in rats was a statistically significant but possibly clinically unimportant, 18% reduction in respiratory rate in rats receiving cobimetinib at a dose of 300 mg/kg. This finding was noted because of the binding to the μ -opioid receptor in nonclinical studies. Since the interpretation of these findings was unclear, the potential for opioid effects was evaluated in the clinical study and the nonclinical review team consulted the Controlled Substance Staff (CSS) regarding the potential for abuse liability with cobimetinib.

In the embryofetal toxicology study conducted in rats, maternal toxicity was observed at exposures below that expected at the recommended dose; embryofetal effects included an increased rate of early resorption, total litter loss, and markedly increased post-implantation loss. Decreased fetal body weights, an increase in skeletal alterations, including decreased ossification malformations of the great vessels (missing and/or misplaced great vessels), and malformations of the eye sockets were also observed. While the nonclinical toxicology review notes that an additional embryofetal study may be required, the data provided were subsequently determined to be sufficient to inform labeling and a PMR will not be required to further investigate this risk to the fetus of pregnant patient.

Cobimetinib was shown to inhibit hERG channel activity with an intermediate affinity (with an IC₅₀ of 0.5 μ M when tested alone and 0.6 μ M when tested in combination with vemurafenib). No cardiovascular effects were observed in dogs at peak exposures 2-fold higher than that predicted in clinical studies. The interpretation of these finding was that there was a low risk for QT prolongation, which should be further investigated in clinical studies.

Cobimetinib was not mutagenic in the Ames bacterial mutagenicity assay and was negative for induction of structural abnormalities in the in vitro and chromosome aberration assay and in the in vivo micronucleus assay. (b) (4)

5. Clinical Pharmacology/Pharmacometrics

I concur with the conclusions reached by the clinical pharmacology/pharmacometrics reviewers that there are no outstanding clinical pharmacology issues that preclude approval.

The NDA contained the results of pharmacokinetics (PK) studies evaluating the PK of cobimetinib alone and when administered with vemurafenib in patients with cancer (primarily metastatic melanoma), food effects studies, studies characterizing absorption, distribution, metabolism, excretion (ADME), drug interactions based on CYP enzymes and transporters. Since the formulation of cobimetinib was modified during the clinical development program, absolute bioavailability and relative bioavailability studies were conducted to support the use of data obtained with the previous formulation (capsule) used in clinical trials in support of the to-be-marketed formulation (tablet). The NDA also contained population PK analyses, exposure-response analyses for efficacy and safety, and assessment of effects on QTc based on serial ECGs obtained in clinical trials.

Cobimetinib administered at 60 mg daily has a half-life of 44 hours; based on this long half-life, product labeling states that missed doses should not be made up. Food effects studies indicate that there is no clinically important differences in exposure when cobimetinib is taken with a high-fat meal or fasting. The major route of metabolism is via the liver, with CYP3A oxidation and UGT2B7 glucuronidation; as discussed below, strong CYP3A inhibitors and inducers have substantial, clinically important effects on exposure. Coadministration of cobimetinib with a strong CYP3A inhibitor resulted in a 6.7-fold increase in cobimetinib exposure. Based on the magnitude of the effect on exposure, product labeling states that the dose of cobimetinib should be decreased from 60 mg to 20 mg daily and patients taking a reduced dose of cobimetinib (40 mg or 20 mg) should not take concomitant strong CYP3A inhibitors as there is no predicted safe dose of cobimetinib. In addition, product labeling notes that administration of a strong CYP3A inducer reduced cobimetinib exposure by more than 80%, which is likely to reduce efficacy.

The population PK analyses indicated that age, sex, and race/ethnicity did not have clinically important effects on cobimetinib exposure. The NDA did not contain the results of a dedicated hepatic impairment study or a dedicated renal impairment study. While population PK analyses supported the safety of dosing in patients with mild or moderate renal impairment at the recommended dose, there was insufficient data to assess the pharmacokinetics of cobimetinib in patients with severe renal impairment. Since the ADME study showed that renal excretion is not a major route of elimination and based on the popPK studies showing no clinically important effects of mild or moderate renal impairment on exposure, a dedicated renal impairment study has not been required. There is insufficient data based on population PK studies to make recommendations on dosing in patients with moderate or severe hepatic impairment. Since the liver is the major route of metabolism, a post-marketing requirement has been required to conduct a dedicated study in patients with mild and moderate hepatic impairment.

The dose chosen for clinical studies (cobimetinib 60 mg daily) was based on evidence of inhibition of the ERK signaling pathway in vitro and on dose finding studies to determine the maximum tolerated dose and clinical activity of cobimetinib and vemurafenib (Study NO25395). There were no evidence of an exposure-response (ER) relationship for efficacy (progression-free survival PFS) or for toxicity (Grade \geq 3 rash, diarrhea; Grade \geq 2 creatine phosphokinase elevation, photosensitivity, laboratory elevations in ALT, AST, alkaline phosphatase or total bilirubin; any grade retinal detachment or serous retinopathy).

Clinically important increases in QTc have been identified with administration of vemurafenib 960 mg twice daily. Based on ECGs obtained in the major efficacy trial, there was no evidence of additional effects on QTc with the addition of cobimetinib to vemurafenib as compared to vemurafenib alone.

6. Clinical Microbiology

Not applicable. Microbiology review of CMC information is included in Section 3 of this Summary Review.

7. Clinical/Statistical-Efficacy

This NDA is supported by the results of a single, adequate and well-controlled clinical trial demonstrating a clinically important and statistically robust effect on progression-free survival and a statistically significant effect on overall survival in an *ad hoc* analysis [REDACTED] (b) (4)

[REDACTED] The key design elements of the protocol, key amendments to the protocol, and results of inspectional findings of clinical study sites are summarized below, following the efficacy results of the clinical trial.

Protocol Design

Protocol GO28141, titled “A Phase III, Double-Blind, Placebo Controlled Study of Vemurafenib versus Vemurafenib Plus GDC-0973 in Previously Untreated BRAFV600-Mutation Positive Patients with Unresectable Locally Advanced or Metastatic Melanoma.”

Design: randomized (1:1), multicenter, international, double-blind, placebo-controlled trial.

Objectives

- Primary endpoint: progression-free survival (PFS) as assessed by clinical investigators using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
- Key secondary efficacy endpoints were overall survival and best overall response rate (BORR).

Key eligibility criteria: no prior treatment for metastatic disease, unresectable locally advanced or metastatic melanoma, BRAF V600 mutation in tumor tissue detected using an FDA-approved real-time polymerase chain reaction assay (cobas® 4800 BRAFV600 Mutation Test, Hoffman-La Roche Molecular Systems, Branchburg, NJ, USA).

Patients were randomly assigned (1:1) to the following treatment arms:

- Experimental arm: vemurafenib 960 mg PO BID on Days 1–28 and cobimetinib 60 mg PO QD on Days 1–21 of each 28-day treatment cycle.
- Control arm: vemurafenib 960 mg by mouth (PO) twice daily (BID) on Days 1–28 and placebo PO once daily (QD) on Days 1–21 of each 28-day treatment cycle.

Treatment continued until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurred earliest. Patients on the control arm were not offered cobimetinib at the time of investigator-assessed disease progression.

Randomization was stratified by geographic region (North America, Europe, Australia/New Zealand/others) and metastatic classification (unresectable Stage IIIc, M1a, and M1b; M1c) (yes vs. no).

Assessment for tumor status was conducted every 8 weeks.

Statistical Analysis Plan

The planned sample size of 500 patients was based on the following assumptions: a median PFS of 5 months in control arm and 11 months in the experimental arm; 206 PFS events would be required to detect a hazard ratio of 0.55 with 95% power at a 2-sided alpha level of 5% using a stratified log-rank test in the intent-to-treat population.

Two interim and a final analysis of overall survival (OS) were planned. Assumptions for the analysis of OS were a median OS of 15 months in the control arm and 20 months in the experimental arm and final analysis to be conducted at 385 deaths, to provide 80% power to detect a hazard ratio of 0.75 with a 2-sided alpha level of 5%. The first was to be conducted when the final analysis of PFS was conducted; the second interim analysis was to be conducted at 256 (67% of the events for final OS analysis) deaths. The O'Brien-Fleming boundary method was utilized to control type I error, with respective alpha allocations of 0.000085 and 0.012 for the first and second interim analyses and 0.0463 at the final analysis.

A hierarchical procedure was used to adjust for multiplicity testing of the secondary endpoints of BORR and OS, in that order. PFS as assessed by blinded independent review was also to be evaluated.

Key amendments to Study GO28141

On June 24, 2014, FDA received an amendment to the protocol with the following changes:

- As requested by FDA on November 29, 2013, the definition of the analysis population for best overall response rate was changed from patients who were randomized at least 18 weeks before the data cutoff date to all randomized patients regardless of whether or not study treatment was received.
- The subgroup analysis for time from metastatic disease diagnosis (<6 months, ≥6 months) will be deleted because the information required for this analysis (the date of metastatic diagnosis) was not collected in the eCRF.

After the primary PFS analysis was performed, using the data cut-off date of July 10, 2014, a post-hoc analysis of PFS and OS were conducted (b) (4).

On March 11, 2015, the revised protocol for Study GO28141 (version 5) and its associated statistical analysis plan (version 3) were submitted to FDA, containing the following changes:

- Revised the schedule for tumor assessments from every 8 weeks (±1 week) to local standard of care and removed the requirement for central collection and review of tumor scans.
- Revised the timing of the final analysis of overall survival from 385 events to 250 events. The rationale provided for this change was to maintain a statistically robust evaluation of the OS benefit in light of the rapid evolution of new therapeutic options in advanced melanoma, which might otherwise confound assessment of survival.

Inspectional Findings

Four clinical sites were chosen for inspection based on enrollment of large numbers of study participants and the contribution of the efficacy results at these sites to the overall study report, pertinent to decision-making. The IND sponsor, Genentech, was also inspected. Inspectional findings indicate that the data generated at three of the four clinical sites and information submitted by Genentech appeared reliable based on available information. Inspection at one study site identified a large number of protocol deviations and GCP compliance violations; sensitivity analyses excluding results from this site did not alter the overall conclusions. Based on the final assessment of the inspectional findings, it was determined that the efficacy results were sufficiently reliable to include in product labeling.

Results

The trial was conducted at 132 clinical study sites in the US, Canada, Australia (15), Europe, Russia, and New Zealand. The study enrolled 495 patients, of whom 247 patients were randomized to cobimetinib plus vemurafenib and 248 patients were randomized to placebo plus vemurafenib. Across the study population, the median age was 55 years (range 23 to 88 years), 58% of patients were male, 93% were White and 5% had no race reported, 60% were stage M1c, 72% had a baseline ECOG performance status of 0, 45% had an elevated baseline serum lactate dehydrogenase, 10% had prior adjuvant therapy, and < 1% had previously treated brain metastases.

The data cut-off date for the definitive (and only pre-specified) analysis of progression-free survival was based on a data cut-off date of May 9, 2014. Although Genentech presented the results using a stratified analysis based on data recorded in the case report forms, the statistical review team conducted the stratified analysis using data entered into the IxRS (interactive randomization system) because this preserved the principles of randomization; the statistician considered the analysis using stratification variables recorded on case report forms as a sensitivity analysis. The results of the pre-specified analysis of overall survival were statistically robust ($p < 0.0001$) and were supported by similar findings in an analysis of PFS based on IRF-determined events, in sensitivity analyses of PFS conducted by the FDA statistical reviewer, and consistent across relevant demographic subgroups (age, gender, and region) and in relevant prognostic subgroups (disease stage, ECOG performance status, and LDH value) as well as in exploratory analyses based on retrospectively determined BRAF V600 mutation subtype (E or K), as discussed in more detail below. At the time of the final PFS analysis, there was also a statistically significant improvement in overall response rate favoring the cobimetinib plus vemurafenib arm. The first interim analysis of overall survival conducted at the time of the final PFS analysis was reported as not having crossed the O'Brien-Fleming boundary based on the number of events.

[REDACTED] (b) (4)

[REDACTED] (b) (4)

An ad-hoc efficacy analysis was performed [REDACTED] (b) (4) based on a data cut-off date of January 16, 2015. FDA requested that Genentech provide this information to the pending NDA. On October 13, 2015, Genentech submitted the results of the updated analyses of PFS, pre-specified subgroup analyses of PFS, and ORR as well as a mature analysis of survival based on the last amended protocol and analysis plan submitted to FDA on March 11, 2015.

As noted by the statistical reviewer, Study GO28141 was originally designed to have three OS analyses with two interim analyses (one was conducted at the final PFS analysis, second interim analysis was planned to be conducted when 256 (67% of the events required for the final OS analysis) events had been observed, and the final OS analysis would be conducted when 385 events had been observed. In February 2015, the protocol was amended (version 5) to reduce the number of the OS interim analyses from 3 to 2 and the final analysis would be conducted when 250 events had been observed. Based on the modification of the protocol, FDA considers this updated OS analysis to be the pre-specified second interim analysis conducted at 75% (188/250) planned events for the final survival analysis. This analysis yielded a stratified log-rank test p-value of 0.0019 based on stratification variables as recorded in the IxRS and has crossed the pre-specified boundary for statistical significance (allocated $\alpha=0.019$) according to the pre-specified OBF method. This analysis is considered the definitive analysis of OS and demonstrates a statistically significant improvement in survival for the cobimetinib plus vemurafenib arm compared with vemurafenib alone. The results from the original data cut-off date for the final analysis of PFS and ORR of May 9, 2014, and the final analysis of OS, with updated results for PFS and ORR as of the data cut-off date of January 16, 2015, are displayed in the table below. The updated PFS results will be included in product labeling in order to provide mature estimates of the treatment effect; it is noted that in the original analysis based on the May 9, 2014, data cut-off date, although the demonstration of a statistical significance based on the hazard ratio was definitive, the estimated median PFS was 9 months in the cobimetinib arm, there were only 46 and 34 patients at risk at 9 months in the cobimetinib plus vemurafenib and vemurafenib arms, respectively, thus these estimates were unstable. Similarly, the characterization of duration of response was challenging as the median duration of response had not been reached in the cobimetinib plus vemurafenib arm. Therefore, updated results for overall response rate and duration of response were included in product labeling in order to provide better approximation of the treatment effect and durability of responses.

The data in the table below were abstracted from the statistical reviewer's original review and review addendum.

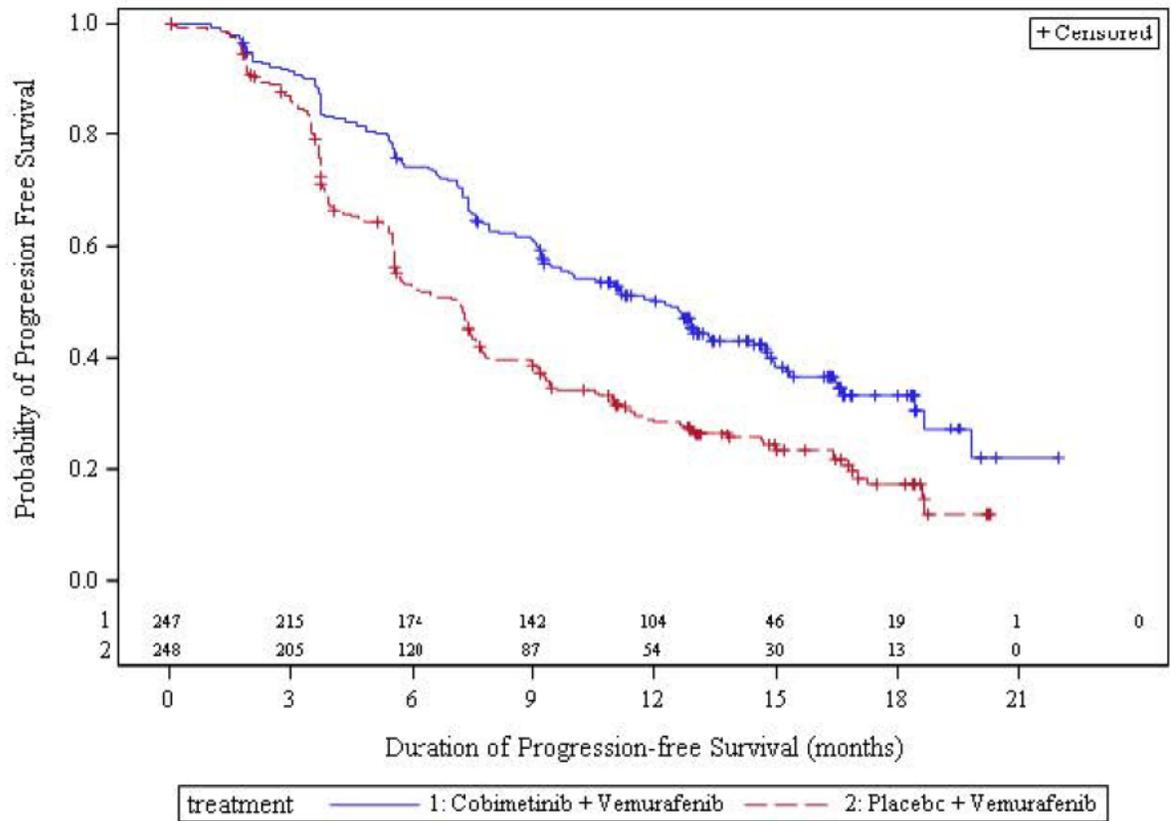
	Updated Efficacy Results January 16, 2015 Data Cut-off		Final Analysis of PFS May 9, 2014 Data Cut-off	
Efficacy Endpoint	Placebo plus Vemurafenib (N=248)	Cobimetinib plus Vemurafenib (N=247)	Placebo plus Vemurafenib (N=248)	Cobimetinib plus Vemurafenib (N=247)
Progression-free Survival (INV)				
Number of Events (%)	180 (52%)	143 (58%)	128 (52%)	79 (32%)
Progression	169	131	125	74
Death	11	12	3	5
Median PFS in months (95% CI)	7.2 (5.6,7.5)	12.3 (9.5, 13.4)	6.2 (5.6, 7.4)	9.9 (9.0, NR)
Hazard Ratio (95% CI)	0.56 (0.45, 0.70)		0.50 (0.38, 0.67)	
p-value (stratified* log-rank)	<0.001		<0.0001	
Progression-free Survival (IRF)				
Number of Events	145	112	117	82
Progression	104	76	--	--
Death	41	36	--	--
Number of Censored (%)	103	135	131	165
Median PFS in months (95% CI)	5.6 (4.6, 6.0)	9.0 (6.3, 10.0)	6.0 (5.6, 7.5)	11.3 (8.5, NR)
Hazard ratio* (95%CI)	0.64 (0.50, 0.83)		0.60 (0.45, 0.79)	
p-value (stratified* log-rank)	0.0007		0.0003	
Overall Survival				
Number of Events (%)	109 (44%)	79 (32%)	51 (21%)	34 (14%)
Number of Censored (%)	139 (56%)	168 (68%)	-	-
Median OS in months (95% CI)	17.0 (15.0, NE)	NE (20.7, NE)	NE	NE
Hazard ratio* (95%CI)	0.63 (0.47, 0.85)		0.65 (0.42, 1.00)	
p-value (stratified* log-rank)	0.0019		0.046	
Response Rate				
Complete Responses (Rate)	26 (10.5%)	39 (15.8%)	11 (4.5%)	25 (10%)
Partial Responses (Rate)	98 (39.5%)	133 (53.8%)	100 (40%)	142 (58%)
Overall Response Rate (95% CI)	50% (44%, 56%)	70% (64%, 75%)	45% (38%, 51%)	68% (61%, 73%)
p-value (χ^2 -test)	<0.0001		<0.0001	
Median Duration of Response (mos); (95% CI)	9.2 (7.5, 12.8)	13.0 (11.1, 16.6)	7.3 (5.8, NR)	NR (9.3, NR)
*stratified by region and metastatic classification using data entered into IVRS CI= confidence interval; NE= not estimable				

The data from the May 9, 2014, data cut-off were evaluated by the primary reviewer for accuracy. Based on the relatively high concordance rates between the INV-assessed and IRF-assessed PFS events using the May 9, 2014, cut-off and the January 16, 2015, cut-off (abstracted from the statistical review and summarized in the table below), the updated dataset was not re-audited for accuracy by FDA.

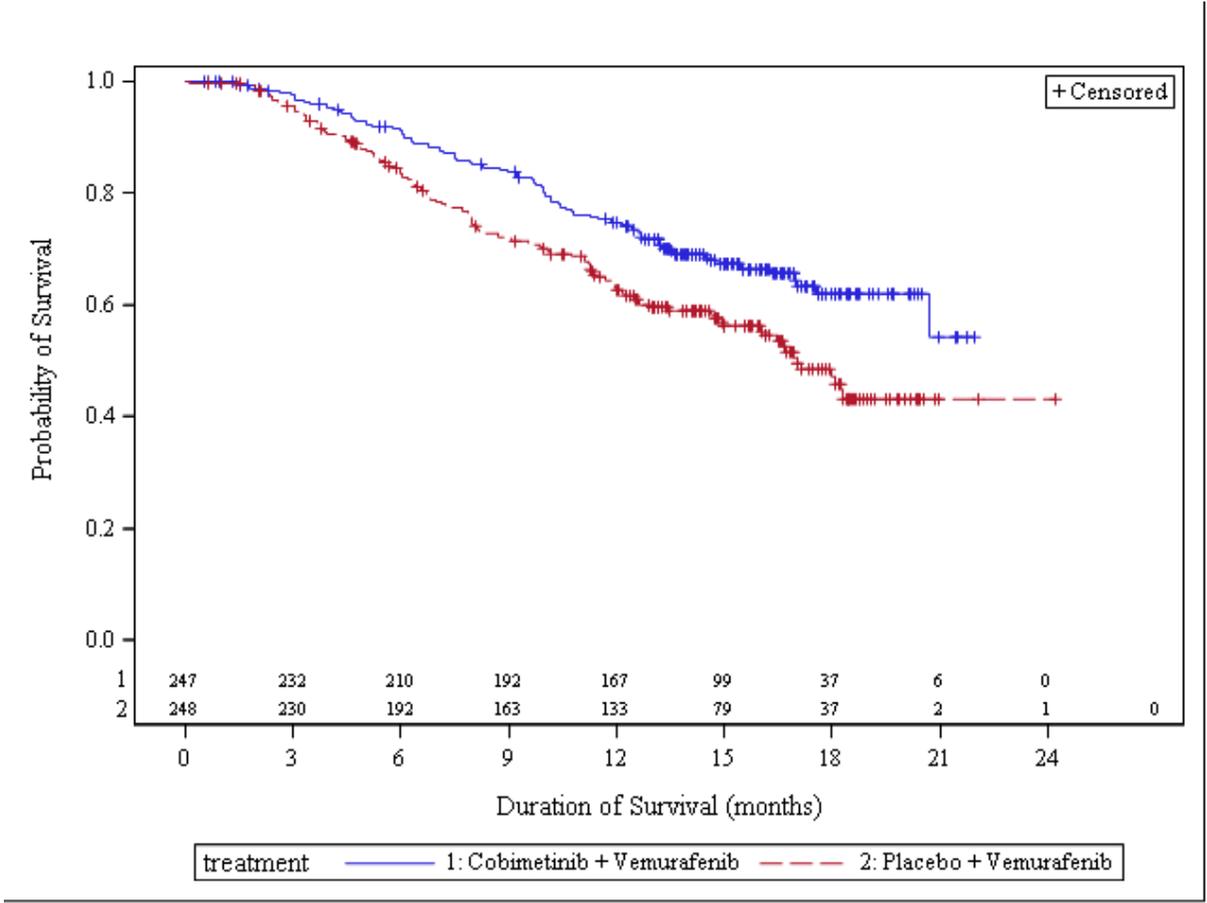
Concordance between investigator (INV)-assessed and independent Radiologic Facility (IRF) – assessed Progression-Free Survival (Jan 2015 cut-off)				
INV Assessment, n (%)	IRF Assessment, n (%)			
	Placebo plus Vemurafenib (n=248)		Cobimetinib plus Vemurafenib (n=247)	
	Event	No Event	Event	No Event
Event	143 (57.7 %)	37	108 (43.7%)	35
No Event	2	66 (26.6%)	4	100 (40.3%)
concordance rates ¹	84.3%		84%	

¹ Concordance rate defined sum of the percentage of concordance for events plus percentage of concordance for censored

Kaplan-Meier Curves for Progression-Free Survival (Investigator-assessed) Based on January 16, 2015 Data Cut-off Date



Kaplan-Meier Curves for Overall Survival Based on January 16, 2015 Data Cut-off Date



Exploratory subgroup analyses

Genentech retrospectively re-tested the tumor samples to identify BRAF V600 mutation subtype: the test used for selection of patients for study entry provides a readout of “positive” or “negative”. The assay reliably identifies those with tumors with BRAF V600E mutations and also detects approximately two-thirds of BRAF V600K mutation-positive melanomas as “positive”. There were 400 (81% of the ITT population) patients for whom tumor samples could be obtained and analyzed retrospectively tested using next generation sequencing to further classify BRAF V600 mutations as V600E or V600K. Of these 400 patients; 86% (n=344) were identified as having a V600E mutation-positive melanoma and 14% (n=56) as having a V600K mutation-positive melanoma. The diagnostic test is not labeled for detection of melanoma tumors with BRAF V600K mutation based on its low sensitivity, which appears to be due to handling of tissues and degradation of DNA in samples rather than a biologic difference in the proportion of cells containing this mutation. An exploratory subgroup analysis of efficacy outcomes (PFS, OS, ORR, and duration of response) was conducted in the two subgroups (V600E or V600K) included in this convenience sample of 81% of the ITT population. Using either the original data cut-off date or the updated analysis dataset, the effect

on PFS appeared to be present in patients with melanoma bearing either a BRAF V600E or V600K mutation subtype. A summary of the hazard ratio for both subgroups, based on the original and updated analysis datasets are provided in the table below.

Efficacy Outcome	Data cut-off Date	BRAF V600 E (n=344)	BRAF V600K (n=56)
Hazard Ratio for PFS (95% CI)	May 9, 2014	0.56 (0.45, 0.70)	0.25 (0.08, 0.70)
Hazard Ratio for PFS (95% CI)	Jan. 16, 2015	0.59 (0.45, 0.78)	0.31 (0.14, 0.69)
Hazard Ratio for OS (95% CI)	May 9, 2014	0.76 (0.45, 1.26)	0.61 (0.16, 2.37)
ORR (experimental arm)	May 9, 2014	68% (116/170)*	67% (16/24)**
Proportion of responses lasting > 6 months	May 9, 2014	21% (24/116)	12% (2/16)

* compared to 48% (83/174) in the vemurafenib arm

** compared with 31 % (10/31) in the vemurafenib arm

Although the data are derived from a retrospectively identified convenience sample that includes 81% of the ITT population and the randomization was not stratified for this variable, the number of patients in the convenience sample is sufficiently large (n=400) such that the principles of randomization are likely to have been preserved. In addition, there is no evidence that patients with BRAF V600K mutation-positive tumors who are identified as “positive” by this assay are biologically different from those who are not identified, based on data reviewed by CDRH at the time of the original approval of this companion diagnostic test. Finally, while these analyses are exploratory, the data for all efficacy endpoints consistently favor the cobimetinib plus vemurafenib arm in both subgroups. With regard to patients with BRAF V600K mutation-positive melanoma, the point estimates for the treatment effects were larger for PFS, OS, and ORR than for those with BRAF V600E mutation-positive melanoma. Given the totality of the data, which is consistent with effects in BRAF V600K mutation-positive melanoma with another FDA-approved MEK inhibitor, when administered with a BRAF inhibitor, the data provide compelling evidence of efficacy in this subgroup. Therefore, the indication will be extended to include this subgroup, with a post-marketing commitment to identify/develop a test for a sensitive test that can be used as a companion diagnostic for cobimetinib.

8. Safety

Size of the database.

The safety database relied primarily on the 247 cobimetinib plus vemurafenib-treated patients in the major efficacy study supplemented by the clinical study report from Study NO25395, which enrolled 129 patients treated according to one of three different schedules of cobimetinib, with twice daily vemurafenib, and cobimetinib doses ranging from 60-100 mg daily. The size of the safety database of 376 patients was sufficient to detect serious risks occurring at an incidence of 1%. In light of the serious risks observed in the safety database of 376 patients in the major efficacy trial, and safety information identified by another approved product in this class, there is sufficient information to formulate a risk:benefit assessment.

The safety of cobimetinib was evaluated primarily in the 247 patients receiving cobimetinib in Study GPO14821; 66% of patients exposed to cobimetinib for more than 6 months and 24% were exposed cobimetinib for more greater than 1 year. Patients with abnormal liver function tests, history of acute coronary syndrome within 6 months, or evidence of Class II or greater congestive heart failure (New York Heart Association) were not eligible for this trial. The most common adverse reactions in patients receiving cobimetinib and vemurafenib ($\geq 20\%$) were diarrhea, nausea, vomiting, rash, arthralgia, fatigue, photosensitivity reaction, and pyrexia. The most common Grade 3 or 4 laboratory abnormalities were elevations in creatine phosphokinase (13%), GGT (13%), ALT (11%), AST (9%). Fifteen percent of patients discontinued cobimetinib and 55% required dose reductions or interruptions for adverse reactions. The most common adverse reactions resulting in permanent discontinuation were elevation in liver enzymes, rash, pyrexia, and retinal detachment. Among the 247 patients receiving COTELLIC, adverse reactions led to dose interruption or reductions in 55%. The most common reasons for dose interruptions or reductions of COTELLIC were rash (11%), diarrhea (9%), chorioretinopathy, (7%), pyrexia (6%), vomiting (6%), nausea (5%), and increased creatine phosphokinase (CPK) (4.9%).

Serious risks of cobimetinib, which are included in the Warnings and Precautions section of product labeling, are summarized in the subsection below.

Major safety concerns related to labeling

- (b) (4) *Malignancies*: This is an established adverse reaction of vemurafenib; the addition of cobimetinib reduced but did not eliminate this risk. The incidences of cutaneous squamous cell carcinoma (cuSCC) or keratoacanthoma (KA) (6% and 20%), and second primary melanoma (0.8% and 2.4%) were lower while the incidence of basal cell carcinoma (4.5% and 2.4%), in the cobimetinib plus vemurafenib and vemurafenib arms, respectively. There were fewer patients (2 patients and 8 patients) diagnosed with non-cutaneous malignancies during Study GO28141 in that there were two patients with non-cutaneous malignancies in the cobimetinib plus vemurafenib and vemurafenib arms, respectively.
- *Hemorrhage*: This was identified as a potential risk based on identification of this as a risk with the other product in this class, trametinib. In Study 18421, the incidence of Grade 3-4

hemorrhages in 1.2% and 0.8% in the cobimetinib plus vemurafenib and vemurafenib arms, respectively and the overall incidence of hemorrhage (Grades 1-4) was 13% and 7% in the cobimetinib plus vemurafenib and vemurafenib arms, respectively. Sites of hemorrhagic events were CNS, gastrointestinal tract, genitourinary tract, and reproductive system, in each of these sites, the incidence was higher in the cobimetinib plus vemurafenib arm compared with the vemurafenib arm.

- *Cardiomyopathy*: This was identified as a potential risk prior to the initiation of Study GO28141; thus the trial was designed to exclude patients with an abnormal left ventricular ejection fraction (LVEF) and to conduct serial monitoring of LVEF (by MUGA or echocardiogram) at baseline, Week 5, Week 17, Week 29, Week 43, and then every 4 to 6 months thereafter while receiving protocol-specified treatment. The incidence of cardiomyopathy, defined as symptomatic and asymptomatic decline in left ventricular ejection fraction (LVEF) of an absolute $\geq 10\%$ and below the lower institutional limit of normal, was increased in patients receiving cobimetinib with vemurafenib compared with vemurafenib alone. Grade 2 -3 decreases in LVEF occurred in 26% and 19% of patients receiving cobimetinib with vemurafenib and vemurafenib, respectively. Recover of LVEF to the normal range or within 10% of baseline values was documented in 62% of patients receiving cobimetinib with vemurafenib; the time to resolution was variable (range: 4 days to 12 months).
- *Severe (b) (4) reactions*: Severe skin toxicity is a labeled risk of vemurafenib and was observed in the development program of cobimetinib with vemurafenib. The incidence of Grade 3 to 4 rash was similar (14% in the cobimetinib with vemurafenib arm and 13% in the vemurafenib arm), however the severity of the skin toxicity was increased with the addition of cobimetinib (Grade 4 rash 1.6% and none) and rash resulting in hospitalization (2.8% and 0.8%) for patients receiving cobimetinib with vemurafenib and vemurafenib, respectively.
- *Hepatotoxicity*, as detected by laboratory monitoring, was increased in patients receiving cobimetinib with vemurafenib compared with vemurafenib alone. The incidence of Hy's law cases [Concurrent elevation in ALT >3 times the upper limit of normal (ULN) and bilirubin >2 X ULN in the absence of significant alkaline phosphatase >2 X ULN] was 0.4% vs. none and of Grade 3 or 4 elevations in alanine aminotransferase (11% vs. 6%), for aspartate aminotransferase (7% vs 2.1%), for total bilirubin (1.6% vs. 1.2%), and for alkaline phosphatase (7% vs 3.3%) in patients receiving cobimetinib plus vemurafenib and vemurafenib, respectively.
- *Rhabdomyolysis*, defined as elevation of serum creatine phosphokinase of more than 10 times the baseline value with a concurrent increase in serum creatinine of 1.5 times or greater compared to baseline, was 3.6% in patients receiving cobimetinib with vemurafenib compared with 0.4% with vemurafenib alone. The incidence of Grade 3 or 4 CPK elevations was 12% and 0.4% in patients receiving cobimetinib with vemurafenib and vemurafenib alone, respectively.

- *Severe Photosensitivity*, defined as Grade 3 photosensitivity, was increased (4% vs. none) in patients receiving cobimetinib with vemurafenib compared to vemurafenib alone. The incidence of Grade 1-2 photosensitivity was 43%.
- *Serous Retinopathy*: Genentech retrospectively collected serial ocular coherence tomography (OCT) scans and reports from clinical study sites who were able to provide raw imaging files that enrolled patients to Studies NO25395 and GO28141, regardless of whether the patient had an on-study serous retinopathy event. Through the retrospective review, Genentech stated that they were able to provide high quality, serial baseline and post-exposure) ophthalmologic assessments for a total of 47 patients, of whom 35 patients (74%) were enrolled in Study GO28141 and 12 patients (26%) were enrolled in Study NO25395. Among these 47 patients, 35 patients (74%) were treated with cobimetinib plus vemurafenib in Studies GO28141 and NO25395 and 12 patients received vemurafenib plus placebo in Study GO28141.

Based on Dr. Chambers' assessment of the data provided, none of the 47 patients had serious retinopathy at baseline. Following study treatment, 9 (26%) of the 35 patients who received cobimetinib 60 mg daily for days 1-21, in combination with vemurafenib 960 mg twice daily, of each 28-day cycle developed serous retinopathy; serous retinopathy was bilateral in 8 patients and unilateral in one patient. Five of these patients were enrolled in Study GO28141 and four patients were enrolled in Study NO25395. Almost all cases of subretinal fluid accumulation were bilateral and subfoveal; in approximately 50% of the cases was multifocal. Dr. Chambers noted that, in contrast to "classical" serous retinopathy which generally presents in young men, unilateral eye involvement and in acute cases, typically presents with a single collection of subretinal fluid secondary, these cases were similar to the cases reported with other MEK inhibitors, with an equal distribution in males and females, bilateral involvement and early onset (median onset less than 34 days after initiation of cobimetinib). Dr. Chambers noted that the OCT scan findings are consistent with the reported incidence of serous retinopathy reported in cobimetinib-treated patients enrolled in Study GO28141 based on submission of adverse reaction reports by investigators; however, the monitoring by OCT was suboptimal and clustered around cycle 1, therefore, the true incidence of serous retinopathy based on systematic serial OCT evaluation in a well-defined population is unknown. Based on the data submitted, cobimetinib-induced serous retinopathy appears to be reversible in most cases without compromising visual acuity following interruption of dosing. The risk of the serous retinopathy may be mitigated by product labeling with recommended dose modifications, however a post-marketing requirement under 505(o) has been identified to further characterize the incidence and outcomes of this risk.

An additional safety concern arising from the observation that cobimetinib binds to the μ (μ) opioid receptor was evaluated by nonclinical and clinical reviewers and the Controlled Substances Staff (CSS). The CSS reviewers concluded that cobimetinib has moderate affinity at μ opioid receptors in the brain (600 nM); however, there were no abuse-related adverse events (including euphoria) identified in Studies NO25395 and GO28141 and therefore there does not appear to be evidence of abuse potential with cobimetinib, despite having activity at the μ opioid receptor. The CSS reviewers stated that in the absence of abuse-related signals

in humans, it is not necessary to conduct a full abuse potential assessment for a drug indicated for the treatment of patients with cancer who are under close medical supervision for management of the cancer and drug-related toxicity. The CSS reviewers did recommend that this risk be monitored in the post-marketing experience; the Division of Pharmacovigilance was informed of this recommendation for consideration in future monitoring of post-marketing adverse event reports.

REMS

Genentech did not propose Risk Evaluation and Mitigation Strategies. The clinical review team and DRISK reviewer agreed that REMS are not required to ensure safe use; serious risks of cobimetinib can be mitigated through description of the risks and inclusion of recommended monitoring for and management of these risks. FDA requested that a pharmacovigilance plan be developed and submitted by Genentech to monitor for increased severity of these known risks and to monitor for new safety signals.

- *PMRs and PMCs*

FDA has required the following post-marketing requirements under 505(o) to assess the risks of increased toxicity in patients with hepatic impairment where the pharmacokinetics of cobimetinib have not been characterized and are expected to reach toxic levels at the recommended dose and to better characterize the risks and outcomes of cobimetinib-induced serous retinopathy.

- Complete a pharmacokinetic study to determine the appropriate dose of cobimetinib in patients with hepatic impairment in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”
- Provide an integrated safety analyses from an adequate number of randomized controlled clinical trial(s) using cobimetinib to identify and characterize the risk of retinal pigmented epithelial detachments (RPED) and subsequent sequelae, including the frequency, time course and if needed, dose alternation required to minimize the impact of retinal pigmented epithelial detachments including safety evaluations adequate to inform labeling of patient populations at highest risk and to provide evidence-based dose modification and monitoring recommendations in labeling of RPED events.

9. Advisory Committee Meeting

This NDA was not referred to the Oncologic Drugs Advisory Committee (ODAC) for advice because this drug is not the first in its class, the safety profile is similar to that of other drugs approved for this indication, the clinical trial design is acceptable, and the evaluation of the safety data when used in the treatment of BRAF V600 mutation positive metastatic melanoma did not raise significant safety or efficacy issues that were unexpected in the intended population, and outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

10. Pediatrics

On January 31, 2014, Orphan Drug Designation was granted for cobimetinib for Stages IIB, IIC, III and IV melanoma with BRAF V600 mutation. Therefore, this NDA for this proposed indication is exempt from the requirements of the Pediatric Research Equity Act (PREA).

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: On February 13, 2015, FDA issued a “Conditionally Acceptable” letter, stated that the proposed proprietary name, Cotellic, was acceptable.
- Physician labeling (major issues that were discussed, resolved, or not resolved)
 - Boxed Warning: A boxed warning was not proposed and the review team did not identify safety issues requiring a boxed warning
 - Indications and Usage: Revised to include patients with BRAF V600K mutation- (b) (4) melanoma for the reasons discussed in Section 7 of this Summary Review; added limitation of use for patients with BRAF wild type melanoma, because vemurafenib carries this limitation of use and cobimetinib is only indicated for use with vemurafenib.
 - Dosage and Administration: extensively edited for brevity; removed (b) (4) (b) (4) moved information on avoidance of strong CYP3A inhibitors higher in this section to ensure prominence, given the risk of an approximately 7-fold increase in exposure, need to reduce cobimetinib from 60mg to 20mg if a strong CYP3A inhibitor is taken (b) (4)

- (b) (4)
; removed (b) (4)
; placed all dose modifications for adverse reactions in a single table.
- Dosage Forms and Strengths: Included additional information describing appearance as per 21 CFR 201.57
 - Contraindications: no changes
 - Warnings and Precautions: Included all adverse reactions requiring dose modifications and/or specific monitoring to identify risks in this section, specifically the increased risk of (b) (4) primary cancers, hemorrhage, severe (b) (4) toxicity (rash), hepatotoxicity, rhabdomyolysis, and severe photosensitivity reactions. In all subsections, added additional information characterizing the incidence of the risk and steps to mitigate risk including specific monitoring and dose adjustments, per 21 CFR 201.57. Based on mechanism of action and animal data, included a subsection on embryofetal toxicity.
 - Adverse Reactions: removed (b) (4)
 - Drug Interactions: revised to discuss only interactions that are clinically important with information on the lack of clinically important interactions described in Section 12 of the USPI; revised description of interaction between cobimetinib and strong CYP3A inducers which can result in decrease in exposure of 80% (likely to affect efficacy); based on the magnitude of the predicted increase in cobimetinib exposure (7-fold) noted the potential for increase toxicity and added information on avoidance of CYP3A inhibitors to Dosage and Administration section, with directions for use in patients taking 60 mg.
 - Use in Specific Populations: Revised for conformance with the content and format required under the Pregnancy and Lactation Labeling Rule (PLLR); added subsections on use in males and females of reproductive potential; revised section 8.4 to include information on studies conducted in juvenile animals; revised section 8.5 to include statement per 21 CFR 201.57, that insufficient information was available to assess differences in patients ≥ 65 years, based on data in less than 100 elderly patients exposed to cobimetinib. Included information on recommended dose adjustments in patients with hepatic or renal impairment to these subsections.
 - Overdosage: Edited for brevity, removed (b) (4)
 - Description: revised to correct product name (replace (b) (4) with fumarate) as requested by Genentech.
 - Clinical Pharmacology: Mechanism of Action subsection edited for brevity, to accurately reflect description of studies with regard to BRAF V600 in tumor/cell lines evaluated in pharmacology studies, and to remove (b) (4)
Pharmacodynamics subsection revised to include clinical information on cobimetinib effects on cardiac electrophysiology (QTc). Clinical Pharmacology subsection edited to include results of studies assessing drug interactions that were not clinically significant (moved from section 7 of USPI), details of popPK studies assessing for potential effects in patients with hepatic or renal impairment.

- Nonclinical Pharmacology/Toxicology: added information on exposure in animals as compared to exposure with the recommended clinical dose in humans, to provide context.
 - Clinical Studies: Removed [REDACTED] (b) (4)
[REDACTED]
Expanding information characterizing study population for primary efficacy trial, included updated efficacy results for the reasons discussed in Section 7, removed [REDACTED] (b) (4)
[REDACTED].
 - References: No references were proposed; [REDACTED] (b) (4)
[REDACTED]
 - How Supplied/Storage: Removed [REDACTED] (b) (4)
[REDACTED]
 - Patient Counseling: edited to include information on additions to Warnings and Precautions and for conformance to format as per FDA Guidances on product labeling.
- Carton and immediate container labels: Agreement reached on final carton/containing labeling; edited to increase legibility; removed [REDACTED] (b) (4), and for conformance with FDA regulations on carton/container labeling.
 - Patient labeling/Medication guide: Edited for conformance with changes to the USPI and for content and format per regulation and FDA policy.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: I concur with the recommendations of the reviewers and also recommend that this NDA be approved with agreed-upon final labeling.
- Risk Benefit Assessment
Metastatic, BRAF-V600 mutation-positive melanoma is a serious, life-threatening disease with a 5-year survival rate of approximately 16%. The NDA contained the results of an adequate and well-controlled trial that demonstrated a statistically robust and clinically important improvement in overall survival, progression-free survival, and overall response rate when cobimetinib was added to vemurafenib, an FDA-approved treatment for this BRAF mutation-positive metastatic melanoma, as compared to vemurafenib alone, thus advancing and extending the benefits of this genetically targeted treatment approach.

The serious risks of cobimetinib, occurring more commonly in the cobimetinib plus vemurafenib arm compared with vemurafenib alone, were an increased risk of second primary basal cell cancers, hemorrhagic events, cardiomyopathy as detected by clinically important decreases in left ventricular ejection fraction, severe skin toxicity, serous retinopathy, rhabdomyolysis, and severe photosensitivity reactions. In addition, the addition of cobimetinib to vemurafenib, decreases but does not eliminate the risk of an

increased risk of second primary cutaneous (cutaneous squamous cell carcinoma, keratoacanthoma, and melanoma) and non-cutaneous primary cancers. In addition, dose modifications for adverse reactions were common, with 15% of patients discontinuing cobimetinib for adverse reactions and 55% of patients requiring dose reductions or interruptions for adverse reactions. These adverse reactions are considered acceptable by the patient and medical community, given the incurable nature and low 5-year survival rates.

Based on the demonstration of the 37% reduction in the immediate risk of death (hazard ratio of 0.63), prolongation in progression-free survival and increased response rate, the benefit of the addition of cobimetinib to vemurafenib outweigh the serious risks of cobimetinib and provide a favorable risk:benefit assessment. the clinical improvement in overall survival. Therefore, I recommend approval of this NDA for the agreed-upon proposed indication.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
I concur with the recommendations of the clinical review team and DRISK reviewer that REMS are not required to ensure safe use of cobimetinib and that serious risks of cobimetinib can be mitigated through description of the risks and inclusion of recommended monitoring for and management of these risks. FDA requested that a pharmacovigilance plan be developed and submitted by Genentech to monitor for increased severity of these known risks and to monitor for new safety signals.
- Recommendation for other Postmarketing Requirements and Commitments

FDA has required the following post-marketing requirements under 505(o) to assess the risks of increased toxicity in patients with hepatic impairment where the pharmacokinetics of cobimetinib have not been characterized and are expected to reach toxic levels at the recommended dose and to better characterize the risks and outcomes of cobimetinib-induced serous retinopathy.

- Complete a pharmacokinetic study to determine the appropriate dose of cobimetinib in patients with hepatic impairment in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”
- Provide an integrated safety analyses from an adequate number of randomized controlled clinical trial(s) using cobimetinib to identify and characterize the risk of retinal pigmented epithelial detachments (RPED) and subsequent sequelae, including the frequency, time course and if needed, dose alternation required to minimize the impact of retinal pigmented epithelial detachments including safety evaluations adequate to inform labeling of patient populations at highest risk and to provide evidence-based dose modification and monitoring recommendations in labeling of RPED events.

FDA has also requested the following post-marketing commitment to update the companion diagnostic test for selection of patients from whom vemurafenib is indicated, to describe the ability to detect BRAF V600K.

- Submit to CDRH a PMA supplement for the FDA-approved Roche cobas 4800 BRAF Mutation test, to revise the instructions for use to include an updated indications for use statement and updated clinical section to reference the detection of V600K mutations in the trial that supported the FDA approval of cobimetinib with vemurafenib for patients with unresectable or metastatic melanoma with BRAF V600E and V600K mutations.

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/s/

PATRICIA KEEGAN
11/05/2015