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*APPLICATION NUMBER:*

**206192Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	November 9, 2015
<b>From</b>	Marc Theoret, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA # / Supplement#</b>	NDA 206192
<b>Applicant</b>	Genentech, Inc.
<b>Date of Submission</b>	December 11, 2014
<b>PDUFA Goal Date (Extension)</b>	November 11, 2015
<b>Proprietary Name / Established (USAN) names</b>	Cotellic / cobimetinib
<b>Dosage forms / Strength</b>	Tablets / 20 mg
<b>Proposed Indication(s)</b>	for use in combination with Zelboraf <sup>®</sup> (vemurafenib) for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation
<b>Recommended:</b>	Approval

<b>Material Reviewed / Consultants</b>	<b>Primary/ Secondary Reviewer</b>
Clinical Review	Ruthann Giusti, M.D. / Marc Theoret, M.D.
Statistical Review	Xiaoping (Janet) Jiang, Ph.D. / Kun He, Ph.D.
Regulatory Project Manager	Meredith Libeg / Monica Hughes
Pharmacology Toxicology Review	Shawna L Weiss, Ph.D. and Anwar Goheer, Ph.D. / Whitney Helms, Ph.D.
Product Reviews	Substance: Gaetan Ladouceur Product: Donghao Lu Process and Microbiology: Zhengang Ge Facility: Sunita Iyer Biopharmaceutics: Maziar Kakhi Application Technical Lead: Olen Stephens, Ph.D.
Clinical Pharmacology Review	Clin Pharm: Ruby Leong, Pharm, D./ Hong Zhao, Ph.D.
OSE/DRISK	Amarilys Vega, M.D., M.P.H. / Naomi Redd, Pharm.D.
OSE/DMEPA	Otto Townsend, Pharm.D./ Chi-Ming (Alice) Tu, Pharm.D.
OSI	Lauren Iacono-Connor, Ph.D./ Susan D. Thompson, M.D.
Interdisciplinary Review Team for QT Studies	Dinko Rekić / Jiang Liu, Ph.D. / Norman L Stockbridge

## 1. Introduction

On December 11, 2014, Genentech Inc. (Genentech) submitted New Drug Application (NDA) 206192 for approval of cobimetinib (Cotellic) for the following indication:

for use in combination with Zelboraf<sup>®</sup> (vemurafenib) for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation.

On February 13, 2015, FDA issued a Priority Review Designation letter notifying Genentech of the review designation of NDA 206192 as priority review. On February 23, 2015, FDA issued a Filing Communication – Filing Review Issues Identified letter. On June 25, 2015, FDA issued a review extension - major amendment letter informing Genentech that the June 15, 2015, submission of datasets to the NDA constituted a major amendment and that the extended use fee goal date is November 11, 2015.

The Applicant relies on the results from a single adequate and well-controlled trial, Trial GO28141, a multicenter, international, double-blind, randomized (1:1), active-controlled trial, to serve as the primary evidence in support of the safety and efficacy of cobimetinib in patients with unresectable or metastatic, BRAF V600 mutation-positive melanoma (b) (4)

Patients were allocated in a 1:1 ratio to receive vemurafenib 960 mg orally twice daily on Days 1-28 and either cobimetinib 60 mg (n=247) or placebo (n=248) orally once daily on Days 1 to 21 on an every 28-day cycle until disease progression or unacceptable toxicity.

The trial demonstrated improvements in overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) with cobimetinib. Analysis of the primary endpoint, PFS as assessed by the investigator per RECIST v1.1, demonstrated a median PFS of 12.3 months [95% confidence interval (CI): 9.5, 13.4 months] on the cobimetinib plus vemurafenib arm and 7.2 months (95% CI: 5.6, 7.5 months) on the single-agent vemurafenib arm with a HR of 0.56 [95% CI: 0.45, 0.70; p < 0.0001 (two-sided, p-value based on stratified log-rank test)]. An interim analysis of OS based on observation of 75% of the events required for the final analysis crossed the boundary for claiming statistical significance with superiority of the cobimetinib plus vemurafenib arm compared to the single-agent vemurafenib arm, a HR of 0.63 (95% CI: 0.47, 0.85; p value = 0.0019). The confirmed, investigator-assessed overall response rate (ORR) per RECIST v1.1 was 69.6% (95% CI: 63.5, 75.3) on the cobimetinib plus vemurafenib arm and was 50% (95% CI: 43.6, 56.4) on the single-agent vemurafenib arm.

The key issues with this application were:

- Inclusion of results in patients with BRAF V600K mutation-positive melanoma and an indication that identifies this population. The BRAF V600 mutation in melanoma was detected in the GO28141 trial using the cobas 4800 BRAF mutation test kit which is designed to detect the BRAF V600E mutation in melanoma but also reports a positive result in ~66% of melanoma specimens with BRAF V600K mutation.

- Inclusion of analyses of PFS and ORR with 7 months of additional follow-up—analyses that occurred after the primary analyses of these endpoints had demonstrated statistical significance.

These issues are considered further in Section 7 of the review.

## 2. Background

- Indicated Population

Melanoma is the fifth most common cancer in men and seventh most common cancer in women in the United States. In 2015, it is estimated that there will be 73,870 new melanoma cases and 9,940 deaths from melanoma in the U.S.<sup>1</sup> Metastatic melanoma accounts for approximately 4% of all newly diagnosed melanoma cases.<sup>2</sup> Melanoma, once metastatic, carries a grim prognosis—the five year survival rate is historically less than 10%—and develops at a relatively early age which results in a substantial number of years of life lost per person.<sup>3</sup> Melanoma harbors BRAF mutations in approximately 40-60% of patients.<sup>4,5,6</sup> The most common of these BRAF mutations is V600E although patients with melanoma harboring BRAF V600K mutations are a substantial proportion of patients with BRAF V600 mutation-positive melanoma, approximately 5-30%.<sup>7</sup>

In general, FDA-approved treatment options in use for treatment of metastatic melanoma include immunotherapy (interleukin-2, ipilimumab, pembrolizumab, nivolumab), chemotherapy (DTIC), and, if BRAF V600 mutation positive, BRAF inhibitors (vemurafenib, dabrafenib) and/or a MEK inhibitor (trametinib). Of the FDA-approved products for treatment of unresectable or metastatic melanoma, only ipilimumab and vemurafenib have labeling claims of demonstration of improvement in overall survival compared with conventional therapy (Refer to Table Appendix A, reproduced from the FDA Clinical Review of NDA 206192, for description of treatment effects of FDA approved therapies for metastatic melanoma).

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<sup>1</sup> Siegel, R, KD Miller, and A Jemal, 2015, Cancer Statistics, 2015, CA Cancer J Clin, 65:5-29.

<sup>2</sup> Howlader, N, AM Noone, M Krapcho, N Neyman, R Aminou, et al., 2012, SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations), National Cancer Institute. Bethesda, MD, [http://seer.cancer.gov/csr/1975\\_2009\\_pops09/](http://seer.cancer.gov/csr/1975_2009_pops09/), based on November 2011 SEER data submission, posted to the SEER web site, 2012.

<sup>3</sup> Ekwueme, DU, GP Guy, C Li, SH Rim, P Parelkar et al., 2011, The health burden and economic costs of cutaneous melanoma mortality by race/ethnicity-United States, 2000 to 2006, J Am Acad Dermatol, 65 (5 Suppl 1):S133-43.

<sup>4</sup> Davies, H, GR Bignell, C Cox, P Stephens, S Edkins, et al., 2002, Mutations of the BRAF gene in human cancer, Nature, 417:949-954.

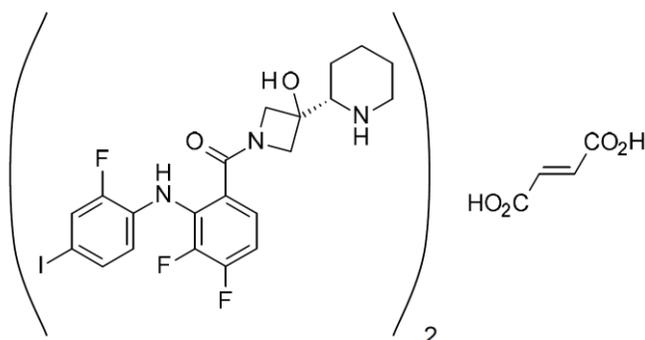
<sup>5</sup> Jakob, JA, RL Bassett, CS Ng, JL Curry, RW Joseph, et al., 2012, NRAS mutation status is an independent prognostic factor in metastatic melanoma, Cancer, 118:4014-4023.

<sup>6</sup> Long, GV, AM Menzies, AM Nagrial, LE Haydu, AL Hamilton, et al., 2011, Prognostic and clinicopathologic associations of oncogenic BRAF in metastatic melanoma, J Clin Oncol, 29:1239-1246.

<sup>7</sup> Rubinstein, JC, M Sznol, AC Pavlick, S Ariyan, E Cheng, et. Al, 2010, Incidence of the V600K mutation among melanoma patients with BRAF mutations, and potential therapeutic response to specific BRAF inhibitor PLX4032, J Transl Med, 8:67-69.

- Mechanism of Action/Pharmacology

Cobimetinib is a kinase inhibitor with the following chemical structure:



BRAF V600E and V600K mutations result in constitutive activation of the BRAF pathway which includes MEK1 and MEK2.

Cobimetinib is a reversible inhibitor of mitogen-activated protein kinase (MAPK)/extracellular signal regulated kinase 1 (MEK1) and MEK2. MEK proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes cellular proliferation. As summarized in the FDA Pharmacology/ Toxicology review, of a panel of 103 recombinant serine-threonine and tyrosine kinases, cobimetinib demonstrated IC<sub>50</sub>s of 0.95 and 199 nM for MEK1 and MEK2, respectively, and no inhibition of the other kinases at concentrations of up to 10 μM.

Although not fully characterized, several mechanisms of resistance of melanoma to BRAF inhibitors have been described in the literature, including: (1) intrinsic resistance factors such as Cyclin D1 amplification, PTEN loss, and hepatocyte growth factor product; (2) acquired resistance factors leading to ERK activation such as receptor tyrosine kinase upregulation, NRAS mutations, splice variants of mutant BRAF, secondary mutations in MEK, and acquired resistance mutations; and (3), acquired resistance factors leading to activation of non-ERK pathways such as the PI3K pathway through platelet derived growth factor receptor beta or insulin-like growth factor 1 receptor.<sup>8</sup> Resistance to BRAF inhibitors used as a single agent for the treatment of BRAF V600E mutation-positive unresectable or metastatic melanoma develops relatively quickly with a median progression-free survival of approximately 5 months and, in patients who achieve an objective response, duration of response of approximately 5 to 6 months.<sup>9,10</sup>

Dabrafenib (a BRAF inhibitor) and trametinib (a MEK inhibitor) were the first to be FDA-approved for use together as a regimen for treatment of patients of BRAF V600E and BRAF V600K mutation-positive, unresectable or metastatic melanoma<sup>7</sup>; however, this was an

<sup>8</sup> Reviewed by Sullivan, RJ, and KT Flaherty, 2013, Resistance to BRAF-targeted therapy in melanoma, *Eu J Cancer*, 49:1297-1304.

<sup>9</sup> Vemurafenib (Zelboraf), Hoffman-La Roche, USPI August 2015, Drugs@FDA.com.

<sup>10</sup> Dabrafenib (Tafinlar), Novartis, USPI January 2014, Drugs@FDA.com

accelerated approval based on demonstration of ORR of large magnitude with prolonged response durations and thus is not considered an available therapy from the regulatory perspective for consideration of an FDA Expedited Program.<sup>11</sup>

As summarized in the FDA Nonclinical Pharmacology and Toxicology Review, cobimetinib inhibited tumor growth in vivo in xenograft experiments in mice implanted with tumor cell lines expressing BRAF V600E. Furthermore, use of cobimetinib with vemurafenib in combination resulted in increased (compared to either drug alone) apoptosis in vitro and reduced tumor growth in xenograft models in mice of A375 tumor cell lines harboring BRAF V600E mutations.

- Regulatory History

I reviewed the presubmission regulatory history for this NDA and agree with the summary as provided in the FDA Clinical Review of NDA 206192 with the following addition.

- November 29, 2013: FDA provided written responses in lieu of a meeting in response to a September 20, 2013, Type C meeting request with the stated purpose of reaching agreement on the proposed content and format of the NDA to support the proposed indication and enable full approval. FDA stated that purpose of the written responses was to provide general technical comments on the format and content of a planned NDA but do not constitute an agreement on the format and content of a complete application under PDUFA V. Furthermore, FDA instructed Hoffman La-Roche to submit a request for a Type B, pre-NDA meeting for Roche and FDA to discuss and reach agreement on the content of a complete application for the proposed indication, if Roche decided to submit an NDA after its review of the results of Trial GO21841. FDA informed Roche that it did not agree with a primary analysis of ORR, as proposed, that violated the ITT principle and the primary analysis of ORR must be conducted in the ITT population and that the objective response must have been confirmed to be durable for at least 4 weeks.
- February 21, 2014: (b) (4) Roche requested the teleconference based on Study NO25395, a Phase 1b, open-label, dose-escalation and expansion study in patients with BRAF V600-mutation positive unresectable or metastatic melanoma. Roche had also submitted Type B, pre-NDA meeting for a potential NDA in the second half of 2014 seeking accelerated approval based on analysis of efficacy and safety data from NO25395. At the meeting, FDA requested that Roche submit the following information (b) (4) (1) demographics for patients who received single-agent vemurafenib including response rate (RR), and duration of response/dose level at a 95% CI across trials using vemurafenib, (2) description of the similarities and differences of patient populations who received single-agent vemurafenib with relevant

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<sup>11</sup> FDA Guidance for Industry “Expedited Programs for Serious Conditions – Drugs and Biologics” at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

clinical experience across clinical trials using historical data and pooled analysis, (3) a detailed description and analysis of the 63 patients receiving cobimetinib with vemurafenib in the Phase 1 trial, including prior therapies, extent of disease and baseline demographics, (4) data that demonstrates cobimetinib in combination with vemurafenib compared to single-agent vemurafenib demonstrates an improvement in response rate over existing therapies, (5) high-level safety and efficacy data (including duration of response and 95% CIs). FDA reiterated that this information is needed because there is insufficient information to make an assessment of cobimetinib vs. vemurafenib.

- February 28, 2014: FDA denied Roche's February 7, 2015, request for a Type B meeting to discuss and reach agreement on the acceptability of the clinical trial results from Study NO25395 and supporting studies to form the basis of an NDA for cobimetinib for use in combination with vemurafenib for the proposed indication and acceptability of the bridging strategy to support approval of the commercial drug formulation; the information contained in the meeting request was insufficient for a productive pre-NDA meeting. FDA advised Roche to resubmit the meeting request as a Type B meeting when the high-level data to support the pivotal trial is available.



- August 6, 2014: FDA communicated an information request for Roche to clarify its June 17, 2014, request for Fast Track designation in order to specify the indication, specifically, the patient population, i.e., BRAF inhibitor naïve or refractory, and the anticipated benefit(s) of use of cobimetinib in support of the fast track designation. On August 15, 2014, FDA designated as a Fast Track development program the investigation of cobimetinib with vemurafenib for the treatment of patients with BRAF V600E-mutation positive, unresectable or metastatic melanoma to demonstrate improved progression-free survival and overall survival.

- October 8, 2014: FDA held a Type B, pre-NDA meeting with Roche to obtain guidance on the acceptability of the clinical trial results from study GO28141 and supporting studies to form the basis of an NDA for cobimetinib in combination with vemurafenib for treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation. FDA stated that the high-level efficacy and safety results as presented in the meeting briefing document appear adequate to support an NDA filing. In response to Roche's proposal to conduct an earlier assessment of final OS, FDA stated that it did not agree to a reduction in the number events for any efficacy analyses after seeing the interim data. However, FDA stated that "considering that the accrual is already completed, all enrolled patients will be continuously followed, and a larger treatment effect will be tested, FDA does not object to the proposed modifications." Furthermore, FDA agreed to Roche's proposal to include the results of the revised final analysis of OS in the label in a supplemental submission if the revised statistical analysis plan (SAP) was found to be acceptable and the trial meets the specified threshold for significance as described under the revised SAP.

FDA agreed with Roche's proposal that, based on the information provided, and provided there were no changes to the device specific to the combination use, a PMA supplement will not be needed for the cobas 4800 BRAF mutation test to support approval of cobimetinib in combination with vemurafenib for 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). Furthermore, FDA stated that if Roche intended to develop cobimetinib for a new indication that requires selection of patients with BRAF V600 mutation-positive tumors, a PMA supplement would be required.

### 3. CMC/Device

The primary reviewers of the product quality sections of the NDA were Gaetan Ladouceur (Drug Substance), Donghao Lu (Drug Product and Environmental Assessment), Zhengfang Ge (Process and Microbiology), Maziar Kakhi (Biopharmaceutics), Peter Perdue Jr. (ORA Lead), and Olen Stephens (Application Technical Lead) from the Office of Pharmaceutical Quality. As summarized by Olen Stephens, NDA 206192 is recommended for approval from a CMC perspective. There are no outstanding deficiencies and the manufacturing facilities have an approval recommendation. Labeling comments will be negotiated through the clinical project manager. A 30-month shelf-life will be granted through the approval letter based on stability data (b) (4). The product should be stored below 30°C (86°F).

- General product quality considerations

Cobimetinib ( (S)-[3,4-difluoro-2-(2-fluoro-4-iodophenylamino) phenyl] [3-hydroxy-3-(piperidin-2-yl) azetidin-1-yl]methanone hemifumarate has a molecular formula of  $C_{46}H_{46}F_6I_2N_6O_8$  ( $2 C_{21}H_{21}F_3IN_3O_2 \cdot C_4H_4O_4$ ) and a molecular weight of 1178.71 g/mol (salt), (b) (4) (free base).

The synthesis of cobimetinib drug substance (DS) consists of

(b) (4)

(b) (4)

The following summary of quality assessments of drug substance is excerpted from the FDA CMC Review of NDA 206192:

Cobimetinib fumarate ((S)-[3,4-difluoro-2-(2-fluoro-4-iodophenylamino) phenyl] [3-hydroxy-3-(piperidin-2-yl) azetidin-1-yl]methanone hemifumarate) is a (b) (4) white to off-white solid with (b) (4)

(b) (4). The drug substance is soluble under physiologically relevant conditions. The single stereogenic center does not racemize under drug substance storage conditions or drug product manufacture. The (b) (4) starting materials and their suppliers are designated as

(b) (4)

Description of these starting materials is described in the review below under section 2.3.S.2.2. The synthesis of cobimetinib fumarate is a (b) (4)

The following summary of quality assessments of drug substance is excerpted from the FDA CMC Review of NDA 206192:

Cobimetinib white, film-coated tablets are debossed with “COB” on one side and contain 20 mg of the free base. These non-sterile, immediate release tablets are formulated with USP/NF compendial excipients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, titanium dioxide, (b) (4) PEG 3350, talc. (b) (4). The tablets are manufactured by (b) (4)

(b) (4). The tablets are stored in 70 mL white, opaque, square, high-density polyethylene bottles (b) (4). Sufficient stability data was submitted at 30°C/75% RH to support a (b) (4) month shelf life with labeling to store the product below 30°C (86 °C). Note that these storage conditions and stability data were established to enable marketing in climate zones warmer and more humid than the US market. This approach is consistent with labeling for other clinical divisions, such as antiviral products.

- Facilities review/inspection

*Drug Substance Facilities*

The following table excerpted from the FDA CMC Review of NDA 206192 summarizes the inspection recommendations for manufacturers of DS:

Establishment name	FEI Number	Responsibilities and profile codes	Current status	Initial Risks Identified	Final Recommendation
F. Hoffmann- La Roche Ltd Grenzacherstrasse 124, Basel Switzerland	3002807200	CSN: Manufacturing of Active Substance (b) (4) analytical release and stability testing, batch disposition, warehousing/storage of active substance (b) (4)	Last inspection: 3/28/2014 (AC)	None	TCM: Acceptable based on district recommendation; re-evaluation date: (b) (4)  (Pre-approval inspection not recommended)
(b) (4)	(b) (4)	CRU: Manufacturing of Active Substance (b) (4)	Last inspection: (b) (4)	None	Acceptable based on profile/history Re-evaluation date: (b) (4) (Pre-approval inspection not recommended)
(b) (4)	(b) (4)	CTL: Alternate analytical testing site for (b) (4)	Last inspection: (b) (4)	None	Acceptable based on profile/history Re-evaluation date (b) (4) (Pre-approval inspection not recommended)

*Drug Product Facilities*

The following table excerpted from the FDA CMC Review of NDA 206192 summarizes the inspection recommendations for manufacturers of DP:

Establishment name	FEI Number	Responsibilities and profile codes	Current status	Initial Risks Identified	Final Recommendation
F. Hoffmann- La Roche Ltd Grenzacherstrasse 124, Basel Switzerland	3002807200	TCM: Bulk Drug Product manufacturing, analytical testing	Last Inspection: 3/28/2014 (AC)	None	TCM: Acceptable based on district recommendation; re-evaluation date: (b) (4) (Pre-approval inspection not recommended)
F. Hoffmann- La Roche Ltd Wurmisweg, Kaiseraugst, Switzerland	3003973536	CTL: Analytical testing of cobimetinib film-coated tablets	Last inspection: 4/08/2014 (AC)	None	Acceptable based on profile/history Re-evaluation date: (b) (4) (Pre-approval inspection not recommended)
Roche S.p.A Via Morelli 2, Segrate, Milan, Italy	3003716872	TCM/CTL: Primary and secondary packaging and analytical testing of cobimetinib film-coated tablets	Last inspection: 09/19/2013 (AC)	None	Acceptable based on profile/history Re-evaluation date: (b) (4) (Pre-approval inspection not recommended)

The Facilities Reviewer, Sunita Iyer, Ph.D., and OPQ/OPF/DIA/Branch 1 Branch Chief, Zhihao (Peter) Qui noted that the facilities involved with the manufacturing, testing, packaging, and labeling of the drug substance and drug product are adequate to support the approval of NDA 206192.

#### 4. Nonclinical Pharmacology/Toxicology

Shawna Weis, Ph.D. and Anwar Goheer, Ph.D., the primary nonclinical reviewers, Whitney Helms, Ph.D., the secondary reviewer, and John Leighton, Ph.D., the tertiary reviewer, concluded that the nonclinical pharmacology and toxicology data in the NDA support the approval of cobimetinib, for use in combination with vemurafenib in the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations.

- General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise).

The following information concerning general pharmacologic properties of cobimetinib was excerpted from the FDA Pharmacology and Toxicology Review of NDA 206192 [references provided in the review]:

Cobimetinib is a kinase inhibitor that inhibits MEK1 and 2 with IC<sub>50</sub>s of 0.95 and 199 nM, respectively, and the affinity appears to be greater for ATP-bound MEK1, suggesting a measure of selectivity for activated forms of MEK. Cobimetinib also bound the human  $\mu$  opioid receptor and L-type calcium channels at clinically achievable concentrations of the total drug. Potentially correlated with its activity on the  $\mu$ -opioid receptor was the observation that in the rat, high-dose (300 mg/kg) cobimetinib administration led to a small (18%) but statistically significant reduction in respiratory rate; however, because cobimetinib exhibited limited CNS penetration, the potential for significant, centrally mediated opioid pharmacology - such as dependency and withdrawal - is unclear.

The Applicant provided data from murine xenografts demonstrating the anti-tumor activity of cobimetinib in combination with vemurafenib in WT BRAF- and

vemurafenib resistant BRAF V600E-bearing tumors. Consistent with previous observations, administration of vemurafenib in the context of WT BRAF (A431 cells) resulted in paradoxically-enhanced tumor growth whereas cobimetinib, alone or in combination with vemurafenib, suppressed tumor growth relative to vehicle controls. Similarly, in vemurafenib-resistant V600E BRAF-bearing tumors, the combination both increased cellular apoptosis and suppressed tumor growth relative to vemurafenib alone.

The Applicant conducted 4 and 13-week general toxicology studies in rats and dogs. In the dog, the predominant target organ was the GI tract. Other potential histological target organs included the kidney, liver, and thyroid. Exposures at the minimum lethal dose (1 mg/kg/day) during the 13-week toxicity study in the dog were similar to those anticipated in humans (approximately 1X on the basis of C<sub>max</sub>, and about 0.5X on the basis of AUC).

In the 4-week rat study, the primary target organ was the skin, which may correlate with observations of rash in patients treated with cobimetinib and vemurafenib. Other potential target organs in the rat included the adrenals, thymus, liver, and lymph nodes. Exposures achieved on Day 16 of the 4-week toxicity study in the rat were approximately 3-fold higher than anticipated clinical exposures on the basis of both C<sub>max</sub> and AUC.

The FDA Pharmacology and Toxicology Review of NDA 206192 also noted that cobimetinib was non-mutagenic and was negative for micronucleus formation in the in vivo clastogenicity assay in rodent.

- Carcinogenicity

As summarized in the FDA Pharmacology/Toxicology Review of NDA 206192, the Applicant did not conduct carcinogenicity studies with cobimetinib and these studies are not required to support the approval of a drug intended to treat patients with advanced cancer, which is in accordance with the International Conference on Harmonization Guideline S9 (Nonclinical Evaluation of Anticancer Pharmaceuticals).

- Reproductive toxicology

As summarized in the FDA Pharmacology/Toxicology Review of NDA 206192, dedicated fertility studies were not conducted with cobimetinib; however, toxicology studies in rats demonstrated reproductive effects including ovarian findings of increased necrosis, decreases in corpora lutea, and cyts as well as increased vaginal epithelial cell apoptosis in female rats administered a high dose (10 mg/kg), which is a dose associated with significant mortality.

The FDA Pharmacology and Toxicology Review of NDA 206192 recommends that cobimetinib labeling contain a Warning for embryofetal toxicity. The following information to support this recommendation is excerpted from the FDA Pharmacology/Toxicology Review of NDA 206192:

In the embryofetal toxicology study in the rat, exposure to cobimetinib during the period of organogenesis was associated with frank maternal toxicity (body weight loss and lethality) at a dose of 10 mg/kg/day. Embryofetal effects observed at the 10 mg/kg dose level included an increased rate of early resorption, including total litter loss in two dams, and markedly increased post-implantation loss. Decreased fetal body weights and an increase in skeletal alterations, including decreased ossification, were observed at the 10 mg/kg dose level. Evidence of teratogenicity was observed at the 10 mg/kg dose level. Findings included malformations of the great vessels (missing and/or misplaced great vessels), and malformations of the eye sockets. Exposures ( $AUC_{0-24}$ ) at this dose level were 0.9 and 1.4X on Day 1 and Day 11, respectively, of human plasma exposures. These findings support a warning for embryofetal risk in the cobimetinib product label.

Because the number of animals used were low (10 pregnant dams per group) and the exposure levels achieved were low relative to therapeutic plasma levels in humans, it is unclear that the embryofetal risk has been adequately characterized for use in a broader patient population. Therefore, while the data from this dose-ranging study are sufficient to support the co-administration of cobimetinib with vemurafenib in patients with advanced melanoma, the Applicant will likely be required to conduct a definitive embryofetal toxicity study in both the rat and the rabbit if they intend to seek to expand the indication to include other therapeutic areas, particularly in patients whose disease is less advanced.

- Other notable issues (resolved or outstanding)

The review team discussed the nonclinical finding of binding of cobimetinib to the  $\mu$ -opioid receptor. The following was excerpted from the FDA Pharmacology/Toxicology Review of NDA 206192:

The binding of cobimetinib to the agonist site of the  $\mu$ -opioid receptor, in combination with a reduced respiratory rate observed in rats, triggered a consult to the Controlled Substance staff regarding the potential for abuse liability with cobimetinib. Given the toxicities associated with use of cobimetinib and the lack of clear dependency signals in patients, the Division does not believe that the potential for abuse is high; however, if the Controlled Substance staff believes that additional nonclinical studies to address abuse potential are warranted, they will be conducted as postmarketing requirements.

The Division consulted the FDA Controlled Substance Staff (CSS) regarding this finding. The following conclusions of the FDA CSS following review of the NDA is excerpted from the FDA CSS Consult Review of NDA 206192:

- Cobimetinib has moderate affinity at mu opioid receptors in the brain (600 nM).
- The Sponsor did not conduct any dedicated abuse-related studies in animals or humans.
- There are no abuse-related adverse events (including euphoria) produced by cobimetinib in Phase 1 or Phase 2/3 clinical studies.

- Based on the information submitted in the NDA, cobimetinib does not appear to have any abuse potential, despite having activity at the mu opioid receptor.
- In the absence of abuse-related signals in humans, it is not necessary to conduct a full abuse potential assessment for a drug indicated for the treatment of patients with cancer under serious medical supervision.

The FDA CSS recommended consideration of monitoring this potential risk in the postmarketing setting. The review team agreed with this recommendation.

## 5. Clinical Pharmacology/Biopharmaceutics

The FDA Clinical Pharmacology Review Team recommended approval of the NDA from the clinical pharmacology perspective. The Office of Clinical Pharmacology recommended one postmarketing requirement, a hepatic impairment trial (see Section 13 of this review).

- General clinical pharmacology/biopharmaceutics considerations, including absorption, metabolism, half-life, food effects, bioavailability, etc.

The clinical dosing regimen for the primary trial (GO28141) submitted in the NDA to support the safety and efficacy of cobimetinib was 60 mg orally once daily on Days 1-21 of each 28-day cycle. In this trial, cobimetinib was administered with the FDA-approved dosing regimen of vemurafenib: 960 mg orally twice daily. The following summary of the clinical dose selection is excerpted from the FDA Clinical Pharmacology Review of NDA 206192:

The proposed dosing regimen for cobimetinib is 60 mg QD for 21 days followed by 7-day rest with or without food in each 28-day cycle until disease progression or unacceptable toxicity. Dosing regimens of 0.05, 0.10, or 0.20 mg/kg, 10, 20, 40, 60, or 80 mg QD on a 21 day on / 7 day off (21/7) dose schedule and dosing regimens of 60, 80, 100, or 125 mg on a 14 day on / 14 day off (14/14) dose schedule were evaluated for cobimetinib as a single agent in Study MEK4592g. The maximum tolerated dose (MTD) of cobimetinib as a single agent was determined to be 60 mg QD on the 21/7 schedule and 100 mg QD on the 14/14 schedule. Dosing regimens of cobimetinib 60 mg QD on a 21/7 dose schedule plus vemurafenib 720 or 960 mg BID; cobimetinib 60, 80, or 100 mg QD on a 14/14 dose schedule plus vemurafenib 720 mg BID and 60 or 80 mg QD on a 14/14 dose schedule plus vemurafenib 960 mg BID; cobimetinib 60 mg QD continuously in each 28-day cycle plus vemurafenib 720 or 960 mg BID were evaluated in Study NO25395. The Applicant states that the 21/7 dose schedule provides a longer duration of cobimetinib exposure and prolonged suppression of MEK, and is associated with a lower incidence of AEs (including Grade  $\geq$  3 AEs) than the 14/14 dose schedule.<sup>2</sup>

The following summary of the pharmacokinetics of cobimetinib is excerpted from the FDA Clinical Pharmacology Review of NDA 206192:

The mean absolute bioavailability of cobimetinib is 46% (90% CI: 40%, 53%). Following oral administration of cobimetinib 60 mg once daily in cancer patients, the median time to achieve peak plasma levels ( $T_{max}$ ) was 2.4 (1, 24) hours with a mean

elimination half-life ( $t_{1/2}$ ) of 44 (23- 70) hours. The geometric mean steady-state  $AUC_{0-24h}$  was 4340 ng·h/mL (61% CV) and  $C_{max}$  was 273 ng/mL (60% CV). Cobimetinib exhibits linear time-independent PK, with exposures that are approximately dose proportional after single and repeat doses in the range of 10 to 100 mg. Following cobimetinib 60 mg QD, steady state is achieved within 9 days with 2.4-fold accumulation. The mean apparent clearance (CL/F) following multiple doses of cobimetinib 60 mg in cancer patients was 13.8 L/hr (61% CV).

- Drug-drug interactions

The following summary of the clinical dose selection is excerpted from the FDA Clinical Pharmacology Review of NDA 206192:

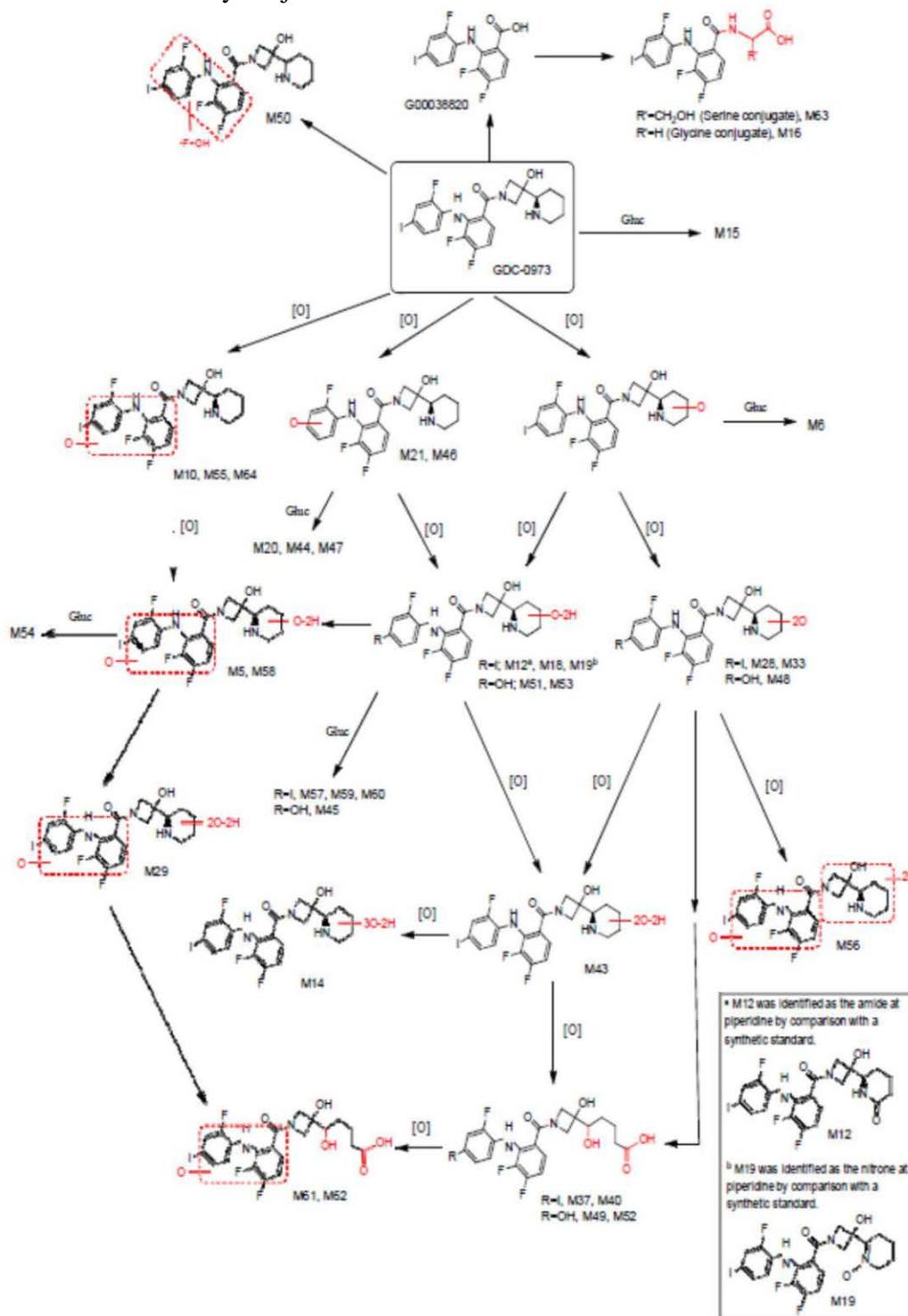
Cobimetinib is primarily metabolized by CYP3A and UGT2B7 in vitro. Coadministration of itraconazole (a strong CYP3A inhibitor) 200 mg QD for 14 days and a single dose of 10 mg cobimetinib increased cobimetinib AUC by 6.7-fold and  $C_{max}$  by 3.2-fold in healthy subjects. Therefore, concomitant use of strong CYP3A inhibitors with cobimetinib should be avoided. Concomitant use of strong CYP3A inducers should also be avoided given that labeling for vemurafenib recommends avoiding concomitant administration with strong CYP3A4 inhibitors or inducers and cobimetinib is administered in combination with vemurafenib. Physiologically based pharmacokinetic modeling (PBPK) predicts that rifampin can decrease cobimetinib exposure (AUC) by 83%. PBPK simulations also suggested that erythromycin and diltiazem (moderate CYP3A inhibitors) can increase cobimetinib exposure (AUC) by 3 to 4-fold; efavirenz (moderate CYP3A inducer) can decrease cobimetinib AUC by 73%. Therefore, concomitant use of moderate CYP3A inhibitors or inducers should be avoided. If avoiding concomitant moderate CYP3A inhibitors is not possible, it is recommended to reduce the dose of cobimetinib to 20 mg during treatment with a moderate CYP3A inhibitor (e.g., antibiotics including erythromycin or ciprofloxacin) for 14 days or less. After discontinuation of a moderate CYP3A inhibitor, the cobimetinib dose that was taken prior to initiating the moderate CYP3A4 inhibitor should be resumed. PBPK simulations predict that fluvoxamine (weak CYP3A inhibitor) does not change cobimetinib exposure.

Cobimetinib is a reversible inhibitor of CYP3A4 and CYP2D6 and also a time-dependent inhibitor of CYP3A4 in vitro. Coadministration of cobimetinib 60 mg QD for 15 days with a single 2 mg doses of midazolam (sensitive CYP3A4 substrate) and dextromethorphan (sensitive CYP2D6 substrate) did not result in clinically important changes in systemic exposure of midazolam or dextromethorphan.

Coadministration of rabeprazole (a proton pump inhibitor) 20 mg QD for 5 days with a single dose of 20 mg cobimetinib increased cobimetinib AUC by 11% and did not affect  $C_{max}$  as compared with cobimetinib alone. Cobimetinib may be administered concomitantly with acid reducing drugs.

- Pathway of elimination

The following applicant figure excerpted from the FDA Clinical Pharmacology Review of NDA 206192 illustrates the metabolism of cobimetinib of a single dose of 20mg [14C]-cobimetinib in five healthy subjects:



The following information on drug excretion is excerpted from the FDA Clinical Pharmacology Review of NDA 206192:

The ADME study (GP28369) showed that the mean total recovery of 20 mg [<sup>14</sup>C]-cobimetinib was 94.3% with 76.5% of the dose (6.6% as unchanged drug) recovered in the feces, and 17.8% (1.6% as unchanged drug) recovered in the urine of healthy subjects

- Demographic interactions/special populations

The FDA Clinical Pharmacology review did not identify any clinical important effects of age, sex, body weight, mild or moderate renal impairment, and mild hepatic impairment on clearance or volume of distribution of cobimetinib.

- Thorough QT study or other QT assessment

According to the FDA Pharmacology and Toxicology Review of NDA 206192, cobimetinib is an inhibitor of the hERG potassium channel:

Cobimetinib inhibited the hERG potassium channel, with an IC<sub>50</sub> of 0.5 μM when tested alone, and 0.6 μM when tested combination with vemurafenib; however, there were no treatment-related effects on hemodynamics or ECG parameters (including QTc) in the conscious telemetered beagle dog at peak exposure levels of approximately 2-fold greater than the anticipated human C<sub>max</sub>.

The following summary of the clinical evaluation of QT prolongation effects of cobimetinib is excerpted from the FDA Clinical Pharmacology Review of NDA 206192:

Population concentration-QTc analyses using time-matched ECG and PK data showed that there was no evident concentration-QTc relationship for cobimetinib as a single agent. No large changes (i.e., > 20 ms) in QTcF intervals were detected with cobimetinib as a single agent at doses up to 125 mg. Clinically relevant QT prolongation has been reported with vemurafenib as a single agent; however, substantial further increase in QTc was not observed with cobimetinib 60 mg in combination with vemurafenib. Following administration of cobimetinib 60 mg in combination with vemurafenib 960 mg, the largest mean change from baseline (ΔQTcF) was 7.8 ms with the upper bound of the 2-sided 90% confidence interval (CI) of 8.6 ms.

- Other notable issues (resolved or outstanding)

#### *Exposure-Response Analyses*

The FDA Clinical Pharmacology Review of NDA 206192 did not identify exposure-response relationships for efficacy (based on analyses of progression-free survival) or for adverse reactions.

## **6. Clinical Microbiology**

The section is not applicable to the review.

## 7. Clinical/Statistical- Efficacy

I agree with the overall conclusions of the primary FDA Clinical Reviewer, Ruthann Giusti, M.D., and of the primary FDA Statistical Reviewer, Xiaoping (Janet) Jiang, Ph.D., pertaining to the efficacy data submitted in the NDA to support an indication for cobimetinib for the treatment of patients for use in combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with the BRAF V600E and V600K mutations. <sup>(b)</sup>  
<sup>(4)</sup>

- **Efficacy Summary**

*Trial GO28141 Design (based on Protocol Version 4)*

The Applicant submitted data and results of Trial GO28141 titled “A Phase III, Double-Blind, Placebo-Controlled Study Of Vemurafenib Versus Vemurafenib Plus GDC-0973 In Previously Untreated BRAF V600-Mutation Positive Patients With Unresectable Locally Advanced Or Metastatic Melanoma”, a multicenter, international, parallel group, randomized (1:1), double-blind, active-controlled trial in patients with previously untreated, unresectable or metastatic, BRAF V600 mutation-positive melanoma as detected by the cobas 4800 BRAF mutation test.

The primary efficacy objective of the trial is to evaluate the efficacy of vemurafenib in combination with cobimetinib (GDC-0973), compared with vemurafenib and placebo, as measured by prolongation in investigator-assessed PFS. The secondary efficacy objective is to evaluate the efficacy of vemurafenib in combination with cobimetinib (GDC-0973), compared with vemurafenib and placebo, as measured by OS, objective response rate (ORR), DOR, and independent review-assessed PFS.

The Applicant required the following additional key eligibility criteria for patients to enroll in the trial:

- Age 18 years or older
- Histologically confirmed melanoma, either unresectable Stage IIIc or Stage IV metastatic melanoma, as defined as AJCC 7<sup>th</sup> edition. Unresectability of Stage IIIc disease must have been confirmed by a surgical oncologist.
- Naïve to treatment for locally advanced unresectable or metastatic disease (prior adjuvant therapy (including immunotherapy) allowed
- Documentation of BRAF V600 mutation-positive status in melanoma tumor tissue (archival or newly obtained tumor sample) using the cobas 4800 BRAF V600 mutation test
- Measurable disease at baseline (RECIST v1.1)
- ECOG performance status of 0 or 1
- Life expectancy  $\geq$  12 weeks
- No prior RAF or MEK pathway inhibitor treatment
- No history of retinal pathology on ophthalmologic examination considered a risk factor for neurosensory retinal detachment /central serous retinopathy, retinal vein occlusion, or neurovascular macular degeneration
- None of the following risk factors for RVO:
  - o Uncontrolled glaucoma with intra-ocular pressures  $>$  21 mmHg
  - o Serum cholesterol  $\geq$  Grade 2

- Hypertriglyceridemia  $\geq$  Grade 2
- Hyperglycemia (fasting)  $\geq$  Grade 2
- Left ventricular ejection fraction  $\geq$  institutional lower limit of normal (LLN) or  $\geq$  50%, whichever is lower
- No active CNS lesions (including carcinomatous meningitis) –patients eligible if all known CNS lesions treated with stereotactic therapy or surgery and there has been no evidence of clinical and radiographic disease progression in the CNS for  $\geq$  3 weeks after radiotherapy or surgery
- No history of whole brain radiotherapy with the exception of patients who had definitive resection of stereotactic therapy or all radiologically detectable parenchymal brain lesions
- Adequate organ function based on laboratory criteria (see FDA Clinical Review)

Patients were randomized (1:1) to receive:

- Arm A (control arm): vemurafenib 960 mg by mouth (PO) BID on Days 1–28 and placebo PO QD on Days 1–21 of each 28-day treatment cycle
- Arm B (investigational arm): vemurafenib 960 mg PO BID on Days 1–28 and cobimetinib (GDC-0973) 60 mg PO QD on Days 1–21 of each 28-day treatment cycle

Randomization stratification factors were geographic region (North America, Europe, Australia/New Zealand/others) and metastatic classification (unresectable Stage IIIc, M1a, and M1b; or M1c)

This sample size of 500 randomized patients with a final analysis at the time of approximately 206 PFS events provided >95% power to detect an improvement in median PFS from 6 months in the vemurafenib plus placebo arm to 11 months in the vemurafenib plus cobimetinib arm with a hazard ratio (HR) of 0.55, with a two-sided alpha of 0.05. The minimal detectable difference was reported to be a HR of 0.76. No interim analysis of PFS was planned.

For OS, the final analysis was initially planned after the occurrence of approximately 385 deaths. A total of 385 deaths provides approximately 80% power to detect an improvement in median OS from 15 months in the vemurafenib plus placebo arm to 20 months in the vemurafenib plus cobimetinib (GDC-0973) arm (corresponding to a hazard ratio for death of 0.75). Following discussion with FDA (see Section 2), the amended statistical analysis plan dated February 23, 2015, revised the number of deaths to perform the final OS analysis to approximately 250 deaths and removed any further interim analyses of OS. A total of 250 deaths provides approximately 80% power to detect an improvement in median OS from 15 months in the vemurafenib plus placebo arm to 21.4 months in the vemurafenib plus cobimetinib arm (which corresponds to a hazard ratio for death of 0.70) at an overall two-sided alpha of 0.05.

PFS was defined as the time from randomization to the first occurrence of disease progression as determined by the investigator using RECIST v1.1, or death from any cause, whichever comes first. The primary analysis will be a comparison of PFS between the two treatment arms with use of a stratified log-rank test at an overall 0.05 significance level (2 sided). The HR for PFS will be estimated using a stratified Cox model. Two-sided 95% CIs for the HR will be

provided. Kaplan-Meier methodology will be used to estimate median PFS for each treatment arm, and the Kaplan-Meier curves will be provided. The stratified analyses will incorporate two stratification factors: geographic region (North America, Europe, Australia/New Zealand/others) and metastatic classification (unresectable Stage IIIc, M1a, and M1b; M1c).

ORR (confirmed) was defined as a complete response (CR) or partial (PR) as assessed by the investigator per RECIST v 1.1, which required determination of CR or PR by two consecutive investigator assessments that are 4 or more weeks apart. The initial SAP defined the population for analysis of ORR as patients in the intent-to-treat (ITT) population who are randomized for at least 18 weeks before the data cutoff date used for analysis. Version 2 of the SAP dated June 22, 2014, revised the analysis population for ORR to all randomized population (ITT). The SAP specified that treatment difference in ORR between the two arms will be tested using a  $\chi^2$  test with Schouten correction, and a 95% Hauck-Anderson CI will be calculated for the difference in BORRs between treatment groups. In addition, a 95% Clopper-Pearson CI will be calculated for the ORR.

OS is defined as the time from randomization until the date of death from any cause. OS will be compared between the two treatment arms with use of a two-sided stratified log-rank test at an overall two-sided 0.05 significance level. The HR for death will be estimated using a stratified Cox model. Two-sided 95% CIs for the HR will be provided. Stratified analyses will incorporate the same stratification factors as for the analysis of PFS. Kaplan-Meier methodology will be used to estimate median OS and landmark (e.g., annual) OS rates for each treatment arm, and the Kaplan-Meier curves will be provided. Two interim analyses of OS were planned: one interim analysis at the time of the final PFS analysis and a second OS interim analysis after the occurrence of 256 OS events. As above, the second planned interim analysis of OS at 256 OS events was removed and the final analysis revised to occur after the occurrence of 250 OS events as per version 3 of the SAP dated February 23, 2015. The Lan-DeMets implementation of the O'Brien and Fleming use function will be used to control the overall Type I error for the OS comparison at a two-sided 0.05 significance level.

The type I error (alpha) for this study is 0.05 (two sided). The SAP planned a hierarchical approach to testing of the primary and selected secondary endpoints to control for Type I error. If the primary endpoint of PFS meets the criteria for statistical significance at 0.05 (two sided), a hierarchical approach will be employed to evaluate the statistical significance of each of the following secondary endpoints at the 0.05 statistical significance level (two sided) in the following order: confirmed BORR as determined by investigator review and OS. No adjustment to the  $\alpha$  level will be made for the other analyses, including PFS based on IRC-reviewed data. The p-values from these analyses should be interpreted accordingly.

### *Trial GO28141 Results*

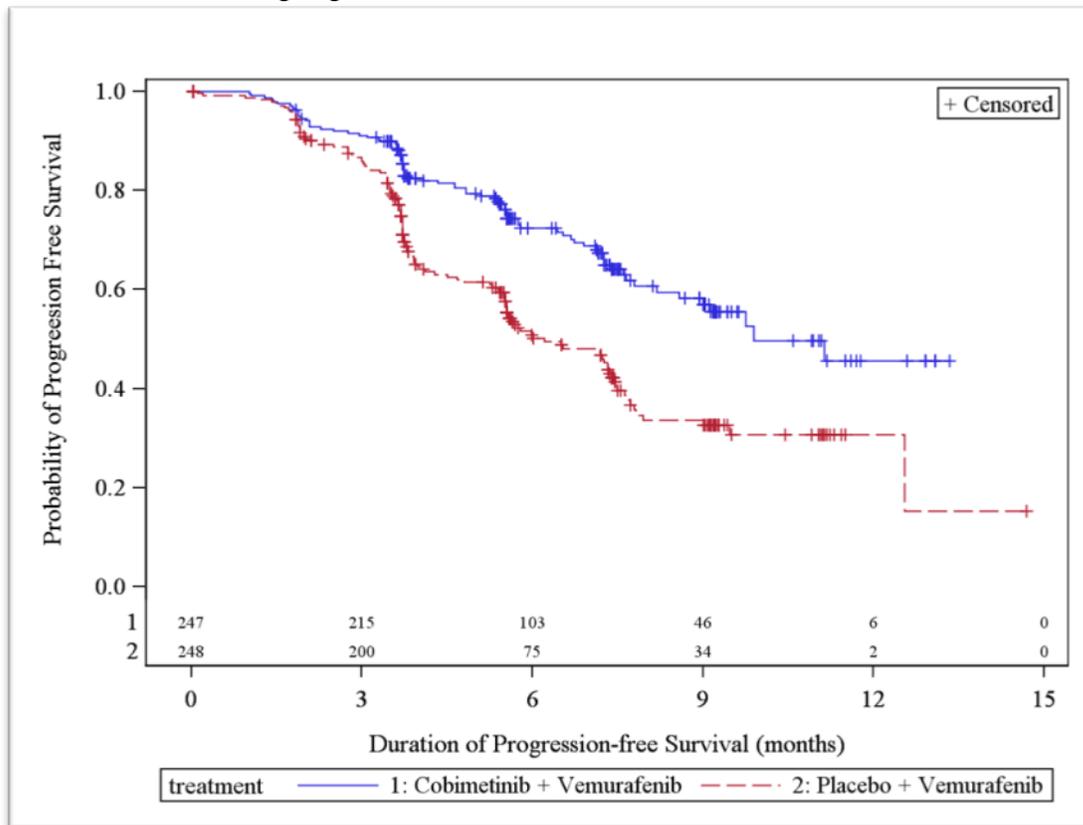
As summarized in the FDA Clinical Review of NDA 206192, the first patient was entered on January 8, 2013, and the last patient entered was on January 31, 2014. The data cutoff date for the primary analysis of PFS (and first interim analysis of OS) was May 9, 2014. The data cutoff date for updated efficacy analyses (OS, PFS, and ORR) was January 16, 2015.

A total of 495 patients were randomized, 247 to the cobimetinib plus vemurafenib arm and 248 patients to the placebo plus vemurafenib arm. The median durations of follow-up were 7.3 months and 14.2 months at the time of the May 9, 2014, and the January 16, 2015, data cutoff dates, respectively.

The trial was conducted in 19 countries at 135 sites (NDA 206192 DM.xpt dataset). The median patient age was 55 years (range: 23 to 88 years); 58% were male; 93% White, 5% race not reported; 60% were stage M1c, 17% were Stage M1b, 16% were Stage M1a, and 7% Stage IIIc; 72% had a baseline ECOG performance status (PS) of 0 and 28% PS of 1, 45% had an elevated baseline serum lactate dehydrogenase, 10% had prior adjuvant therapy, and < 1% had previously treated brain metastases.

The trial demonstrated improvements in PFS, OS, and ORR in the cobimetinib with vemurafenib arm compared to the single-agent vemurafenib arm.

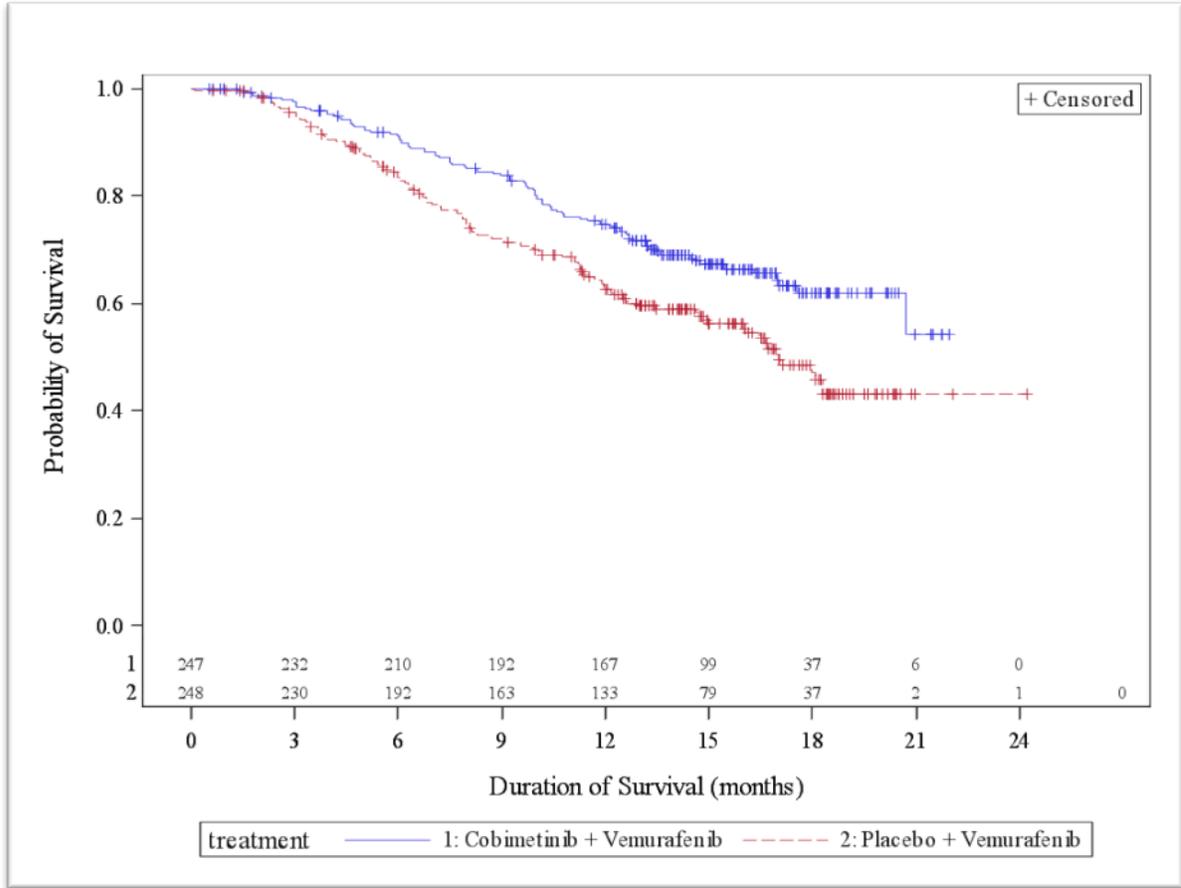
At the time of the data cutoff for the primary analysis of PFS (May 9, 2014), there were 197 PFS events: 79 on the vemurafenib plus cobimetinib arm and 128 on the single-agent vemurafenib arm. Analysis of the primary endpoint, progression-free survival (PFS) as assessed by the investigator per RECIST v1.1, a median PFS of 9.9 months (95% confidence interval (CI): 9, not estimable (NE)) on the cobimetinib arm and 6.2 months (95% CI: 5.6, 7.4 months) on the single-agent vemurafenib arm with a HR of 0.5 [95% CI: 0.4, 0.7;  $p < 0.0001$  (two-sided,  $p$ -value based on stratified log-rank test)]. The Kaplan Meier plots for PFS are shown in the following Figure:



The FDA Biometrics Review of NDA 206192 presents multiple sensitivity analyses of PFS, including the planned secondary endpoint PFS as assessed by a blinded independent central committee review per RECIST v1.1, all supporting a PFS treatment effect of cobimetinib. Exploratory subgroup analyses of PFS based on demographics and baseline disease characteristics demonstrated PFS HR point estimates that were less than 1 (refer to FDA Biostatistics Review of NDA 206192 for details).

Genentech performed an updated analysis of the efficacy endpoints using the January 16, 2015, data cutoff date [REDACTED] <sup>(b) (4)</sup>. Based on observation of 323 PFS events, 143 on the vemurafenib plus cobimetinib arm and 180 on the single-agent vemurafenib arm, the median PFS was 12.3 months (95% CI: 9.5, 13.4 months) on the vemurafenib plus cobimetinib arm and 7.2 months (95% CI: 5.6, 7.5 months) on the vemurafenib arm with a HR of 0.56 (95% CI: 0.45, 0.70).

Genentech amended the GO28141 protocol (March 11, 2015) to reduce the number events required for the final OS analysis to 250 as agreed to at the October 8, 2014, pre-NDA meeting. FDA held a teleconference with Genentech on October 8, 2015, to discuss the ad-hoc interim analysis of overall survival and agreed upon the datasets required for FDA to verify the results of this OS analysis. An interim analysis of overall survival (OS) based on observation of 75% of the events required for the final analysis (data cutoff date of January 16, 2015) crossed the boundary for claiming statistical significance with superiority of the cobimetinib plus vemurafenib arm compared to the vemurafenib arm, a HR of 0.63 (95% CI: 0.47, 0.85; p value = 0.0019). The median OS on the cobimetinib plus vemurafenib arm was NE (95% CI: 20.7 months, NE) and on the single-agent vemurafenib arm was 17.0 months (15.0, NE) The stratification factors in this analysis were as documented in the IxRS at randomization. The Kaplan Meier plots for OS are shown in the following Figure:



Reproduced from the FDA statistical review

The confirmed, investigator-assessed overall response rate (ORR) per RECIST v1.1 was 68% (95% CI: 61, 73) on the cobimetinib plus vemurafenib arm and was 45% (95% CI: 39, 51) on the vemurafenib arm (data cutoff date May 9, 2014). The median duration of response was NR (95% CI: 9.3 months, NR) on the vemurafenib plus cobimetinib arm and was 7.3 months (95% CI; 5.8, NR) on the single-agent vemurafenib arm. Genentech performed an updated analysis of ORR based on the data cutoff date of January 16, 2015. The confirmed, investigator-assessed overall response rate (ORR) per RECIST v1.1 was 69.6% (95% CI: 63.5, 75.3) on the cobimetinib plus vemurafenib arm and was 50% (95% CI: 43.6, 56.4) on the single-agent vemurafenib arm. The median duration of response was 13.0 months (95% CI: 11.1, 16.6) on the vemurafenib plus cobimetinib arm and was 9.2 months (95% CI; 7.5, 12.8) on the single-agent vemurafenib arm.

*Reviewer Comment:*

*According to the FDA Statistical Review Addendum to NDA 206192:*

*the PFS result submitted in the original NDA showed statistically significant difference in favor of the combination of cobimetinib and vemurafenib, hence conducting an PFS analysis based on the updated data will not inflate type I error rate.*

*Compared with the primary analysis of PFS, the updated analysis provides approximately 7 months of additional follow-up (14.2 months follow-up in the efficacy update vs. 7.3 months*

*follow-up according in the original NDA). The mature PFS data allows a more reliable estimate of median PFS and of the upper and lower bounds of the 95% CI for median PFS. While the PFS hazard ratio is similar between the primary and the updated PFS analyses, the median PFS and corresponding confidence intervals in the updated PFS analysis would be more informative to prescribers in the discussion with patients as the maturity of the analysis affords more precision around the estimate of the treatment effect. Similarly, the updated analyses of ORR provide mature estimates of response durations. Please refer to the FDA Clinical Review of NDA 206192 and the FDA Statistical Review and Review Addendum for NDA 206192 for further details of the updated efficacy analyses.*

*Exploratory Subgroup Analyses Based on BRAF V600 Mutation Subtype (BRAF V600E or V600K)*

In Trial GO28141, the device used to detect BRAF V600 mutations in melanoma specimens was the FDA-approved, cobas 4800 BRAF V600 Mutation test. Based on the FDA Summary of Safety and Effectiveness Data for this device, the test has positive percent agreement of 97.3% (95% CI: 94.2, 98.8) and negative percent agreement of 84.6% (95% CI: 79.3, 88.7) based for detection of BRAF V600E mutation in DNA extracted from formalin-fixed, paraffin-embedded human melanoma tissue as compared to the reference standard (bi-directional sequencing). The cobas 4800 BRAF V600 Mutation test was cross-reactive for BRAF V600K in 66% (25/38) of the samples with BRAF V600K mutations as determined by the reference method. Thus the test is not labeled to detect BRAF V600K mutations based on this low sensitivity; however, the low sensitivity appears to be related to DNA quality issues rather than systematic differences in tumor burden.

Genentech performed exploratory subgroup analyses of the efficacy endpoints (PFS, OS, ORR) based on BRAF V600 mutation subtype as identified by next generation sequencing. Genentech stated that next generation sequencing was performed on tumor tissue from 400 of 495 patients (81%) who submitted archival or baseline tumor tissues or had sufficient DNA after central testing using the cobas 4800 BRAF V600 Mutation Test. In those patients for which sequencing was performed, 344/400 (86%) tumors carried a V600E mutation and 56/400 (14%) had V600K. The distribution of V600E versus V600K was similar in each trial arm, 70% and 69% and 10% and 13% in the cobimetinib plus vemurafenib and single-agent vemurafenib arms, respectively. These exploratory subgroup analyses (data cutoff date May 9, 2014, unless otherwise noted) support a treatment effect of cobimetinib in patients with melanoma identified as BRAF V600E mutation positive with prolongation of PFS [HR of 0.56 (95% CI: 0.45, 0.70); HR of 0.59 (95% CI: 0.45, 0.78) based on January 16, 2015, data cutoff date], prolongation of OS [HR of 0.76 (95% CI: 0.45, 1.26)], and increased ORR (68% vs. 48%) as compared to the single-agent vemurafenib; furthermore, a treatment effect was apparent in the subgroup of patients with BRAF V600K mutation-positive melanoma (selected into the trial by the cobas BRAF V600 Mutation test)—with point estimates of treatment effects that were nominally larger than in the BRAF V600E mutation positive subgroup—with a prolongation of PFS [HR of 0.25 (95% CI: 0.08, 0.70); HR of 0.31 (95% CI: 0.14, 0.69) based on January 16, 2015, cutoff date], prolongation of OS [HR of 0.61 (95% CI: 0.16, 2.37)], and increased ORR (67% vs. 31%) as compared to single-agent vemurafenib. In

totality, this information supports description of the BRAF V600 mutation subtypes in the indication statement of cobimetinib.

## 8. Safety

I agree with the overall conclusions of the primary FDA Clinical Reviewer, Dr. Ruthann Giusti, regarding the safety data submitted in the NDA. I agree that a REMS is not required for this application and that a postmarketing requirement is necessary to further evaluate and characterize a risk of serous retinopathy (see recommended PMRs in Section 13).

The safety profile of cobimetinib was primarily evaluated in Trial GO28141, a multicenter, international, parallel group, randomized (1:1), double-blind, active-controlled trial in which 493 patients with previously untreated, unresectable or metastatic, BRAF V600 mutation-positive melanoma received vemurafenib 960 mg orally twice daily with cobimetinib 60 mg orally once daily or placebo on Days 1-21 on an every 28-day cycle. The safety update data cutoff date was September 19, 2014, which was the data cutoff date used for analyses of safety of Trial GO28141 described in labeling. The FDA clinical reviewer of safety performed the initial safety analyses using the datasets pertaining to safety that were submitted in the original NDA. However, these analyses were replaced with analyses using the datasets to support the safety update report based on incorrect assignments in the original NDA of patients to the cobimetinib-exposed group (see FDA Clinical Review of NDA 206192 for details).

The median duration of exposure to cobimetinib (or placebo on single-agent vemurafenib arm) was 8.8 months (range 4 days to 18.5 months) among the 247 patients who received cobimetinib plus vemurafenib and was 5.7 months (range: 5 days to 16.9 months) among the 246 patients who received single-agent vemurafenib on Trial GO28141. In this trial, the demographics and baseline characteristics of the safety population was similar to those described for the efficacy population.

The key safety findings of cobimetinib are as follows (Trial GO28141 unless otherwise noted):

- Five patients (2.0%) receiving cobimetinib and three patients (1.2%) receiving single-agent vemurafenib with fatal adverse events. No Grade 5 adverse events occurred in more than one patient. Grade 5 events occurring in cobimetinib exposed patients were: death (unspecified), cardiac arrest, coma, pneumonia, and clostridium difficile colitis.
- Non-fatal serious adverse events occurred in 35% of patients receiving cobimetinib and vemurafenib and 26% of the patients receiving single-agent vemurafenib. The most frequent ( $\geq 2\%$ ) non-fatal serious adverse events in patients receiving cobimetinib plus vemurafenib compared with single-agent vemurafenib were pyrexia (3% vs. 1%) and dehydration (2% vs. 0)
- Discontinuations of cobimetinib (vs. placebo on the single-agent vemurafenib arm) due to adverse events (AE) occurred in 19% of patients receiving cobimetinib plus vemurafenib and 10% of patients receiving single-agent vemurafenib. Discontinuations of vemurafenib due to AEs occurred in 16% of patients receiving

- cobimetinib plus vemurafenib and 10% of patients receiving single-agent vemurafenib. AEs leading to discontinuation of cobimetinib occurring in  $\geq 2\%$  patients receiving cobimetinib with vemurafenib were increased AST (2.4%) and retinal detachment (2.0%).
- Adverse events leading to dose reduction or interruption of cobimetinib (vs. placebo on the single-agent vemurafenib arm) occurred in 55% of patients receiving cobimetinib plus vemurafenib and 37% of patients receiving single-agent vemurafenib. The most frequent ( $\geq 2\%$ ) adverse events leading to dose reduction or interruption of cobimetinib (or placebo) in patients receiving cobimetinib plus vemurafenib and compared with single-agent vemurafenib were diarrhea (9% vs. 4%), chorioretinopathy (7% vs. 0%), pyrexia (6% vs. 3%), vomiting (6% vs. 5%), nausea (5% vs. 4%), increased blood CPK (5% vs. 1%), rash (5% vs. 6%), and rash maculo-papular (5% vs. 4%).
  - Grade 3-4 treatment-emergent adverse events (TEAE) occurring in  $\geq 5\%$  of patients receiving cobimetinib plus vemurafenib and occurring at a greater incidence ( $\geq 2\%$  increase in Grades 3-4) compared with patients receiving single-agent vemurafenib were GGT increase (13% vs. 10%), ALT increased (11% vs. 6%), increased CPK (11% vs. 0), AST increased (9% vs. 2%), diarrhea (7% vs. 1%), and basal cell carcinoma (5% vs. 2%).
  - Common ( $\geq 20\%$ ) adverse reactions with cobimetinib compared with single-agent vemurafenib were diarrhea (60% vs. 31%), photosensitivity reaction (46% vs. 35%), nausea (41% vs. 25%), and vomiting (24% vs. 13%).
  - Common Grade 3-4 laboratory abnormalities worsening from baseline (i.e., increase in toxicity grade) occurring in  $\geq 5\%$  of patients (as calculated using the safety population as the denominator) receiving cobimetinib plus vemurafenib and at a higher incidence ( $\geq 2\%$  Grades 3-4) than in patients receiving single-agent vemurafenib were increased GGT (20% vs. 16%), increased CPK (12% vs.  $<1\%$ ), hypophosphatemia (11% vs. 6%), increased ALT (11% vs. 5%), lymphopenia (8% vs. 6%), increased AST (7% vs. 2%), increased alkaline phosphatase (7% vs. 3%), and hyponatremia (6% vs. 2%).

The following major safety risks of cobimetinib identified in the clinical program were included in the Warnings and Precautions section: new primary cutaneous malignancies, hemorrhage, cardiomyopathy, severe dermatologic reactions, serous retinopathy and retinal vein occlusion, hepatotoxicity, rhabdomyolysis, and severe photosensitivity. The following is a summary of these safety risks:

- New Primary Malignancies
  - Cutaneous malignancies: cutaneous squamous cell carcinoma/keratoacanthoma occurred in 6% of patients receiving cobimetinib plus vemurafenib and in 20% of patients receiving single-agent vemurafenib. Basal cell carcinoma occurred in 4.5% and 2.4% of patients receiving cobimetinib plus vemurafenib and single-agent vemurafenib, respectively. Second primary melanoma occurred in 0.8% and 2.4% of patients receiving cobimetinib plus vemurafenib and single-agent vemurafenib, respectively.

- Non-cutaneous malignancies: there were two patients and three patients diagnosed with non-cutaneous malignancies in the cobimetinib with vemurafenib arm and single-agent vemurafenib arm, respectively.

*Reviewer Comment: Review of Genentech's November 7, 2015, response to an FDA information request regarding details of cases of new primary non-cutaneous malignancies determined that there were two patients and three patients with new primary non-cutaneous malignancies in the cobimetinib with vemurafenib and single-agent vemurafenib groups, respectively.*

- Hemorrhage: Intracerebral hemorrhage occurred in 0.8% of patients receiving Cotellic and in none of the patients receiving single-agent vemurafenib.
- Cardiomyopathy: cardiomyopathy (including asymptomatic and symptomatic decline in left ventricular ejection fraction [LVEF]) based on serial LVEF assessments (echocardiogram or MUGA) occurred in 26% of patients receiving cobimetinib with vemurafenib and in 19% of patients receiving vemurafenib) in Trial GO28141. Of the patients receiving cobimetinib with decreased LVEF, 14% required permanent discontinuation.
- Severe Dermatologic Reactions: The incidence Grade 4 rash was increased on the cobimetinib arm compared with the single-agent vemurafenib arm, 1.6% vs. 0.4%, respectively. Grade 3 to 4 rash completely resolved in 95% of patients receiving cobimetinib.
- Serous Retinopathy and Retinal Vein Occlusion: The incidence of serous retinopathy was 26% in patients receiving cobimetinib. The time to first onset of serous retinopathy ranged from 2 days to 9 months. Two percent of patients receiving cobimetinib with vemurafenib permanently discontinued cobimetinib due to retinal detachment. Serous retinopathy requires further characterization to inform prescribers on the clinical significance of serous retinopathy and appropriate dose modifications of cobimetinib.
- Hepatotoxicity: the incidence of Grade 3 to 4 elevated liver function tests was increased on the cobimetinib plus vemurafenib arm compared with the single-agent vemurafenib arm: 11% vs. 6% for alanine aminotransferase, 7% vs. 2.1% for aspartate aminotransferase, 1.6% vs. 1.2% for total bilirubin, and 7% vs. 3.3% for alkaline phosphatase. Drug induced liver injury (defined as concurrent elevation in ALT or AST of more than three times the upper limit of normal, alkaline phosphatase less than two times the upper limit of normal, and total bilirubin at least two times the upper limit of normal) occurred in 1 patient (0.4%) on the cobimetinib arm and in none of the patients receiving single-agent vemurafenib.
- Rhabdomyolysis: Grade 3 or 4 CPK elevations occurred in 12% of patients receiving cobimetinib with vemurafenib and 0.4% of patients receiving vemurafenib. The median time to first occurrence of Grade 3 or 4 CPK elevations was 16 days (range: 12 days to 11 months) in patients receiving cobimetinib with vemurafenib; the median time to complete resolution was 15 days (range: 9 days to 11 months). Elevation of serum CPK increase of more than 10 times the baseline value with a concurrent increase in serum creatinine of 1.5 times or greater compared to baseline occurred in 3.6% of patients

receiving cobimetinib with vemurafenib and in 0.4% of patients receiving single-agent vemurafenib.

- **Severe Photosensitivity:** photosensitivity was reported in 47% of patients receiving cobimetinib with vemurafenib and in 35% of patients receiving single-agent vemurafenib, including Grade 3 to 4 reactions in 4% of patients receiving cobimetinib and in none of the patients receiving single-agent vemurafenib. Among the 47% of patients with photosensitivity reactions on COTELLIC with vemurafenib, 63% experienced resolution of photosensitivity reactions.

## 9. Advisory Committee Meeting

The application was not referred to an Oncologic Drug Advisory Committee (ODAC) as this drug is not the first in its class; the clinical trial design is acceptable; the safety profile is acceptable for the treatment of patients with (b) (4) unresectable or metastatic BRAF V600 mutation-positive melanoma (b) (4) and the application did not raise significant public health questions on the role of cobimetinib for this indication and outside expertise was not necessary as there were no controversial issues that would benefit from advisory committee discussion.

## 10. Pediatrics

Cobimetinib is exempt from the pediatric study requirements of the Pediatric Research Equity Act (PREA), i.e., to assess the safety and effectiveness of the product for the claimed indication(s) in pediatric patients, because FDA granted this product orphan designation for the proposed indication on November 21, 2013.

## 11. Other Relevant Regulatory Issues

- **Application Integrity Policy (AIP):** No issues.
- **Financial Disclosures:** No issues which raised concerns about the integrity of the data. There were three investigators with disclosable financial interests; these investigators enrolled a total of six patients into Trial GO28141, including one investigator site which no patients were enrolled (see FDA Clinical Review of NDA 206192).
- **Office of Scientific Investigation (OSI) Audits:**  
Four clinical sites and the Sponsor (Genentech) were selected for inspections. The final classification of the inspections was no action indicated (NAI) for two of the clinical sites (Dr. Gabriella Liskay and Dr. Michele Maio) and for Genentech. The classification was voluntary action indicated (VAI) at the remaining two clinical sites (Dr. Paolo Ascierio and Dr. Virginia Ferraresi). At one site (Dr. Ferraresi), the execution of the protocol was found to be marginal and the site was issued a Form 483 cited five inspection observations concerning protocol deviations and GCP

compliance issues; sensitivity analyses which excluded data from this site did not alter the interpretation of the efficacy results. As summarized in the FDA OSI Clinical Inspection Summary of NDA 206192, the data submitted by Genentech to NDA 206192 appeared reliable.

## 12. Labeling

- **Proprietary name:** In the FDA Proprietary Name Memorandum dated February 13, 2015, Otto Townsend, Pharm.D., DMEPA, concluded that the proposed proprietary name, Cotellic, is acceptable. Todd Bridges, RPh, DMEPA, issued a Proprietary Name Request Conditionally Acceptable letter to Genentech Inc., on February 13, 2015.
- **OSE /Division of Medication Error Prevention and Analysis (DMEPA):** Dr. Otto Townsend, PharmD, DMEPA, provided recommendations for revised carton and container labeling in the review dated November 2, 2015. On November 4, 2015, Genentech provided carton and container labeling addressing the recommended revisions. In a Label and Labeling Review dated May 20, 2015, DMEPA provided recommendations regarding the preparation and administration section of labeling.
- **Maternal Health:** Miriam Dinatale, D.O. / Tamara Johnson, MD, MS (Acting Team Leader) / Lynne P. Yao, MD (Acting Division Director), Division of Pediatric and Maternal Health: Maternal Health participated in labeling discussions and provided recommendations consistent with the Pregnancy and Lactation Labeling Rule (PLLR).

## 13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Approval

According to the review of the data submitted in the NDA, as amended, this reviewer recommends approval of cobimetinib for the following indication:

Treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation, in combination with vemurafenib.

- Risk Benefit Assessment

Melanoma develops at a relatively early age which results in a substantial number of years of life lost per person,<sup>3</sup> and once metastatic carries a grim prognosis—the five year survival rate is historically less than 10% for patients. Melanoma harbors BRAF mutations in approximately 40-60% of patients.<sup>4,5,6</sup> The most common of these BRAF mutations is V600E although patients with melanoma harboring BRAF V600K mutations are a substantial proportion of patients with BRAF V600 mutation-positive melanoma, approximately 5-30%.<sup>7</sup> While the number of treatment options for patients with unresectable or metastatic melanoma has increased steadily since 2011—ipilimumab, vemurafenib, dabrafenib, trametinib, pembrolizumab, nivolumab—this remains a serious disease with a high unmet medical need.

The recommendation for approval of NDA 206192 is primarily based on Trial GO28141, which demonstrated improvements in OS, PFS, and ORR with the addition of cobimetinib to vemurafenib:

- *Progression-free survival*, the primary analysis of the primary endpoint, progression-free survival (PFS) as assessed by the investigator per RECIST v1.1, demonstrated a median PFS of 9.9 months (95% CI: 9, NE) on the cobimetinib with vemurafenib arm and 6.2 months (95% CI: 5.6, 7.4 months) on the single-agent vemurafenib arm with a HR of 0.5 [95% CI: 0.4, 0.7;  $p < 0.0001$  (two-sided,  $p$ -value based on stratified log-rank test)]. At the time of the primary PFS analysis, there were approximately 19% and 14% of the subjects at risk at 9 months on the cobimetinib arm and the single-agent vemurafenib arm, respectively. With an additional 7 months of follow-up, the updated PFS analysis demonstrated a median PFS of 12.3 months (95% CI: 9.5, 13.4 months) on the cobimetinib arm and 7.2 months (95% CI: 5.6, 7.5 months) on the single-agent vemurafenib arm with a HR of 0.56 (95% CI: 0.45, 0.70).
- *Overall Survival*, an interim analysis of OS, based on observation of 75% of the events required for the final analysis crossed the boundary for claiming statistical significance with superiority of the cobimetinib with vemurafenib arm compared to the single-agent vemurafenib arm, a HR of 0.63 (95% CI: 0.47, 0.85;  $p$  value = 0.0019).
- *Objective response rates and response durations*, the confirmed, investigator-assessed ORR per RECIST v1.1 was 68% (95% CI: 61, 73) on the cobimetinib plus vemurafenib arm and was 45% (95% CI: 39, 51) on the single-agent vemurafenib arm at the time of the primary analysis of PFS. This difference was highly statistically significant ( $p$ -value,  $X^2 < 0.0001$ ). The median durations of response were NE (9.3, NE) and 7.3 months (5.8, NE) in cobimetinib with vemurafenib and the single-agent vemurafenib arms, respectively. At the time of the interim analysis of OS (75% events required for the final analysis), the confirmed ORRs were 70% (95% CI: 64, 75) on the cobimetinib with vemurafenib arm and was 50% (95% CI: 44, 56) on the single-agent vemurafenib arm; the median duration of responses were 13 months (95% CI: 11.1, 16.6 months) and 9.2 months (95% CI: 7.5, 12.8 months) on the cobimetinib with vemurafenib and single-agent vemurafenib arms, respectively.

The safety of cobimetinib was primarily evaluated in the 247 patients who received at least one dose of cobimetinib in Trial GO28141. The FDA clinical review of safety was also supplemented by evaluation of an additional 129 patients received cobimetinib at various doses and schedules with vemurafenib, which included 39 patients with unresectable or metastatic melanoma who received cobimetinib with vemurafenib at the recommended dosages. Major safety risks with cobimetinib are new primary cutaneous malignancies, hemorrhage, cardiomyopathy, severe dermatologic reactions, serous retinopathy, hepatotoxicity, rhabdomyolysis, and severe photosensitivity. Mitigation of these risks will be through product labeling.

The risk-benefit assessment of cobimetinib is favorable, when added to vemurafenib, for the treatment of patients with BRAF V600E or V600K mutation-positive, unresectable or metastatic melanoma—a population for which inhibition of the MAPK pathway with a BRAF inhibitor as a single agent results in objective responses in approximately half of patients with BRAF V600E mutation-positive melanoma, but response durations are relatively short.

Treatment effects with single-agent BRAF inhibitors appear to be even less in patients with BRAF V600K mutation-positive melanoma. Addition of the MEK inhibitor, cobimetinib, to vemurafenib therapy demonstrated a statistically robust, clinically meaningful improvement in median PFS of approximately 5 months with a 44% reduction in PFS events as well as a statistically significant, clinically important 37% decrease in the risk of death. Treatment effects of cobimetinib appear to be present in patients with either BRAF V600E or BRAF V600K mutation-positive melanoma as selected by the FDA-approved test for vemurafenib. The major safety risks with cobimetinib were generally manageable with dose modifications and supportive care.

Once patients have progressed on BRAF inhibitor therapy, the clinical activity of cobimetinib with vemurafenib appears modest with ORR of ~15% (Trial NO25395, refer to FDA Clinical Review of NDA 206192 for details) and the clinical benefit of cobimetinib has not been established in this setting. Presentation in labeling of mature efficacy results from Trial GO28141 will provide a more informed benefit-risk discussion with patients in consideration of adding cobimetinib to vemurafenib therapy. FDA approval of cobimetinib will represent an important addition to the therapeutic options for treatment of the indicated population.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

I agree with the recommendations of the NDA review team, including DRISK, that a REMS is not required to ensure safe use of cobimetinib. Risk mitigation will occur through product labeling.

- Recommendation for other Postmarketing Requirements and Commitments

The following postmarketing requirements are recommended:

1. Provide an integrated safety analyses from an adequate number of 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 alteration required to minimize the impact of retinal pigmented epithelial detachments. This will include 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.
2. Complete a clinical pharmacokinetic trial 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.

The following postmarketing commitments are recommended:

3. Submit the clinical report at the time of the final analysis of Trial GO28141, A Phase III, Double-Blind, Placebo-Controlled Study of Vemurafenib Versus Vemurafenib Plus Cobimetinib (GDC-0973) in Previously Untreated BRAF V600-Mutation Positive

Patients with Unresectable Locally Advanced or Metastatic Melanoma (coBRIM) to update the label with mature overall survival data.

4. 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.

**Appendix A: FDA-Approved Therapies Indicated for the Treatment of Patients with Metastatic Melanoma**

FDA Approved Drug <sup>1</sup> mechanism of action	Approved	Trial Design Study Population	Approval Endpoint(s)	Clinical Benefit/Effect	Most Common and Most Severe Toxicities
<b>DTIC (dacarbazine)<sup>2</sup></b>  <b>Alkylating agent</b>	1975	Single-arm	ORR	ORR of 5-20%	The most common AEs were: hematopoietic depression (leukopenia, thrombocytopenia, anemia, anaphylaxis anorexia, nausea, vomiting Other clinically important AEs (<10%) were: hepatic toxicity (hepatic vein thrombosis, hepatocellular necrosis, fever, myalgias, malaise, erythematous and urticarial rashes and photosensitivity reactions.
<b>Proleukin[3] (interleukin-2)<sup>2</sup></b>  <b>Human recombinant interleukin-2</b>	1998	Multicenter, single-arm  High performance status; prior treatment unspecified	ORR	ORR 16% (CR 6%); DOR CR: 59+m (3 to 122+ m) CR or PR: 59+ m (1 to1 22+m)	The most common AEs (>20%) were: hypotension, diarrhea, oliguria, chills, vomiting, dyspnea, rash, bilirubinemia, thrombocytopenia, nausea, confusion, creatinine increase, fever, peripheral edema), malaise (27%), enterocolitis, hepatotoxicity, dermatitis, neuropathy, endocrinopathy (hypopituitarism, adrenal insufficiency), pneumonitis, meningitis, nephritis, eosinophilia, pericarditis. Other clinically important AEs (<10%) were: hypotension, myocardial infarct, ventricular tachycardia and cardiac arrest, diarrhea, oliguria, anuria and acute kidney failure, and coma.
<b>Yervoy[4] (ipilimumab[ipi])<sup>2</sup></b>  <b>Human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking</b>	2011	Multicenter, randomized, blinded, active-controlled three-arm  One prior regimen, chemotherapy or interleukin-2	OS ORR	<b>ipi vs. gp100:</b> OS: HR 0.66 (95% CI: 0.51, 0.87) median 10 vs. 6 m BORR: 10.9% vs. 1.5% mDOR: not reached in either arm  <b>ipi+gp100 vs. gp100:</b>	The most common AEs (≥5%) were: fatigue, diarrhea, pruritis, rash, and colitis. Other clinically important AEs (<10%) were: Severe/fatal immune-mediated AEs (enterocolitis, hepatotoxicity, dermatitis, neuropathy, hypopituitarism, adrenal insufficiency, pneumonitis, meningitis, nephritis, eosinophilia, pericarditis)

<b>antibody</b>				OS: HR 0.68 (95% CI: 0.55, 0.85) median 10 vs. 6 m BORR: 5.7% vs. 1.5% mDoR: 11.5 m vs. NR	
<b>Zelboraf[1] (Vemurafenib)<sup>3</sup> BRAF inhibitor</b>  <b>BRAF V600E mutation as detected by an FDA-approved test</b>  <b>BRAF inhibitor</b>	2011	Randomized, open-label active-controlled, two-arm  Treatment naïve; One prior therapy	OS PFS ORR	<b>Vemurafenib vs. DTIC</b> mOS: 13.6 vs. 10.3 m HR: 0.47 (95% CI: 0.35, 0.62) mPFS: 5.3 vs. 1.6 m HR: 0.26 (95% CI: 0.20, 0.33) cORR: Vemurafenib: 48.4% (95% CI: 41.6%, 55.2%) CR 0.9% PR 47.4% DTIC: 5.5% (95% CI: 2.8%, 9.3%) PR: 5.5%	The most common AEs (≥ 25%) were: arthralgia (49%), rash (36%), alopecia (33%), fatigue (32%), nausea (30%), photosensitivity reaction (30%), and diarrhea (25%). Other clinically important AEs (<10%) were: cutaneous malignancies (squamous cell carcinomas, keratoacanthomas and melanomas), non-cutaneous squamous cell carcinomas, other malignancies, hypersensitivity reactions (Drug Reaction with eosinophilia and systemic symptoms), dermatologic reactions (Stevens-Johnson, toxic epidermal necrolysis), QT prolongation, hepatotoxicity, photosensitivity, ocular toxicity (retinal vein occlusion, iritis, uveitis, photophobia), vasculitis, atrial fibrillation, and peripheral neuropathy.
<b>Tafinlar (dabrafenib)</b>  <b>BRAF V600E mutation as detected by an FDA-approved test</b>  <b>BRAF inhibitor</b>	2013	Randomized, open-label, active controlled, two arm  Treatment naïve	PFS ORR	<b>Dabrafenib vs. dacarbazine</b>  mPFS: 5.1 vs. 2.7 m HR: 0.33 (95% CI: 0.20, 0.54) cORR: Dabrafenib: 52% (95% CI: 44%, 59%) CR 3% PR 48% DTIC: 17% (95% CI: 9%, 29%) PR: 17%	Most common adverse reactions (≥20%) for TAFINLAR as a single agent are hyperkeratosis, headache, pyrexia, arthralgia, papilloma, alopecia, and palmar-plantar erythrodysesthesia syndrome.
<b>Mekinist[6] (trametinib)<sup>4</sup></b>  <b>BRAF V600E or</b>	2013	Randomized, open-label active-controlled, two arm	PFS ORR	<b>Trametinib vs. Dacarbazine</b> mPFS: 4.8 vs. 1.5 m HR: 0.47 (95% CI: 0.34, 0.65) cORR:	The most common AEs (>20%) were: hypertension, rash, diarrhea, peripheral edema, fatigue, and dermatitis acneiform. Cardiomyopathy, retinal pigment epithelial

<p><b>V600K mutations, as detected by an FDA-approved test</b></p> <p><b>MEK inhibitor</b></p>		<p>≤ 1 prior therapy; no prior BRAF or MEK inhibitor</p>		<p>Trametinib: 22% (95% CI: 17%, 28%) CR 2% PR 20% DTIC: 8% (95% CI: 4%, 15%) CR 0% PR 9%</p>	<p>detachment, retinal vein occlusion, and serious skin toxicity were noted as toxicities. Other clinically important AEs (&lt;10%) were: cardiomyopathy, retinal vein occlusion, retinal pigment epithelial detachment, interstitial lung disease, serious skin toxicity (rash, dermatitis acneiform rash, palmar-plantar erythrodysesthesia syndrome and erythema)</p>
<p><b>Tafinlar and Mekinist[5] (dabrafenib and trametinib)<sup>5</sup></b></p> <p><b>BRAF V600E or V600K mutations, as detected by an FDA-approved test</b></p> <p><b>combined BRAF/ MEK inhibitors</b></p>	<p>2014<sup>6</sup></p>	<p>Randomized, open-label, active-controlled, three-arm portion of dose-escalation study</p> <p>≤ 1 prior therapy; no prior BRAF or MEK inhibitor</p>	<p>ORR</p>	<p><b><u>Dabrafenib plus Trametinib (2 mg or 1 mg once daily) vs. single-agent Dabrafenib</u></b> Dabrafenib plus Trametinib (2mg) vs. Tafinlar (single agent)</p> <p>ORR 76% vs. 54% mDoR 10.5m vs. 5.6m mPFS: 9.4m vs. 5.8m HR: 0.39 (95% CI: 0.25, 0.62)</p>	<p>The most common AEs (≥20%) in patients treated with dabrafenib in combination with trametinib were: pyrexia, chills, fatigue, rash, nausea, vomiting, diarrhea, abdominal pain, peripheral edema, cough, headache, arthralgia, night sweats, decreased appetite, constipation, and myalgia. Other clinically important AEs (&lt;10%) were: cutaneous malignancies (basal cell carcinoma, keratoacanthoma, squamous cell carcinoma), non-cutaneous malignancies, hemorrhage, venous thrombosis, cardiomyopathies, ocular toxicities (uveitis, iritis, retinal pigment epithelial detachment), and serious febrile and skin toxicities.</p> <p>Pyrexia, hemorrhagic events and thromboembolic events occurred at a higher incidence and cutaneous malignancies at a lower incidence with the combination compared to single-agent dabrafenib</p>
<p><b>Keytruda[7] (pembrolizumab)</b></p> <p><b>Human programmed death receptor-1 (PD-1) blocking</b></p>	<p>2014<sup>6</sup></p>	<p>Randomized, open-label, two-arm, dose finding expansion cohort of a dose-escalation study</p> <p>Ipilimumab refractory;</p>	<p>PFS</p>	<p><b><u>Pembrolizumab 2 mg/kg vs. 10 mg/kg IV q 3 weeks</u></b> ORR 24% vs. 24% mDoR not reached</p>	<p>The most common AEs (≥20%) were: fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgia, and diarrhea. Other clinically important AEs (&lt;10%) were: immune-mediated adverse events (pneumonitis, colitis, hepatitis, nephritis and renal failure, hypo- and</p>

<b>antibody</b>		prior treatment with BRAF or MEK inhibitor if BRAF V600 mutation positive			hyperthyroidism, exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, hemolytic anemia, adrenal insufficiency.
<b>Opdivo[8] (nivolumab)</b>  <b>Human programmed death receptor-1 (PD-1) blocking antibody</b>	2014 <sup>6</sup>	Randomized, open-label active-controlled, two arm  Ipilimumab refractory; prior treatment with BRAF or MEK inhibitor if BRAF V600 mutation positive	ORR <sup>7</sup>	<b><u>Nivolumab 3 mg/kg q 2 weeks vs. dacarbazine 1000 mg/m<sup>2</sup> every 3 weeks or carboplatin AUC6 plus paclitaxel 175 mg/m<sup>2</sup> q 3 weeks</u></b> Nivolumab arm - OR 32% (95% CI: 23, 41) 33 (87%) patients reported with duration of 2.6+ to 10+ m Responses were noted in patients with and without BRAF V600 mutated melanoma	The most common adverse reactions (≥ 20%) AEs were: fatigue, dyspnea, musculoskeletal pain, decreased appetite, cough, nausea, and constipation. Other clinically important AEs (<10%) were: immune-mediated adverse events (pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, hypo- and hyperthyroidism, adrenal insufficiency, uveitis, pancreatitis, facial and abducens nerve paresis, demyelination, autoimmune neuropathy, motor dysfunction and vasculitis.

Source: Proleukin (USPI); Yervoy (USPI); Zelboraf (USPI); Dacarbazine (USPI); Tafinlar (USPI); Mekinist (USPI); Keytruda (USPI).

Abbreviations in Table: m, months; BORR, best overall response rate; CR, complete response; cORR, confirmed objective response rate; DOR, duration of response; HR, hazard ratio; Ipi, ipilimumab; mDoR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; NR, not reached; ORR, objective response rate; OS, overall survival; PR, partial response; +, response is ongoing.

<sup>1</sup> Hydroxyurea was also FDA-approved for treatment of melanoma but is of historical interest only

<sup>2</sup> BRAF V600 mutation status unknown.

<sup>3</sup> Patient selection based on BRAF V600E mutation-positive tumors.

<sup>4</sup> Patient selection based on BRAF V600E or V600K mutation-positive tumors

<sup>5</sup> Patient selection based on BRAF V600E, V600K, or V600D mutation-positive tumors

<sup>6</sup> Accelerated approval as per 21 CFR 314.510, subpart H or 21 CFR 314.601, subpart E

<sup>7</sup> Based on a single-arm, non-comparative, planned interim analysis of the first 120 patients in whom the minimum duration of follow-up was 6 months

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARC R THEORET  
11/10/2015