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RESEARCH**

APPLICATION NUMBER:

206192Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	206192
Priority or Standard	Priority
Submit Date(s)	December 11, 2014
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Division / Office	DOP2/OHOP
Reviewer Name(s)	Ruthann M. Giusti Marc Theoret, Team Leader
Review Completion Date	October 31, 2015
Established Name	Cobimetinib (GDC-0973)
(Proposed) Trade Name	Cotellic [®]
Therapeutic Class	Kinase inhibitor
Applicant	Genentech, Inc.
Formulation(s)	Cobimetinib: 20 mg film-coated tablets
Dosing Regimen	Cobimetinib 60 mg PO QD Days 1-21 of each 28-day treatment cycle in combination with vemurafenib 960 mg PO BID on Days 1-28
Indication(s)	COTELLIC [®] is indicated for use in combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with the BRAF V600E and V600K mutations, (b) (4)
Intended Population(s)	≥ 18 years of age

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on the findings described in this clinical review of the new drug application for cobimetinib (NDA 206192), this reviewer recommends regular approval of cobimetinib for the following indication:

COTELLIC[®] is indicated for use in combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with the BRAF V600E and V600K mutations, [REDACTED] (b) (4)

This reviewer recommends labeling revisions to Section 14 CLINICAL STUDIES to communicate to providers the basis of the extension of the approval from BRAF V600E mutations, the BRAF V600 mutation subtype indicated in the label for vemurafenib, to also include with the BRAF V600K mutation subtype, i.e., a retrospective subset analysis conducted in patients with BRAF V600K mutations who were entered into the primary trial based on a positive results using the FDA-approved cobas[®] 4800 V600 mutation test and identified to have a BRAF V600K mutation based on Next Generation (Next Gen) sequencing.

As COTELLIC[®] is proposed for use only in combination with vemurafenib, consistent with the current US Package Insert (USPI) for vemurafenib, the following limitation of use is proposed:

Limitation of use: Cotellic is not indicated for treatment of patients with wild-type BRAF melanoma.

1.2 Risk Benefit Assessment

Introduction

COTELLIC[®] (cobimetinib) is indicated for use in combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with the BRAF V600E and V600K mutations [REDACTED] (b) (4). The proposed dose and schedule is cobimetinib 60 mg PO daily on days 1-21 of each 28-day treatment cycle in patients receiving vemurafenib 960 mg PO BID on Days 1-28.

The assessment of clinical benefit was based on the demonstration of a statistically significant improvement in progression-free and overall survival in a single randomized, placebo controlled trial, GO28141, of 495 patients randomized (1:1) to receive vemurafenib in combination with cobimetinib (Vem/Cobi) or vemurafenib in combination with a matched placebo (Vem/Placebo). Consistency across all secondary endpoints and relevant subgroups including BRAF mutation subgroups, V600E and V600K, was demonstrated. Based on the demonstration of efficacy and the favorable benefit/risk assessment, this reviewer recommends approval with post-marketing requirements as detailed below.

Analysis of Condition and Current Treatment Options

Metastatic melanoma is considered serious and life threatening and an orphan disease, affecting fewer than 200,000 people in the U.S. annually. Historically, the median survival of these patients has been 6 to 9 months. BRAF V600-mutation positive unresectable or metastatic melanoma accounts for 50-60% of all melanoma. While the prognostic significance of mutation status is unclear, the identification of mutation subtypes has led to the development of BRAF-targeted therapy, and more recently to treatment combinations blocking multiple targets within the RAS/RAF/MEK/ERK pathway. Treatment with combined BRAF- and MEK-inhibitors has become standard of care for this patient population as the addition of a MEK inhibitor to a BRAF inhibitor appears to delay the onset of acquired resistance to BRAF inhibition [16, 22, 23]. Combined BRAF and MEK inhibition has the additional benefit of suppressing the paradoxical activation of the ERK signaling in a RAS-dependent manner in tumors, pre-malignant and normal tissues which is thought to explain the occurrence of cutaneous neoplasms such as keratoacanthomas and squamous-cell carcinomas, melanomas, and other tumors seen with this class of drugs [24].

Treatment with the MEK inhibitor, Mekinist (trametinib), in patients receiving the BRAF inhibitor, Tafenlar (dabrafenib), has received accelerated approval for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.

Benefit

The GO28141 trial demonstrated a statistically significant 50% improvement in investigator assessed progression-free survival in patients randomized to receive Vem/Cobi compared to patients randomized to receive Vem/Placebo [HR 0.50 (95% CI:

0.38, 0.67; $p < 0.0001$]. The median PFS was estimated to be 9.9 months (95% CI: 9.0, NR) for patients randomized to the Vem/Cobi arm and 6.2 months (95% CI: 5.6, 7.4) in patients randomized to the Vem/Placebo arm. Pre-specified secondary endpoints included progression-free survival as assessed by a blinded independent radiology committee (BIRC), overall survival (OS) and BIRC-confirmed overall response rate (ORR). PFS analysis based on BIRC review showed results consistent with the primary analysis [HR: 0.60 (95% CI: 0.45, 0.79); $p < 0.001$] and all secondary analyses showed consistent results across relevant subgroups. A statistically significant improvement in OS was observed for patients randomized to receive Vem/Cobi compared to those randomized to receive Vem/Placebo [HR: 0.63 (95% CI: 0.47, 0.85); stratified log-rank p -value=0.0019 is less than the nominal significance level of 0.019 based on the interim analysis]. The estimated median OS for patients randomized to receive Vem/Cobi was not reached (NR) at the time of the analysis (95% CI: 20.7, NR) and was 17.0 months (95% CI: 15.0, NR) for patients randomized to receive Vem/Placebo. The BIRC-confirmed ORR per RECIST v1.1 was significantly improved in patients randomized to receive Vem/Cobi compared to patients randomized to receive Vem/Placebo [67% (95% CI: 61%, 73%) vs. 45% (95% CI: 39%, 51%); Chi-Square test p -value < 0.0001]. Complete responses were reported in 10% of patients randomized to receive Vem/Cobi and in 5% of patients randomized to receive Vem/Placebo. The median duration of response among responders in the Vem/Cobi arm was not reached (NR) at the time of the analysis (range: 9.3, NA) and was 7.3 months (range: 5.8, NR) among responders in the Vem/Cobi arm. Responses lasting at least 6 months were seen in 25% of responders randomized to the Vem/Cobi arm and in 20% of responders randomized to the Vem/Placebo arm

An exploratory analyses of PFS and OS to assess the treatment effect by BRAF mutation subset (V600E and V600K retrospectively classified using Next Gen sequencing in patients pre-screened for study entry using the cobas[®] test) was conducted in 81% of patients in the ITT study population who had adequate tissue remaining for analysis. This analysis suggested a similar treatment effect on PFS in both mutation subtypes with no apparent decrement in OS.

In summary, the GO28141 trial, the single randomized trial supporting efficacy in this NDA, demonstrated a robust, statistically significant and clinically relevant improvement in PFS, OS, and ORR with consistency across all secondary endpoints and relevant subgroups with the addition of cobimetinib to vemurafenib therapy. Within the limits of the study design, patients with tumors harboring a BRAF V600E and those with a BRAF V600K appeared to derive a similar benefit with the addition of cobimetinib to vemurafenib therapy.

Risk

In the GO28141, the median duration of exposure to cobimetinib/placebo was 267 days (range 4-563 days) in the Vem/Cobi treatment group and 173 days (range: 5-515 days) in the Vem/Placebo treatment group. The median duration of exposure to vemurafenib was 279 days (range 4-563 days) in the Vem/Cobi treatment group and 175 days (range 5-516 days) in the Vem/Placebo arm. Forty-five percent of Vem/Cobi treated patients and 35% of Vem/Placebo treated patients required a dose modification or interruption during treatment due to an adverse event. The AEs which most commonly resulted in a reduction/interruption of cobimetinib/placebo were: gastrointestinal disorders (diarrhea: 9% vs. 4%; vomiting: 6% vs. 5%; and nausea: 5% vs. 4%), rash (rash, unspecified: 5% vs. 6%; and rash, maculo-papular: 5% vs. 4%), pyrexia (6% vs. 3%), increased blood CPK (5% vs. 1%), and chorioretinopathy (7% vs. 0%).

Overall, the most frequent ($\geq 20\%$) adverse reactions among patients who received cobimetinib with vemurafenib were: gastrointestinal [diarrhea (60%), nausea (41%) vomiting (24%), rash (rash, unspecified, generalized, macular, maculo-papular and morbilliform) (55%) photosensitivity reaction (46%), arthralgia (36%), fatigue (34%), increased blood creatinine phosphokinase (32%), pyrexia (28%), and elevated alanine aminotransferase (25%) and aspartate aminotransferase (23%).

Adverse reactions which occurred in $\geq 20\%$ of patients with a higher frequency (between arm difference $\geq 5\%$, all CTCAE grades or $\geq 2\%$ CTCAE grades 3-4) in patients treated with cobimetinib in addition to vemurafenib compared to vemurafenib alone included: diarrhea (60% vs. 31%), nausea (41% vs. 25%), vomiting (24% vs. 13%), photosensitivity reaction (45% vs. 35%), increased blood creatinine phosphokinase (32% vs. 3%), pyrexia (28% vs. 23%), elevated alanine aminotransferase (25% vs. 18%) and aspartate aminotransferase (23% vs. 18%).

Serious adverse events (SAEs) were more common among patients who received vemurafenib with cobimetinib than among patients who received vemurafenib alone (35% vs. 26%) as were CTCAE Grade 3-4 AEs (28% vs. 22%). The most common ($\geq 5\%$) Grade 3-4 adverse reactions among patients receiving cobimetinib with vemurafenib included diarrhea (7% vs. 1%), increased blood creatinine phosphokinase (11% vs. 0%), elevated alanine aminotransferase (11% vs. 6%) and aspartate aminotransferase (9% vs. 2%), and basal cell carcinoma (5% vs 2%).

The following were adverse events of special interest:

New Primary Malignancies:

- a. Cutaneous Malignancies: A lower rate of cutaneous squamous cell carcinoma (cusCC)/keratoacanthoma (KA) (6% and 19%) and of second primary melanoma (1% and 2%) were seen among patients treated with Vem/Cobi compared to patients treated with Vem/Placebo. A higher rate of basal cell

carcinoma was seen in the Vem/Cobi treatment group compared to the Vem/Placebo group (4% and 2%). The median time to detection of basal cell carcinoma was 4 months (range: less than 1 to 13 months), the median time to detection of first cutaneous squamous cell carcinoma (cSCC)/KA was 3 months (range 1-8 months), and the median time to detection of second melanoma was 9.4 months (range: 7-12 months).

- b. Non-Cutaneous Malignancies: there were two patients with non-cutaneous malignancies in the COTELLIC plus vemurafenib arm (transitional cell carcinoma: n=2) and 4 patients with non-cutaneous malignancies in the vemurafenib arm (mucinous breast carcinoma: n=1; adenocarcinoma of the colon: n=1; Genitourinary tract neoplasm: n=1; Kaposi's sarcoma: n=1).

Hemorrhage: The incidence of hemorrhage (all grades) was 10% in patients receiving Vem/Cobi and was 6% in patients receiving Vem/Placebo. Grade 3-5 hemorrhages occurred in 1% of patients receiving Vem/Cobi and in 0.4% of patients receiving Vem/Placebo. Cerebral hemorrhage occurred in 1% of patients receiving Vem/Cobi and in none of the patients receiving Vem/Placebo. GI tract hemorrhage (3% vs 1%), reproductive system hemorrhage (2% vs 1%), and hematuria (2% vs 1%) also occurred at a higher incidence in patients receiving Vem/Cobi compared to patients receiving Vem/Placebo. However, there were no CTCAE Grade 4 or 5 hemorrhagic events in either arm.

Reviewer's comment: While hemorrhage may be an emerging signal, this reviewer does not feel that there is sufficient evidence at the present time to include this event in the Warnings and Precautions section of the USPI. This event should be monitored as part of routine post-marketing surveillance.

Cardiomyopathy: Decreased left ventricular ejection fraction (LVEF) of Grade 2 or 3 detected by serial assessment using ECHO/MUGA was reported in 64 (26%) patients receiving Vem/Cobi and in 47 (19%) patients receiving Vem/Placebo. No Grade 4 or 5 events were reported. Median time to first onset of LVEF decrease was 4 months (range 1 to 7 months) in patients receiving Vem/Cobi. Two patients with symptomatic LVEF decrease required permanent discontinuation of cobimetinib; the remaining patients required dosing interruption or decrease.

Serious Skin Toxicity: The overall incidence of skin and subcutaneous tissue disorders was 85% among patients treated with Vem/Cobi and 87% among patients treated with Vem/Placebo. Grade 3-4 skin and subcutaneous tissue adverse reactions occurred in 60 (24%) patients treated with Vem/Cobi and in 47 (19%) patients treated with Vem/Placebo. Photosensitivity reactions (46% vs. 35%) and acneiform dermatitis (16% vs. 11%) were more common among patients in the Vem/Cobi treatment group. Rash (rash, unspecified, generalized, macular, maculopapular and morbilliform) (55% vs. 53%), pruritis (19% vs. 19%), and erythema (10%

vs. 13%) occurred with a similar frequency in both arms. The median time to onset of Grade \geq 3 skin rash was 15 days (range: 3 to 125 days). Skin and subcutaneous adverse reactions resulted in hospitalization in 10 (4%) patients treated with Vem/Cobi and included one patient diagnosed with DRESS and one patient thought to have early Steven's Johnson Syndrome.

Ocular toxicity: Chorioretinopathy (13% vs. <1%), retinal detachment (9% vs. <1%), and blurred vision (10% vs. 2%) occurred more frequently among patients treated with Vem/Cobi than in patients treated with Vem/Placebo. Median time to first onset of serous retinopathy events was 1 month (range 0-9 months). The median duration of serious retinopathy was 5.7 months (range .2 to 16.4). Serous retinal events were reported as resolved in 41% patients following cobimetinib dose interruption or reduction. One patient in each arm developed retinal vein occlusion.

Hepatotoxicity: The incidences of Grade 3 or 4 liver test abnormalities among patients receiving Vem/Cobi compared to patients receiving Vem/Placebo were: alanine aminotransferase (11% vs. 6%), aspartate aminotransferase (7% vs 3%), total bilirubin (2% vs. 1%) and alkaline phosphatase (7% vs 3). One patient treated with Vem/Cobi met Hy's Law criteria. One additional patient met the criteria for Hy's Law but interpretation of the event was confounded by concomitant medications rarely causing hepatotoxicity.

Serum Creatinine Kinase (CK) Elevations/Musculoskeletal Adverse Reactions: CK elevation over baseline occurred in 59% of patients treated with Vem/Cobi and in 9% of patients treated with Vem/Placebo and Grade 3-4 CK elevation over baseline occurred in 10% of patients treated with Vem/Cobi and in <1% of patients treated with Vem/Placebo. Rhabdomyolysis (defined as serum CK increase of more than 10 times the baseline value with a concurrent 1.5 –fold or greater increase in serum creatinine above baseline value) occurred in eight (3%) patients treated with Vem/Cobi and in one (<1%) patient treated with Vem/Placebo. Two additional patients (one in each treatment arm) were reported to have rhabdomyolysis but did not meet this definition. However, musculoskeletal adverse reactions occurred less frequently among patients treated with Vem/Cobi than among patients treated with Vem/Placebo (All Grades: 51% vs. 61%; Grade 3-4 6% vs.10%) and resulted in hospitalization in 2% of patients in each study arm. Arthralgias (36% vs. 40%), myalgias (11% vs. 12%), and extremity pain (10% vs. 14%) occurred less commonly among patients treated with Vem/Cobi than with Vem/Placebo.

Reviewer's comment: While the incidence of Grade 3-4 CK elevation among patients in the Vem/Cobi treatment group was high and while a number of patients met the laboratory definition of rhabdomyolysis, these events did not appear to correlate with musculoskeletal symptoms. Nonetheless, given the relatively safety database, this reviewer advocates inclusion of this event in the Warnings and Precaution, along with routine post-marketing surveillance.

Photosensitivity: Photosensitivity was reported in 47% of patients receiving COTELLIC plus vemurafenib: Grades 1 or 2 events occurred in 43% and the remaining 4% were Grade 3 events. Median time to first onset of photosensitivity events of any grade was 1 month (range 0-14 months). Ninety-five percent of patients with photosensitivity adverse reactions were managed without a change in cobimetinib or vemurafenib.

No differences were noted in the safety profile of vemurafenib used in combination with cobimetinib in patient subsets defined by age, gender or BRAF V600 mutation subset.

Analysis and Recommendation

Unresectable/metastatic melanoma is a serious and life threatening condition. The identification of mutations in BRAF V600 in a large subset of patients with this disease has led to the development of new targeted therapies, including inhibition of multiple tyrosine kinase targets within the RAS/RAF/MEK/ERK pathway. For patients with an identified BRAF V600 mutation, the combined use of BRAF- and MEK- targeted therapies has become a standard of care. Genentech proposes cobimetinib (COTELLIC) for use with vemurafenib (ZELBORAF), for the treatment of patients with unresectable or metastatic melanoma with the BRAF V600 mutations (b) (4). As demonstrated in the GO28141 trial, the addition of cobimetinib to vemurafenib demonstrates substantial evidence of improvement in PFS, OS, and ORR (efficacy) with a tolerable safety profile in this patient population. The safety profile appears similar to that observed with trametinib, administered with dabrafenib, currently marketed for this patient population under the provisions of the accelerated approval regulations.

A robust and clinically significant improvement in progression-free and overall survival was demonstrated in the GO28141 which was consistent across secondary endpoints and across relevant subgroups. Based on an analysis of 493 patients treated in the GO28141, 247 patients who received cobimetinib/vemurafenib, and supported by a small number of patients in an open-label dose-finding trial (NO25395), the safety profile and risk/benefit assessment of the addition of cobimetinib to vemurafenib was demonstrated to be acceptable for use in this patient population.

Patients in the GO28141 trial were selected for study entry based on a positive cobas® 4800 V600 mutation test which is an approved companion diagnostic test that “is

intended to be used as an aid in selecting melanoma patients whose tumors carry the BRAF V600E mutation for treatment with vemurafenib". This diagnostic has been demonstrated to be highly sensitive for the detection of this mutation but has also been demonstrated to identify a subset of tumors with BRAF V600K mutations. When compared to Bi-Directional Sequencing, the cobas test detected approximately 2/3 of samples with a V600K mutation. In a retrospective analysis of stored tissue available on 81% of the intent-to-treat (ITT) study population of the GO28141, BRAF mutation subset (V600E and V600K) was determined using Next Gen sequencing. The risk-benefit assessment is favorable and appears to be of a similar magnitude in both BRAF V600E and V600K mutation-subsets.

This reviewer recommends approval for the following indication:

COTELLIC[®] is indicated for use in combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with the BRAF V600E and V600K mutations (b) (4)

The following key labeling requirements are recommended:

1. Since use is proposed only for patients who are also taking vemurafenib, for which there is a labeling Limitation of Use, a parallel limitation of use in the COTELLIC label is recommended:

Limitation of use: Cotellic is not indicated for treatment of patients with wild-type BRAF melanoma.

2. Warnings and Precautions for the following adverse reactions are recommended in the COTELLIC label:
 - a. New primary malignancies, cutaneous and non-cutaneous
 - b. Serious skin toxicity
 - c. Cardiomyopathy
 - d. Ocular toxicities
 - e. Hepatotoxicity
 - f. Elevation in CPK/Rhabdomyolysis
 - g. Photosensitivity
3. Referral to the ZELBORAF (vemurafenib) label for the following adverse reactions is recommended:
 - a. Tumor promotion in BRAF wild-type melanoma
 - b. Hypersensitivity Reactions
 - c. QT prolongation
 - d. Radiation sensitization and radiation recall

4. A description of the basis for approval in BRAF V600E and V600K mutation subsets within the CLINICAL STUDIES section of the COTELLIC label is recommended

Post-marketing requirements and commitments as detailed in Section 1.4 are recommended.

This reviewer does not recommend a Risk Evaluation and Mitigation Strategy (REMS) based on the information provided in the submission

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

Post Marketing Requirements:

1. To design and conduct a trial to assess the incidence, severity, and reversibility of ocular toxicities of cobimetinib

Post Marketing Commitments:

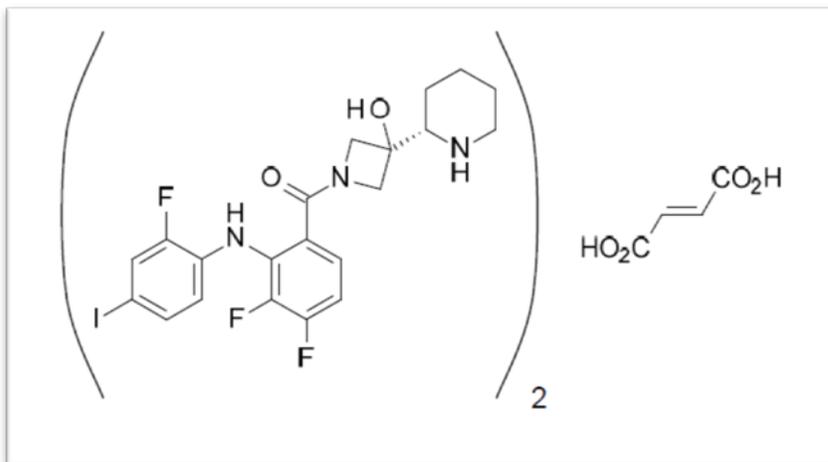
1. Complete and submit the final study report for the ongoing randomized controlled trial, GO28141 with the final and post-final analysis of overall survival.

2 Introduction and Regulatory Background

2.1 Product Information

Cobimetinib hemifumarate (GDC-0973, EXEL-04285518, XL518, RO5514041) is a small molecule kinase inhibitor with selective allosteric inhibitor of MEK1/2. The chemical name is (S)-[3,4-difluoro-2-(2-fluoro-4-iodophenylamino)phenyl] [3-hydroxy-3-(piperidin-2-yl)azetidin-1-yl]methanone hemifumarate. It has a molecular formula: C₄₆H₄₆F₆I₂N₆O₈ (2 C₂₁H₂₁F₃I₂N₃O₂ · C₄H₄O₄) and molecular weight of 1178.71 g/mol. Cobimetinib is available as a 20 mg film-coated round, white tablet for oral administration. The structural formula is below.

Figure 1: Structural Formula of Cobimetinib



2.2 Tables of Currently Available Treatments for Proposed Indications

The therapies currently approved for use in the U.S. and the regulatory bases for these approvals are shown below in Table 1. Rows with gray backgrounds delineate products with accelerated approval at the time of this review and are not considered “available therapy” for regulatory purposes.

Table 1: FDA-Approved Therapies Indicated for the Treatment of Patients with Metastatic Melanoma

FDA Approved Drug ¹ mechanism of action	Approved	Trial Design Study Population	Approval Endpoint(s)	Clinical Benefit/Effect	Most Common and Most Severe Toxicities
DTIC (dacarbazine)² Alkylating agent	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.
Proleukin[3] (interleukin-2)² Human recombinant interleukin-2	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 to 1 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.
Yervoy[4] (ipilimumab[ipi])² Human cytotoxic T-lymphocyte	2011	Multicenter, randomized, blinded, active-controlled three-arm One prior regimen,	OS ORR	ipi vs. gp100: 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	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

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antigen 4 (CTLA-4)-blocking antibody		chemotherapy or interleukin-2		<u>lpi+gp100 vs. gp100:</u> 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	insufficiency, pneumonitis, meningitis, nephritis, eosinophilia, pericarditis)
Zelboraf[1] (Vemurafenib)³ BRAF inhibitor BRAF V600E mutation as detected by an FDA-approved test BRAF inhibitor	2011	Randomized, open-label active-controlled, two-arm Treatment naïve; One prior therapy	OS PFS ORR	<u>Vemurafenib vs. DTIC</u> 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.
Tafinlar (dabrafenib) BRAF V600E mutation as detected by an FDA-approved test BRAF inhibitor	2013	Randomized, open-label, active controlled, two arm Treatment naïve	PFS ORR	<u>Dabrafenib vs. dacarbazine</u> 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.

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Mekinist[6] (trametinib)⁴ BRAF V600E or V600K mutations, as detected by an FDA-approved test MEK inhibitor	2013	Randomized, open-label active-controlled, two arm ≤ 1 prior therapy; no prior BRAF or MEK inhibitor	PFS ORR	<u>Trametinib vs. Dacarbazine</u> mPFS: 4.8 vs. 1.5 m HR: 0.47 (95% CI: 0.34, 0.65) cORR: Trametinib: 22% (95% CI: 17%, 28%) CR 2% PR 20% DTIC: 8% (95% CI: 4%, 15%) CR 0% PR 9%	The most common AEs (>20%) were: hypertension, rash, diarrhea, peripheral edema, fatigue, and dermatitis acneiform. Cardiomyopathy, retinal pigment epithelial detachment, retinal vein occlusion, and serious skin toxicity were noted as toxicities. Other clinically important AEs (<10%) were: cardiomyopathy, retinal vein occlusion, retinal pigment epithelial detachment, interstitial lung disease, serious skin toxicity (rash, dermatitis acneiform rash, palmar-plantar erythroesthesia syndrome and erythema)
Tafinlar and Mekinist[5] (dabrafenib and trametinib)⁵ BRAF V600E or V600K mutations, as detected by an FDA-approved test combined BRAF/ MEK inhibitors	2014 ⁶	Randomized, open-label, active-controlled, three-arm portion of dose-escalation study ≤ 1 prior therapy; no prior BRAF or MEK inhibitor	ORR	<u>Dabrafenib plus Trametinib (2 mg or 1 mg once daily) vs. single-agent Dabrafenib</u> Dabrafenib plus Trametinib (2mg) vs. Tafinlar (single agent) 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)	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 (<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. 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
Keytruda[7]	2014 ⁶	Randomized, open-	PFS	<u>Pembrolizumab 2 mg/kg vs. 10</u>	The most common AEs (≥20%) were: fatigue,

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<p>(pembrolizumab)</p> <p>Human programmed death receptor-1 (PD-1) blocking antibody</p>		<p>label, two-arm, dose finding expansion cohort of a dose-escalation study</p> <p>Ipilimumab refractory; prior treatment with BRAF or MEK inhibitor if BRAF V600 mutation positive</p>		<p>mg/kg IV q 3 weeks ORR 24% vs. 24% mDoR not reached</p>	<p>cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgia, and diarrhea. Other clinically important AEs (<10%) were: immune-mediated adverse events (pneumonitis, colitis, hepatitis, nephritis and renal failure, hypo- and hyperthyroidism, exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, hemolytic anemia, adrenal insufficiency.</p>
<p>Opdivo[8] (nivolumab)</p> <p>Human programmed death receptor-1 (PD-1) blocking antibody</p>	<p>2014⁶</p>	<p>Randomized, open-label active-controlled, two arm</p> <p>Ipilimumab refractory; prior treatment with BRAF or MEK inhibitor if BRAF V600 mutation positive</p>	<p>ORR⁷</p>	<p>Nivolumab 3 mg/kg q 2 weeks vs. dacarbazine 1000 mg/m2 every 3 weeks or carboplatin AUC6 plus paclitaxel 175 mg/m² q 3 weeks 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</p>	<p>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.</p>

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.

¹ Hydroxyurea is also FDA-approved for treatment of melanoma but is of historical interest only.

² BRAF V600 mutation status unknown.

³ Patient selection based on BRAF V600E mutation-positive tumors.

⁴ Patient selection based on BRAF V600E or V600K mutation-positive tumors

⁵ Patient selection based on BRAF V600E, V600K, or V600D mutation-positive tumors

⁶ Accelerated approval as per 21 CFR 314.510, subpart H or 21 CFR 314.601, subpart E

⁷ 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.

Because there is evidence that RAF inhibitors induce carcinogenesis or promote tumor progression via a paradoxical stimulation of the MAPK signaling pathway in RAF wild-types cells[9], the USPI for the BRAF inhibitors (dabrafenib and vemurafenib) require BRAF mutation status be determined using an FDA- approved test and carry a limitation of use stating that BRAF inhibitor therapy is not indicated for treatment of patients with wild-type BRAF melanoma. A list of approved companion diagnostics for use in detection of BRAF V600 mutations can be found at

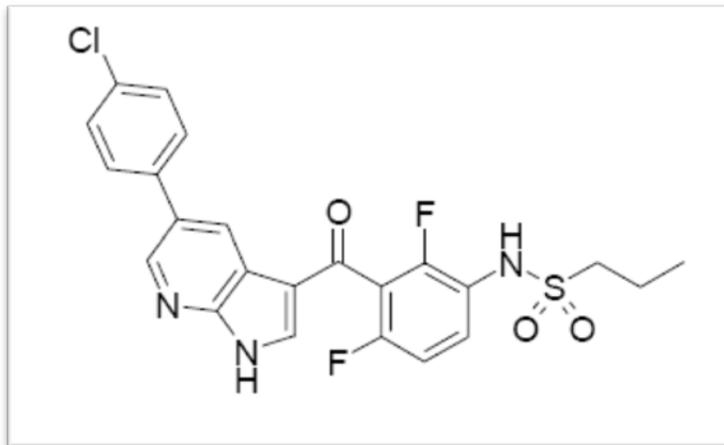
<http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm>

The proposed indication for cobimetinib states that it is to be given with vemurafenib. The following additional information regarding vemurafenib, for the US full prescribing information, is reproduced below.

“Vemurafenib is a low molecular weight, orally available inhibitor of some mutated forms of BRAF serine-threonine kinase, including BRAF V600E. Vemurafenib also inhibits other kinases in vitro such as CRAF, ARAF, wild-type BRAF, SRMS, ACK1, MAP4K5, and FGR at similar concentrations. Some mutations in the BRAF gene including V600E result in constitutively activated BRAF proteins, which can cause cell proliferation in the absence of growth factors that would normally be required for proliferation. Vemurafenib has anti-tumor effects in cellular and animal models of melanomas with mutated BRAF V600E”[1].

Vemurafenib has the chemical name propane-1-sulfonic acid [3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4difluoro-phenyl]-amide. It has the molecular formula C₂₃H₁₈ClF₂N₃O₃S and a molecular weight of 489.9. Vemurafenib is available as light pink, oval, 240 mg tablets for oral use.

Figure 2: Structural Formula of Vemurafenib



2.3 Availability of Proposed Active Ingredient in the United States

Cobimetinib is not available in the U.S.

2.4 Important Safety Issues With Consideration to Related Drugs

Important safety issues for the BRAF inhibitors dabrafenib and vemurafenib, for the MEK inhibitor trametinib, and dabrafenib and trametinib when administered together, as reflected in the USPI for each of these compounds are summarized below in Table 2.

Table 2: Important Safety Issues With Related Drugs

	Warnings/Precautions	Common Adverse Events	Drug Interactions
Vemurafenib[1]	<ul style="list-style-type: none"> • CusCC*, new primary melanoma • Hypersensitivity reactions • Severe dermatologic reactions: Stevens-Johnson syndrome, toxic epidermal necrolysis • QT prolongation • Liver function abnormalities • Photosensitivity • Serious ophthalmologic reactions: uveitis, iritis, RVO 	arthralgias, rash, alopecia, fatigue, photosensitivity reaction, nausea, pruritus, skin papilloma	CYP Substrates
Dabrafenib[5]	<ul style="list-style-type: none"> • New primary malignances, cutaneous and non-cutaneous, new primary melanoma • Serious dermatologic reactions • Hyperglycemia 	hyperkeratosis, headache, pyrexia, arthralgia, papilloma, alopecia, and palmar-plantar erythrodysesthesia syndrome	CYP Substrates G-6-PD, hemolytic anemia
Trametinib[6]	<ul style="list-style-type: none"> • Major hemorrhagic events • Cardiomyopathy • Ocular toxicities: RVO, RPED • Interstitial lung disease (ILD), pneumonitis • Serious skin toxicity: acneiform rash, PPEDS, erythema 	rash, diarrhea, and lymphedema	-
Dabrafenib/Trametinib[5]	<ul style="list-style-type: none"> • Major hemorrhagic events • Venous thrombosis and pulmonary embolism • Cardiomyopathy, LVEF reduction • Ocular toxicities: RPED, uveitis, iritis • Serious febrile reactions, pyrexia • New primary malignances, cutaneous and non-cutaneous, new primary melanoma (risk appears reduced compared to dabrafenib alone) • Hyperglycemia 	pyrexia, chills, fatigue, rash, nausea, vomiting, diarrhea, abdominal pain, peripheral edema, cough, headache, arthralgia, night sweats, decreased appetite, constipation, and myalgia	CYP Substrates G-6-PD, hemolytic anemia

*CusCC – cutaneous squamous cell carcinoma; PPEDS - palmar-plantar erythrodysesthesia syndrome; retinal vein occlusion; RPED - retinal pigment epithelial detachment

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Major regulatory milestones along with key FDA recommendations prior to the NDA submission are summarized in Table.

FDA agreed to accept the NDA as a rolling submission. The initial component of the NDA submission was received on October 30, 2014 with the remaining components received on December 11, 2014. FDA agreed to Genentech's request for priority review. No significant filing issues were identified.

Table 3: Key Regulatory Milestones related to clinical development, NDA 206192

Date	Milestone	Key Recommendations/Agreements
Aug 31, 2010		<ul style="list-style-type: none"> IND 109307 submitted for vemurafenib (named RO5185426), a selective inhibitor of oncogenic BRAF kinase, for use in combination with GDC-0973 (cobimetinib) for the treatment of solid tumors.
Sep 2010 – Jun 2012	Phase I/II development	<ul style="list-style-type: none"> The dose-escalation trial of RO5185426 (vemurafenib) in combination with GDC-0973 in patients with BRAF V600E mutated metastatic melanoma (NO25395) was evaluated and found to be safe to proceed. The dose of 960 mg PO BID vemurafenib in combination with 60 mg PO QD GDC-0973; 21 days on with 7 days off administered in 28 day cycle until progression or excessive toxicity was determined to be the recommended phase 2 dose.
Jun 12, 2012	End-of-Phase 1/Pre-Phase 3	<ul style="list-style-type: none"> The design of the single randomized, multicenter, placebo-controlled trial of vemurafenib with cobimetinib/placebo in patients with unresectable or metastatic melanoma with BRAF V600 mutations selected using the cobas test was discussed. It was agreed that the demonstration of a robust, statistically significant and clinically meaningful effect on investigator-assessed PFS, subject to a blinded, independent review could support registration, provided the trial was found to be well-designed and well-conducted. FDA recommended that the final OS analysis should be sufficiently powered to detect a clinically significant effect on survival. FDA provided recommendations for monitoring of second primary malignancies, QTc prolongation and ocular toxicity.
Aug 9, 2012	New Clinical Protocol, GO28141	<ul style="list-style-type: none"> Randomized, double-blind, placebo controlled study of vemurafenib vs. vemurafenib plus GDC-0973 in previously untreated patients with BRAF V600E mutated unresectable/metastatic melanoma submitted to IND 109307.
Nov 27, 2012	End-of-Phase 2; CMC	<ul style="list-style-type: none"> FDA concurred with Genentech's proposals for technical development of GDC-0973 and quality control testing of the

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		registration batches and commercial drug product for release.
Apr 22, 2013	Type C (Written Responses)	<ul style="list-style-type: none"> FDA provided written responses to Genentech's questions concerning the proposed clinical pharmacology plan to assess single- and multiple-dose pharmacokinetics, relative bioavailability and food effect, absolute bioavailability, mass balance and metabolism profile, drug-drug interaction potential and QT prolongation potential. FDA indicated that the conducted and planned clinical pharmacology studies were generally adequate.
Nov 21, 2013	Orphan-Drug Designation Granted	<ul style="list-style-type: none"> Cobimetinib was granted orphan-drug designation for the <i>treatment of stage IIb, IIc, III and IV melanoma with BRAF V600E mutation.</i>
Mar 5, 2014	Pre-NDA, CMC	<ul style="list-style-type: none"> Genentech's proposed commercial specification for cobimetinib 20 mg tablet was discussed. FDA requested that the complete multi-point dissolution profile data for the pivotal trial and registration stability batches at release and on storage be included in the NDA to support setting the final acceptance criterion. FDA requested that a clear overview of formulation changes throughout development and the effects of these changes on dissolution performance and bioavailability be included. FDA requested a proposal for acceptance criterion for (b) (4) be provided. Genentech indicated that they plan to launch the commercial cobimetinib 20 mg tablets in bottles for an alternate Genentech packaging site (Segrate [Italy]). FDA requested that three batches with three months accelerated stability data from the new site be provided no later than 60 days after NDA submission and that long term stability data be submitted in the annual report.
(b) (4)		
Jun 17, 2014	Fast Track Designation (FTD) request	<ul style="list-style-type: none"> FTD granted Aug 15, 2014 for the investigation of cobimetinib and

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	submitted	vemurafenib for the treatment of patients with BRAF V600E-mutation positive, unresectable or metastatic melanoma to demonstrate improved progression-free survival and overall survival
Jul 3, 2014	Proprietary Name/Request for Review	<ul style="list-style-type: none"> Request for the proprietary name Cotellic was approved Oct 10, 2014.
Oct 8, 2014	Pre-NDA – Type B	<ul style="list-style-type: none"> FDA agreed that the high level efficacy and safety results from the GO28141 supported by NO25395, MEK4592g and additional clinical pharmacology trials were adequate to support NDA filing. FDA concurred that the non-clinical and clinical pharmacology information appeared sufficient to support filing of the non-clinical and clinical pharmacology sections of the proposed NDA. FDA indicated that there were insufficient data to determine whether a Risk Evaluation and Mitigation Strategy (REMS) was required. FDA indicated that provided there were no changes to the device specific to the combination use, a PMA supplement would not be required for the cobas[®] 4800 BRAF Mutation Test to support the approval of cobimetinib in combination with vemurafenib because the test is used in accordance with the vemurafenib label. However if cobimetinib is developed for use in a new indication that requires a selection of patients with BRAF V600 mutation-positive tumors, a PMA supplement will be required. Genentech indicated their intent to amend the GO28148 Statistical Analysis Plan (SAP) and protocol to conduct an earlier assessment of final OS. FDA indicated that in general reducing the number of events for any efficacy analyses after seeing the interim data is not acceptable, accrual to the study is complete and all enrolled patients will be continuously followed. FDA indicated that if the revised SAP was found to be acceptable and if the trial meets the specified threshold for significance as described under the revised SAP, the OS results may be included in the label.
Oct 10, 2014	Request for Rolling Review	<ul style="list-style-type: none"> Granted Oct 28, 2014
Oct 30, 2014	Original New Drug Application Submission (NDA) 206192	<ul style="list-style-type: none"> Partial Module 1, Partial Module 2, Module 3, Module 4
Dec 11, 2014	Original New Drug Application Submission (NDA) 206192	<ul style="list-style-type: none"> Complete Module 1, Complete Module 2, Module 5
October 8, 2015	Teleconference	<ul style="list-style-type: none"> On October 8, 2015, FDA held an informal teleconference with

		<p>Genentech to discuss the results of a post-final analysis of data from the GO28141 trial (data cut-off date: January 16, 2015). (b) (4)</p> <p>Based on this analysis (done using CFR) with 188 OS events reported, and with a median follow-up of 14.2 months, the median survival continued to demonstrate a positive effect on OS in favor of the cobimetinib with vemurafenib treatment arm (HR=0.65, 95% CI: 0.49-0.87). FDA agreed to consider this additional data for inclusion in labeling. The Efficacy Update Report and supporting datasets were submitted to FDA on 10/16, 2015.</p>
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2.6 Other Relevant Background Information

In 2015, it is estimated that there will be 73,870 new melanoma cases and 9,940 deaths from melanoma in the U.S [10]. According to Surveillance, Epidemiology and End Results (SEER) data, between 2005 and 2011, approximately 84% of patients were diagnosed with localized disease, 9% with regional disease, and 4% with distant metastatic disease [11]. While patients with localized disease have an excellent long-term prognosis, patients who are diagnosed with or develop metastatic disease have a median overall survival of less than one year [11].

The identification of the BRAF oncogene in 50% – 60% patients with metastatic melanoma tumors has led to the identification BRAF as a therapeutic target [12]. The most prevalent BRAF mutations in melanoma are BRAF V600E (about 80%) and BRAF V600K (5-30%). Other mutations are rare. The frequency of BRAF V600K mutation has been reported to increase with age, and to be associated with cumulative sun induced skin damage [13], which may account for some of the differences in population frequencies observed. BRAF V600K may be associated with the occurrence of brain and lung metastases and a shorter time from diagnosis to metastasis and death [14]. The ability to detect the BRAF V600K mutation varies with the characteristics of the test kit. The cobas[®] 4800 BRAF V600 mutation Test is an in vitro diagnostic co-developed with vemurafenib to specifically designed to detect the BRAF V600E mutation in DNA extracted from formalin-fixed, paraffin-embedded melanoma. However, the minimum mutation load in tumor samples required for detection of the V600K mutation by cobas test is 30% [15].

Mutations of the BRAF gene can result in constitutive activation of the RAF-MEK-ERK pathway; dysregulated downstream signaling via MEK and ERK leads to excessive cell proliferation and survival [12]. It is estimated that approximately 50% of patients with metastatic melanoma carry an activating mutation of BRAF [16, 17].

While BRAF inhibitor therapy represented an unprecedented advance over prior therapies based on objective response rates in the subset of patients with BRAF-mutated melanoma, progression-free survival with BRAF-inhibitor therapy is brief, 5 to 6 months with eventual disease progression. Several mechanisms were found to lead to acquired resistance to BRAF inhibitors resulting in the reactivation of the MAPK pathway through activation of downstream MEK [20, 21]. Nonclinical models demonstrated that the addition of a MEK inhibitor to a BRAF inhibitor can overcome acquired resistance of BRAF inhibition and can delay the onset of acquired resistance to BRAF inhibition [16, 22, 23]. Combined BRAF and MEK inhibition has the additional benefit of suppressing the paradoxical activation of the ERK signaling in a RAS-dependent manner in tumors, pre-malignant and normal tissues which is thought to

explain the occurrence of cutaneous neoplasms such as keratoacanthomas and squamous-cell carcinomas, melanomas and other tumors seen with this class of drugs [24]. Because BRAF inhibitors have not been shown to be effective in patients with a wild-type BRAF and because of the increased risk of tumor promotion in patients with wild-type BRAF tumors, vemurafenib and dabrafenib carry a limitation of use contraindicating the use of these agents in patients with wild type BRAF tumors.

Clinical evidence supporting the proof of principal that concurrent BRAF and MEK inhibition results in greater anti-tumor activity than with inhibition of BRAF or MEK alone was seen with the greater overall response rate in patients receiving dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) compared with dabrafenib or trametinib as single agents [25]. This resulted in accelerated approvals in January 2014 for dabrafenib, in combination with trametinib, and for trametinib, in combination with dabrafenib, for the treatment of patients with BRAF V600 mutated melanoma based on the demonstration of superior overall response rates [5].

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission contained all required components of the eCTD. The overall quality and integrity of the application was adequate. However, several data quality and integrity issues affected the efficiency and timeliness of the review:

- The Applicant submitted a Study Data Reviewers Guide for the two major studies used to support the submission, GO28141 and NO25395. However many of the sponsor's explanations in the data conformance sections for both studies are simply acknowledgements and not quality clarifications.
- The MedDRA version identified in the Define.xml in study was 16.1. However the Study Data Reviewer's Guide (SDRG) listed the MedDRA version as 17.0. The MedDRA version was confirmed to be version 17.0.
- In GO28141, data definition files did not contain informative definitions of multiple variables which reduced the efficiency of the review.
- Differing data cutoffs resulted in data discrepancies in some of the datasets, for example, the number of deaths recorded in the DM coded with the DMDTHFL – Y and the DTHDTC value populated in study GO28141 differed from the number of patients recorded as having "DEATH" recorded in DS.
- The overall quality of the clinical narratives was poor. Narratives failed to integrate relevant collaborating laboratory, EKG and radiographic details, requiring extensive review of case report forms and clinical databases to verify and assess findings.

- In the NO25395 trial, data were not collected regarding whether an adverse event was serious or not, making it difficult to independently verify whether an adverse event was serious or not.
- Misclassification of patients randomized to the Vem/Placebo arm (this issue is discussed in more detail below).

The misclassification of the treatment assignment of eight patients originally randomized to the Vem/Placebo arm was identified as an issue by Genentech in the original submission. Re-classification of seven of these patients based on drug kit reconciliation and identification of data entry errors at the time the data lock called into question the overall data integrity of the data for Trial GO28141 in the submission based on potential inadequate drug reconciliation procedures and inadequate on-site monitoring. These concerns required re-analysis of the safety data and ultimately led to a major amendment requiring extension of the review clock.

At the time of the original submission, Genentech noted that eight patients treated at seven study sites who had been originally randomized to receive Vem/Placebo had inadvertently received cobimetinib. As defined by the statistical analysis plan, these patients were classified with the Vem/Cobi arm for purposes of the safety analysis. At the time of the safety update, Genentech clarified that only one of these errors represented a dispensing error; seven of these patients were later identified as having data entry errors in the site medication dispensing information. These patients were re-assigned to the Vem/Placebo arm. In response to an information request dated May 14, 2015, May 19, 2015, and May 27, 2015, Genentech further clarified that drug dispensation and data entry errors occurred in both treatment arms. There were 11 patients randomized to the Vem/Cobi arm who were identified as having received a dose of placebo at the time of the original submission; four of these were identified as having a dispensing error (actually received placebo) and seven were identified as having data entry errors in the site medication dispensing information. Since these patients all received at least one dose of cobimetinib, there was not a change in the treatment assignment for these patients in the safety analysis dataset. Genentech was required to provide a revised safety analysis using the data from the May 9, 2014, data cut-off date with the corrected treatment assignment and to provide updated data sets from the safety update for verification by the FDA.

Reviewer's comment: Re-analysis of the safety data with the data cut-off date of May 9, 2014, corrected for treatment assignment did not materially change the safety findings

3.2 Compliance with Good Clinical Practices

Data from the GO28141 were monitored by an external data safety monitoring board (DSMB). The DSMB consisted of clinicians who are experts in the disease area and one statistician. The DSMB reviewed the available safety data from this trial at regularly

scheduled intervals specified in the DSMB charter. In addition, for this study the DSMB reviewed the results of the interim analysis of OS and the pre-specified final analysis for PFS performed at the time of the interim analysis for OS. Following each data review, the DSMB made recommendations to the Sponsor regarding the conduct of the study according to the DSMB charter. An independent Data Coordinating Center provided the safety and efficacy results to the DSMB.

The investigator ensured that this study was conducted in full conformance with the principles of the "Declaration of Helsinki," or with the laws and regulations of the country in which the research was conducted, whichever afforded greater protection to the individual. The Applicant stated that study fully adhered to the principles outlined in the current "Guideline for Good Clinical Practice (GCP)" International Conference on Harmonization (ICH) Tripartite Guideline (January 1997), or with local law if it afforded greater protection to the patient. This was documented by the investigator's signature on the protocol agreeing to carry out all of its terms in accordance with applicable regulations and law and to follow ICH GCP guidelines. For studies conducted in the U.S or under a U.S. IND, the investigator ensured adherence to the basic principles of "Good Clinical Practice" as outlined in the current version of 21 CFR, subchapter D, part 312, "Responsibilities of Sponsors and Investigators"; part 50, "Protection of Human Patients"; and part 56, "Institutional Review Boards." In other countries where "Guideline for Good Clinical Practice" exists, the Applicant and participating investigators strictly ensured adherence to the stated provisions.

It was the responsibility of the investigator or designee (if acceptable by local regulations) to ensure that the informed consent form (ICF) from each patient was signed and dated prior to participation in this study after adequate explanation of the aims, methods, objectives and potential hazards of the study. It was explained to the patients that they were completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

Based on irregularities identified during routine monitoring of GO28140, Genentech conducted audits at three clinical sites as shown below

Investigator Site Audit	Location	Audit Date
Dr. Paolo Ascierto	Italy	10-11 FEB 2014
Dr. Virginia Ferraresi	Italy	12-13 FEB 2014
Prof. Peter Hersey	Australia	18-19 March 2014

The purpose of the audits was to evaluate compliance with Good Clinical Practice (GCP) guidelines, relevant local regulation, the clinical trial protocol and applicable standard operating procedures (SOP).

Genentech reported critical findings of non-compliance at one site, Site Number: 252736 (Dr. Hersey, Lake Macquarie Private Hospital, Gateshead, Australia). This site enrolled six patients onto GO28141. Genentech reported the following deficiencies:

The Investigator was instructed via a Genentech Safety Notification Memo to inform subjects of new safety information while waiting for the release of a Protocol Amendment and corresponding updated informed consent form (ICF). Confirmation of this verbal communication and the subjects' willingness to continue in the study was not documented in medical records. In addition, there was a delay in the implementation of the protocol amendment and corresponding updated ICF, during which time subjects were not consented with new safety information that may have been relevant to their willingness to participate in the study.

As a corrective action, the new safety information was communicated to subjects, documented in medical records, and their willingness to continue in the study confirmed via the signing of the updated ICF. Clinical Research Associates (CRAs) on the study were. The CRAs were also prompted to monitor the communication and documentation of new safety information to subjects, confirming this verification in site visit reports.

Genentech reported that no other critical audit findings were observed at the remaining two sites.

A consult was requested from the Office of Scientific Integrity (OSI) to conduct inspections of clinical sites enrolling patients into the GO28141. Four clinical sites were chosen for inspection: Site 256859 (Dr. Gabriella Liskay, Budapest, Hungary), Site 253588 (Dr. Paolo Ascierio, Napoli, Italy), Site 257793 (Dr. Virginia Ferraresi, Rome, Italy) and Site 255078 (Dr. Michele Maio, Siena, Italy) based on enrollment of large numbers of study subjects. The study Sponsor, Genentech, was also inspected. The preliminary FDA inspection reports are shown below.

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

NAI = No deviation from regulations. No action indicated
VAI = deviation(s) from regulations, voluntary Action Indicated.
OAI = Significant deviations from regulations. Data deemed to be unreliable.
VAI = deviation(s) from regulations,
Voluntary Action Indicated.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

No significant deviations were found at two of the sites, Dr. Gabriella Liskay's and Dr. Michele Maio's sites. Some deviations were noted at Dr. Paolo Ascierto's site, however, these deviations were not considered to be major and deviations, once discovered were corrected by the investigator and were not deemed to effect patient safety and the data from this site was judged to be reliable.

Dr. Virginia Ferraresi's site, which screened 19 patients and enrolled 15 patients onto GO28141, was assessed by the FDA inspector to have significant deviations. From the inspection report:

Generally, the investigator's execution of the protocol was found to be marginal. The inspection revealed numerous protocol deviations and GCP compliance deficiencies. The site enrolled one subject into the study without documentation of informed consent. Subsequently, this subject underwent study procedures and treatment with study drug. The site had instances where the protocol specified imaging for subjects were either not done or delayed to a point where the imaging was out of window for that cycle. For example, Subject 2011 did not have tumor assessments performed following protocol timeline (every 8 weeks +/- 1 week); at Cycle 7 the tumor assessment was not done, and at Cycle 9 and Cycle 11 tumor assessments were performed but were more than 21 days out of window.

There was also evidence of underreporting of adverse events. The firm had transcription errors where AEs were inadvertently not transcribed onto the eCRF, and in some cases AEs that occurred prior to the data analyses cutoff date were not transcribed onto the eCRF until after the data cut-off date, May 2014. Therefore, the AEs were not included in the data listings submitted to the application. For example, AEs and concomitant medications that were documented in subject medical records and subject diaries were not always entered in the case report forms. Subjects' diary data not entered into the CRF included headache, nausea, rash, diarrhea, and use of heparin.

A Form FDA 483 was issued citing five inspectional observations for this site. However, the final classification of this site was VAI.

Reviewer's comment: Despite significant deviations which occurred at at least one study site, the major efficacy findings were not materially changed with elimination of this site from the primary analysis, as discussed in Section 6.4.1. Elimination of this study site was not deemed to be warranted and data from this study site was included in the final analysis and in labeling.

3.3 Financial Disclosures

Debarment certification was submitted and certified by Michelle H. Rohrer, Ph.D., Vice President, U.S. Regulatory Affairs, Genentech, Inc. and dated 12/4/2014.

Disclosure of financial interests of the investigators who conducted the clinical trials supporting this NDA (GO28141, NO25395, and MEK4592g) was submitted in the FDA Form 3453. The disclosure was certified by Michelle H. Rohrer, Ph.D., Vice President, U.S. Regulatory Affairs, Genentech, Inc., and dated 12/4/2014. Findings are summarized for the randomized clinical trial, GO28414.

Patients were enrolled into GO28141 at 133 sites in 19 countries. A signed financial disclosure was obtained from 1239 of 1245 (99.6%) of principal investigators and sub-investigators. Disclosure was not obtained for 6 sub-investigators. Disclosable financial interests were recorded by 3 of 1239 (< 1%) of investigators in GO28141.

Table 4: Investigators with Disclosable Financial Interests, GO28141

Clinical Site Number	Patients Enrolled at Site	Investigator Name	Disclosure
		(b) (6)	Payments received from Genentech/GNE greater than \$25k - Honoraria with Genentech > \$25,000
			Payments received from Genentech/GNE greater than \$25,000 – Multiple payments diverse causes
			Payments received from Genentech/GNE greater than \$25,000 - Honoraria for speaking/consulting

^aSub-Investigator

Reviewer's comment: The total number of patients enrolled at the three sites (n=(b) (6)) at which investigators had a financial conflict of interest did not drive the efficacy or safety data and does not appear to influence the outcome of the trial.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Refer to the CMC review.

4.2 Clinical Microbiology

Cobimetinib is administered by mouth and was not reviewed for clinical microbiology.

4.3 Preclinical Pharmacology/Toxicology

Please refer to the FDA Pharmacology/Toxicology review.

4.4 Clinical Pharmacology

Please refer to the Clinical Pharmacology review.

4.4.1 *Mechanism of Action*

From the draft package insert:



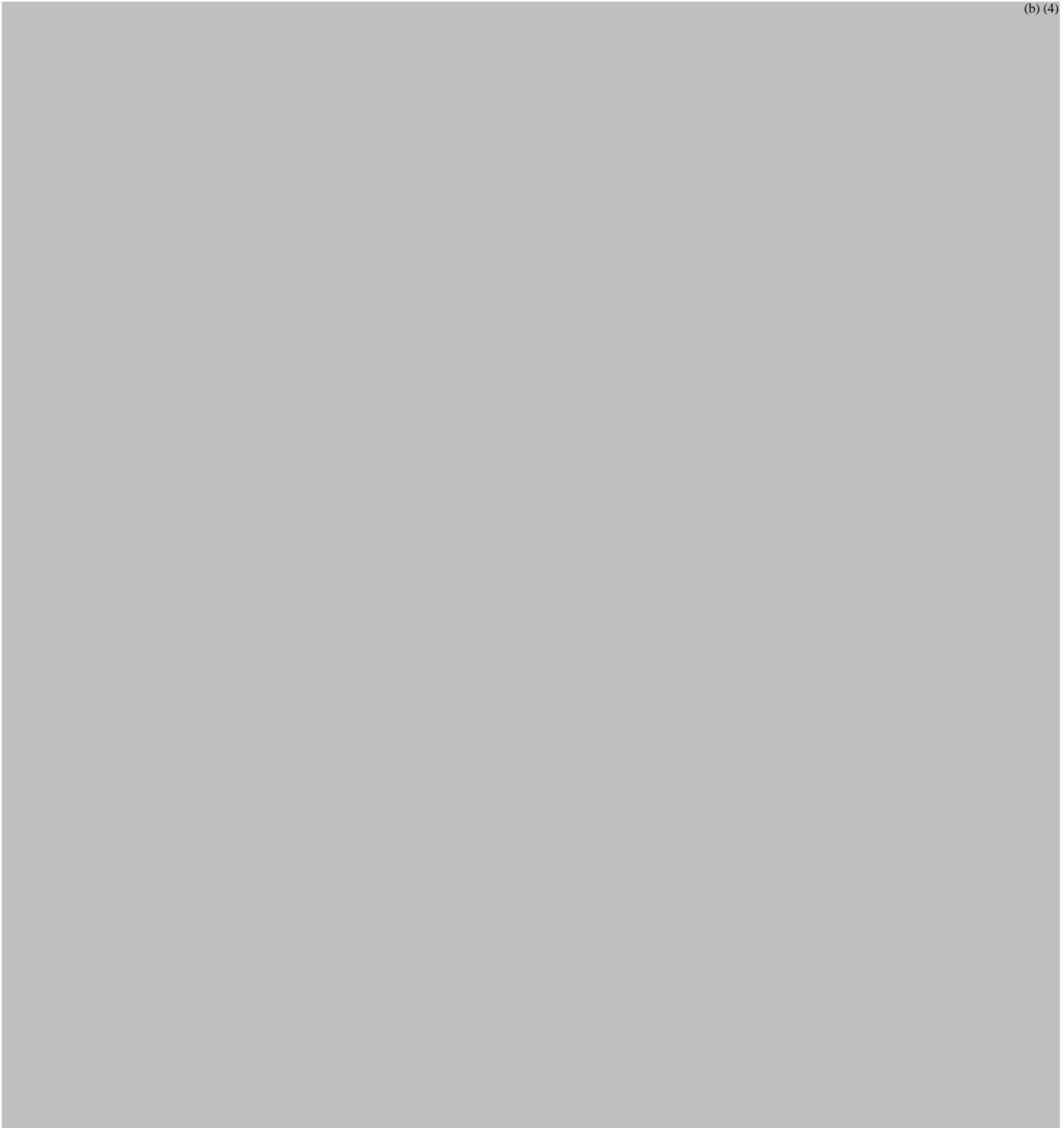
4.4.2 *Pharmacodynamics*

Please refer to the Clinical Pharmacology review for details.

4.4.3 *Pharmacokinetics*

Please refer to the Clinical Pharmacology review for details.

From the package insert:



5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The submission includes the trials shown in Table 5 to support the efficacy and safety of the addition of cobimetinib to vemurafenib in the indicated patient population.

Table 5: Clinical Trials to Support Efficacy and Safety, NDA 206192

Trial	Objectives	Study Design	Test Product(s); Dosage regimen; Route of Admin	N	Diagnosis of Patients	Treatment Duration	Status:
NO25395 (BRIM7) SCS/ISS* SCE**	To evaluate the safety, tolerability, pK and efficacy of VEM/COBI	Multicenter, non-randomized open-label, dose-escalation study	Dose escalation: Vem: 720 or 960 mg BID Cobi: QD14/14 60, 80, 100 mg or – QD 21/7, 60 mg or – QD 28/0, 60 mg Expansion: Vem: 720 or 960mg BID Cobi: 60 mg QD 21/7	129	Advanced BRAFV600 mutated MEL (1) BRAFi-naïve or (ii) who progressed after treatment with VEM	Until progression, Intolerable toxicity, withdrawal or death	Accrual complete; trial ongoing with patients in follow-up
GO28141 (coBRIM) SCS/ISS SCE	To evaluate PFS/INV(1°), OS, ORR, DOR, PFS/IRC (2°), Safety, PK, PRO	Randomized double blind, placebo/ active controlled	Vem/Cobi or Vem/Placebo Vem: 960mg BID COBI 60mg QD 21/7	495	First line advanced BRAFV600 mutated MEL	Until progression, Intolerable toxicity, withdrawal or death	Accrual complete; trial ongoing with patients in follow-up
MIK4592g SCS/ISS	Safety, PK, MTD	Multicenter, non-randomized open-label, dose-escalation	Stage I: cobimetinib QD; 21/7 0.05, 0.10 0.20,10, 20, 40, 60 and 80 mg Stage IA: cobimetinib QD; 14/14 60, 80, 100 and 125 mg Stage II: cobimetinib QD 21/7 60 mg Stage IIA: cobimetinib QD14/14 100 mg	97	Solid tumors	Until progression, Intolerable toxicity, withdrawal or death	Study completed; Full CSR (Stage I, IA, II, IIA)

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Abbreviations in table: VEM – Vemurafenib; COBI- cobimetinib; MEL-melanoma; PFS- progression-free survival; INV- Investigator-assessed; IRC- Independent Review Committee; OS- Overall Survival, ORR- Objective Response Rate; DOR-Duration of Response; PK- Pharmacokinetics; PRO- Patient Reported Outcome(s); BRAFi – BRAF inhibitor; 14/14 – 14 days on treatment and 14 days off treatment in a 28 day treatment cycle; 21/7- 21 days on treatment and 7 days off treatment in a 28 day treatment cycle; 28/0- 28 days on treatment in a 28 day treatment cycle; QD- daily; BID- Twice daily

*SCS/ISS – Study included in Summary of Clinical Safety/Integrated Summary of Safety

**SCE – Study included in Summary of Clinical Efficacy

5.2 Review Strategy

The clinical review is based primarily on the analysis of progression-free and overall survival from the single, randomized trial submitted by the applicant, GO28141 (coBRIM). This trial is discussed in detail in section 5.3.1. The literature relevant to the prognosis and treatment of BRAF-V600 mutated melanoma and MEK- and BRAF-inhibition was reviewed. Additionally, Module 2 summaries, including the integrated review of safety and efficacy (ISS, ISE), the Study Report for GO28141, the study case report forms, patient safety narratives, primary data sets for efficacy and safety, the FDA reviews for statistics, clinical pharmacology, pharmacology/toxicology and chemistry and the Applicant's presentation slides for this trial were reviewed in detail. Patient reported outcomes evaluated were evaluated by the Applicant using the EORTC QLQ-C30 and health economic measures evaluated using the EQ-5D were assessed by the applicant. However, since no claims resulted from these analyses, these measures were not independently reviewed.

The Study Report for NO25395, safety narratives and primary data sets were reviewed in detail.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 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)

First Patient Entered:	8 Jan 2013
Last Patient Entered:	31 January 2014
Data Cutoff Date (Original Submission):	9 May 2014
Data Cutoff Date (90-Day Safety Update):	19 September 2014
Number of Subjects	N=495 Vemurafenib/Placebo: n=248 Vemurafenib/Cobimetinib: n=247
Trial Sites:	133 Sites in 19 countries

GO28141 Study Design:

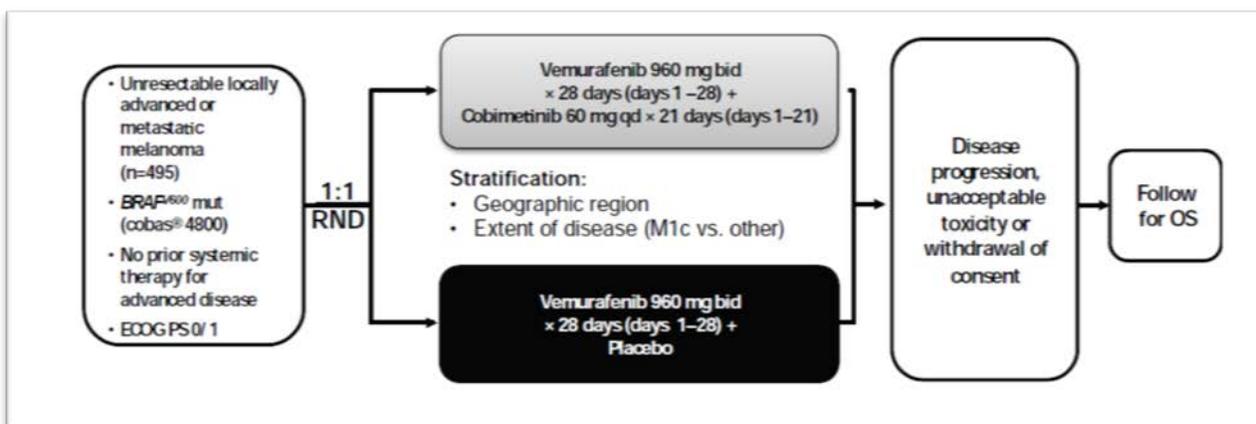
GO28141 is a multicenter, double-blind, placebo-controlled trial which enrolled approximately 500 patients with previously untreated BRAF V600 mutation-positive

unresectable locally advanced or metastatic melanoma and randomized (1:1) patients to receive treatment on either:

- Vem/Placebo: Vemurafenib 960 mg orally (PO) twice daily (BID) on Days 1-28 and placebo once daily (PD) on Days 1-21 of each 28-day treatment cycle, or
- Vem/Cobi: 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

Patients were randomized using a permuted-block randomization scheme which stratified on two factors: geographic region (North America vs. Europe vs. Australia/New Zealand/others) and stage (unresectable Stage IIIc, M1a, and M1b; or M1c).

Figure 3: GO28141 Study Design



Source: Clinical Study Report – Protocol GO28141, page 37

Treatment continued until disease progression, death, unacceptable toxicity or withdrawal of consent, whichever occurred earliest. Patients randomized to the Vem/Placebo arm were not eligible to receive cobimetinib at the time of progression. All patients were followed for survival.

Patients were monitored for safety every 2 weeks during the first 2 cycles then prior to each subsequent cycle. Adverse events were characterized using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.

Response was assessed by the investigator at 8-week intervals. At the investigator's discretion, CT/MRI scans could be obtained at any time if progressive disease (PD) was suspected. Tumor response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. A blinded Independent Review Committee (BIRC) was employed to independently evaluate the presence and timing of progression.

The primary efficacy endpoint was progression-free survival (PFS) defined as the time from randomization to first documentation of progressive disease (PD) as assessed by study investigators or death from any cause. Key secondary endpoints overall survival (OS), PFS as assessed by the BIRC, BIRC- confirmed overall response rate (ORR), and duration of response (DoR).

Data from this study were monitored by an external Data Safety and Monitoring Board (DSMB). The DSMB consisted of clinicians who were experts in the disease area, and one statistician. The DSMB reviewed available safety data from this trial at regularly scheduled intervals as specified in the DSMB charter. In addition, the DSMB reviewed the results of the interim analysis of OS and the pre-specified final analysis for PFS performed at the time of the interim analysis for OS.

Study Population

Eligibility Criteria:

BRAF mutation positivity was required for study eligibility. BRAF mutation testing was performed using the cobas[®] 4800 BRAF V600 Mutation Test, either locally or at a central laboratory. When local BRAF mutation test results were used to determine eligibility, documentation confirming the results and use of the cobas test was required.

Inclusion Criteria:

1. Patients with histologically confirmed, unresectable Stage IIIc (confirmed by a surgical oncologist) or Stage IV metastatic melanoma
2. Patients must have received no prior systemic anti-cancer therapy for advanced disease. Prior adjuvant therapy (including immunotherapy, e.g., ipilimumab) is allowed
3. Documentation of BRAF V600 mutation-positive melanoma in tumor tissue (archival or newly obtained) using the cobas[®] 4800 BRAF V600 mutation test (assessed in a central laboratory)
4. Disease is measurable by RECIST v1.1 criteria
5. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
6. Male or female patient aged 18 years or older
7. Adequate hematologic and end organ function as defined by the following tests obtained within 14 days prior to the first dose of study drug:

ANC	$\geq 1.5 \times 10^9/L$
Platelet count	$\geq 100 \times 10^9/L$
Hemoglobin	$\geq 9 \text{ g/dL}$

Albumin	≥ 2.5 g/dL
Bilirubin	≤ 1.5 x the upper limit of normal (ULN)
AST, ALT, Alkaline phosphatase	≤ 3 x ULN
Serum creatinine	≤ 1.5 ULN or creatinine clearance (CrCl) ≥ 40 (24-hour urine collection or Cockcroft-Gault estimation)

Exclusion Criteria:

1. History of prior treatment with RAF or MEK pathway inhibitor
2. Palliative radiotherapy within 14 days prior to the first dose of study treatment
3. Major surgery or traumatic injury within 14 days prior to first dose of study treatment
4. History of or evidence of retinal pathology on ophthalmologic exam that is considered a risk factor for neurosensory retinal detachment/central serous chorioretinopathy (CSCR), retinal vein occlusion (RVO), or neovascular macular degeneration
5. Patients were excluded if they had any of the following risk factors for RVO:
 - a. Uncontrolled glaucoma with intra-ocular pressures ≥ 21 mmHg
 - b. Serum cholesterol \geq Grade 2
 - c. Hypertriglyceridemia \geq Grade 2
 - d. Hyperglycemia (fasting) \geq Grade 2
6. History of clinically significant cardiac dysfunction, including any of the following:
 - a. Current unstable angina
 - b. Symptomatic congestive heart failure New York Heart Association (NYHA) class 2 or higher
 - c. History of congenital long QT syndrome or mean QTcF ≥ 450 msec at baseline (assessed as the average of triplicate measurements) or uncorrectable abnormalities in serum electrolytes (sodium, potassium, calcium, magnesium, phosphorus)
 - d. Uncontrolled hypertension \geq Grade 2 (patients with a history of hypertension controlled with anti-hypertensive drugs to \leq Grade 1 are eligible)
 - e. Left ventricular ejection fraction (LVEF) below institutional lower limit of normal (LLN) or below 50%, whichever is lower
7. Patients with active central nervous system (CNS) metastases are excluded. However, patients are eligible if:
 - a. All known CNS lesions have been treated with stereotactic therapy or surgery, AND
 - b. There has been no evidence of clinical and radiographic disease progression in the CNS for ≥ 3 weeks after radiotherapy or surgery

- c. Whole brain radiotherapy is not allowed, with the exception of patients who have parenchymal brain lesions
- 8. Current severe, uncontrolled systemic disease
- 9. History of malabsorption or other conditions that would interfere with absorption of study drugs
- 10. The following foods/supplements are prohibited at least 7 days prior to initiation of and during study treatment:
 - a. St. John's Wort or hyperforin (potent CYP3A4 enzyme inducer)
 - b. Grapefruit juice (potent cytochrome P450 CYP3A4 enzyme inhibitor)
- 11. Pregnant, lactating or breast feeding

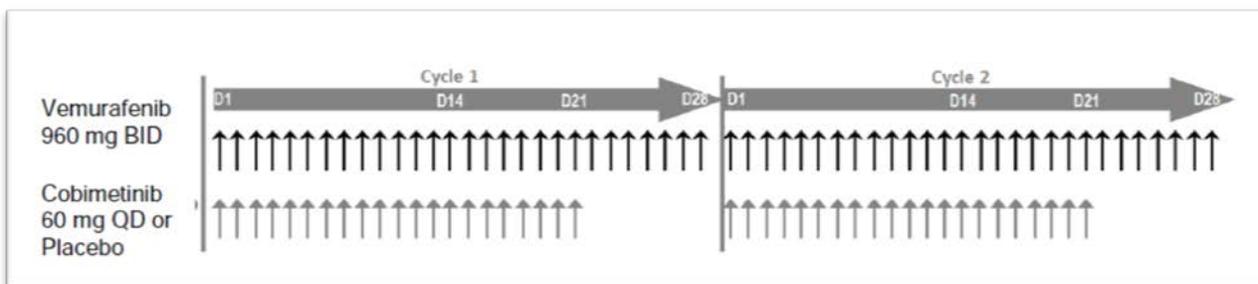
Study Treatment

Cobimetinib (60-mg dose) or matched placebo was taken as three tablets orally once per day at approximately the same time each day on Day 1 through Day 21 of each 28-day treatment cycle. At least seven days without cobimetinib was required prior to starting a new treatment cycle. Cobimetinib or placebo was taken with the vemurafenib dose preferably in the morning with water, with or without a meal. Vemurafenib (960 mg dose) was taken as four tablets orally twice daily (in the morning and evening).

If a dose was not taken within four hours after the scheduled dosing time, the patient was instructed to resume dosing with the next scheduled dose.

Treatment continued until disease progression, death, unacceptable toxicity or withdrawal of consent, whichever occurred earliest.

Figure 4: GO28141 Dosing Scheme



GO28141 Study Report Figure 2, page 47.

Rationale for Dose Selection

The maximally tolerated dose (MTD) of cobimetinib as a single agent was determined in the first-in-human study, MEK4592g, to be 60 mg daily, on a 21-day on, 7-day off (21/7) schedule. This schedule was determined to provide a longer duration of MEK suppression at a lower dose with less toxicity than did an alternative 14-day on, 14-day off (14/14) schedule explored in this study.

Study NO25395 (BRIM7), a dose-escalation study of to determine a tolerable and active dose and schedule of cobimetinib, administered with vemurafenib, determined that both drugs could be administered at the respective single-agent MTDs (vemurafenib, 960 mg BID, Days 1-28; cobimetinib 60 mg QD, Days 1-21) which was the recommended dose for future trials of the combination.

Reviewer's comment: Patients in the control arm of GO28141 received the recommended starting dose of Vemurafenib for patients with advanced BRAF V600 mutation-positive melanoma. Prior to the accelerated approval of Tafinlar and Mekinist (dabrafenib and trametinib), this was an accepted standard of care for patients in this subset. Vemurafenib and dabrafenib remain an accepted standard of care in patients with advanced BRAF V600 mutation-positive melanoma who are unable to tolerate the additional toxicity of a MEK inhibitor.

Dose Modifications and Supportive Care Guidelines

Recommendations for management of anticipated toxicities (rash, photosensitivity reaction, diarrhea, visual symptoms, new cutaneous primary malignancies, CPK and LFT elevation, QTcF interval prolongation, LVEF reduction and other Grade 4 non-hematologic laboratory abnormalities) and guidelines for dose modifications, interruptions, and delays of vemurafenib and/or cobimetinib/placebo treatment were provided in the clinical protocol (see CSR, 5.1.5.3, Table 10, page 7214). Reduction of each study drug was independent and no re-escalation of dose was allowed. Up to two dose level reductions were allowed before the study drug was discontinued. The recommended dose reductions are shown below.

Table 6: Dose Level Reductions, GO28141

Dose reduction	Starting Dose	
	Vemurafenib 960 mg BID	Cobimetinib 60 mg QD
1 dose level	720 mg BID	40 mg QD
2 dose levels	480 mg BID	20 mg QD

See section 9.3 of this review for the table of recommended management (dose interruptions and delays) for anticipated toxicities.

Monitoring Plan

See Table 66 for the Table of Study Assessments.

Statistics and Analysis Plan

The reader is referred to Dr. Xiaoping Jian's statistical review for details of the statistical analysis plan for GO28141 which is summarized below.

As discussed above in Section 5.3.1.1, patients were randomized (1:1) using an interactive response system (IxRS) which employed a permuted-block randomization scheme which stratified on two factors: Geographic region (North America, Europe, Australia/New Zealand/others) and Metastatic classification (unresectable Stage IIIc, M1a, and M1b; or M1c). Patients were assigned to receive one of two study treatments:

- Vem/Placebo: vemurafenib 960 mg orally (PO) twice daily (BID) on Days 1-28 and placebo once daily (PD) on Days 1-21 of each 28-day treatment cycle, or
- Vem/Cobi: 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

Patients continued on treatment until disease progression, death, unacceptable toxicity, or withdrawal of consent, whichever occurred earliest. Patients on the Vem/Placebo treatment arm were not offered cobimetinib at the time of disease progression. All patients were followed up for survival.

The protocol-defined primary endpoint was progression-free survival (PFS) assessed by the study investigator and defined as the time from randomization to the first occurrence of disease progression using RECIST v1.1, or death from any cause, whichever came first. For patients with no PFS event were censored at the date of the last tumor assessment. Patients with no post-baseline tumor assessment were censored at the randomization date.

The primary analysis of PFS was a log-rank test stratified by geographic region (North America, Europe, Australia/New Zealand/others) and disease stage (unresectable Stage IIIc, M1a, and M1b; M1c) conducted at a two-sided significance level of 0.05. The primary analysis was based on the intent-to-treat (ITT) population, defined as all randomized patients. The Kaplan-Meier method was used to estimate the median PFS and 95% confidence intervals (CIs) for each treatment arm. Hazard ratio and 95% confidence intervals were estimated using the Cox proportional hazards model stratified by region and metastatic classification.

The sample size calculation was based on the assumptions that the true PFS hazard ratio was 0.55 corresponding to median PFS of 6 months in the Vem/Placebo arm and 11 months in the Vem/Cobi arm. A total of 206 events were needed to detect a hazard ratio of 0.55 with 95% power at a 2-sided alpha level of 0.05. Taking consideration of enrollment rate of 65 patients per month and 5% dropout rate, approximately 500 patients were planned to be randomized.

The secondary endpoints for the trial were PFS assessed by a BIRC, overall survival (OS), confirmed overall response rate (ORR) determined by two consecutive investigator assessments performed four or more weeks apart with responses assessed using RECIST v1.1 criteria, and duration of response (DoR).

The secondary endpoint OS was analyzed using Kaplan-Meier product-limit estimates and compared between two treatment arms using a stratified log-rank test. The stratified OS analyses used the same stratification factors as did the primary PFS analysis. The final analysis will be conducted after 385 events have been observed (at approximately 46 months after the first patient was randomized). ORR was tested by using χ^2 test at two-sided alpha of 0.05. A hierarchical order to control the overall family-wise error rate at level $\alpha = 0.05$ for the secondary endpoints ORR and OS was pre-specified in the protocol and SAP: if the primary analysis of PFS showed statistical significance the ORR would be tested first at the 0.05 level. Only if the comparison of PFS was significant, would the comparison of OS then be tested at the 0.05 level.

There were two planned interim OS analyses. The first OS interim analysis was conducted at the time of the final PFS; second one would be when 256 (67%) OS events have been observed (it was estimated that the timing would be at approximately 27 months after the first patient was randomized.) The Lan-DeMets implementation of the O'Brien and Fleming spending function was used to control the overall Type I error rate at a significance level of 0.05 (2-sided) for all OS comparisons.

Patients report outcomes (PRO) measured by EORTC QLQ-C30, were evaluated for patients with a baseline assessment and at least one post-baseline QLQ-C30 assessment that generate a score. Summary statistics (mean, standard deviation, median, 25th and 75th percentiles, and range) of absolute scores of the QLQ-C30 and their changes from baseline were summarized at each assessment time point for the two treatment arms.

Procedures for Retrospective Assessment of BRAF V600 Mutations

Only patients whose melanoma tumor tested positive for the BRAF V600 mutation assessed locally or centrally using the cobas[®] 4800 BRAF V600 mutation test and who met all other eligibility criteria were eligible for enrollment into the trial. Archival or newly obtained tumor samples could be used for BRAF testing. If cobas[®] test was locally performed, verification of the mutation status at a central laboratory selected by the

Applicant was required. Patients without central verification of BRAF mutation status were excluded from analysis.

After randomization, an additional analysis was retrospectively performed using next generation (Next Gen) sequencing to evaluate BRAF mutation genotype using DNA from patients who submitted archival or baseline tumor tissues and had sufficient DNA remaining after central testing using the cobas[®] 4800 BRAF V600 mutation test.

Major Protocol Amendments

As of the cutoff date for the clinical study report, the original protocol, dated August 3, 2012, was amended three times. The major revisions are outlined in the table below.

Reviewer's comment: The only substantive revision during the conduct of GO28141 was the revision to the statistical analysis plan instituted in version 3 of the clinical protocol which provided for an analysis of PFS as assessed by the BIRC as a secondary endpoint. The other changes implemented in the clinical protocol would not be expected to have a major impact in the assessment of patient safety or efficacy. After the primary analysis for PFS was completed, the protocol was revised (version 5) to provide for a final OS analysis at an earlier timepoint.

(b) (4)

Table 7: GO28141, Major Protocol Amendments

Version	Version Date	Major Changes
1	Aug 3, 2012	Original protocol
2	Oct 4, 2012	<ul style="list-style-type: none"> • The cardiovascular exclusion criteria were modified to exclude uncorrectable serum electrolyte abnormalities • Other editorial changes for clarification
3	Apr 24, 2013	<ul style="list-style-type: none"> • PFS as assessed by independent review was added as a secondary endpoint • Clarified that power in sample size of PFS events was > 95% • Exclusion criteria 4 clarified to allow patients with previously resected early stage melanoma on study • Clarified that any non-cutaneous primary malignancy is a reportable SAE • Grade ≥ 2 LVEF reduction was added as an AE of special interest • Clarified that dose reduction of each study drug is independent of the other study drug and that dose re-escalation is not allowed. • Clarified that confirmation of response will be done no earlier than 28 days and that stable disease requires a

		<ul style="list-style-type: none"> minimum assessment interval of not less than 6 weeks Clarification of supportive care in the management of ocular toxicity GDC-0973 named cobimetinib throughout. Other editorial changes for clarification
4	Sep 12, 2013	<ul style="list-style-type: none"> Protocol amended to update the safety information to be consistent with the vemurafenib Investigator's Brochure. The revised safety information included the risk of progression of malignancies associated with RAS mutation and drug rash with eosinophilia and systemic symptoms (DRESS Syndrome) Inclusion criteria number 2 was clarified to indicate that adjuvant therapy including immunotherapy is allowed. Exclusion criterion number 4 was clarified to indicate that patients with active malignancies are excluded. Management guidelines for neurosensory retinal detachment were optimized; guidelines for uveitis/iritis and other ocular events were provided. Clarification that any retinal detachment, including retinal pigment epithelium detachment, neurosensory retinal detachment and central serous chorioretinopathy should be reported as non-serious adverse events of special interest. Guidelines for dose modification, management of isolated γ-glutamyltransferase elevation and Grade \geq 3 diarrhea were optimized.
5	Mar 11, 2015	<ul style="list-style-type: none"> Update the safety information to be consistent with recent updates to the vemurafenib and cobimetinib Investigator's Brochures (IB). Revise the schedule of assessments following the final efficacy analysis (data cutoff 9 May 2014) to reflect the changes detailed in the protocol. Revise the overall survival (OS) analyses plan. After the primary PFS analysis was performed on July 10, 2014, a post-hoc analysis of PFS and OS were conducted (b) (4). The revised analysis plan reduced the events required from 385 to 250 events, the Type-I error rate (2-sided) was defined at 0.05 with a power of 80% to detect an HR= 0.70 (median 15 vs. 21.4 months).

5.3.2 NO25395

A Phase Ib, open label, dose escalation study evaluating the safety, tolerability and pharmacokinetics of vemurafenib in combination with GDC-0973 (cobimetinib) when administered in BRAF V600E mutation-positive patients previously treated (but without prior exposure to BRAF or MEK inhibitor therapy) or previously untreated for locally

advanced or unresectable or metastatic melanoma or those who have progressed after treatment with vemurafenib (BRIM7)

First Patient Entered:	17Feb 2011
Last Patient Entered:	23Jul 2013
Data Cutoff Date:	01Oct2013
Number of Subjects	131: Total Enrollment 129: Treated with Vem/Cobi 63: BRAF-inhibitor naïve 66: Progressed on Vemurafenib
Trial Sites:	10: U.S. (9); Australia (1)

NO25395 Study Design

NO25395 (BRIM7) is an open-label, multicenter, dose-escalation trial to assess the safety, tolerability and pharmacokinetics of cobimetinib administered concurrently with vemurafenib and to obtain preliminary evidence of efficacy and determine the recommended dose and schedule for cobimetinib and for vemurafenib, when administered concurrently. Patients with locally-advanced and unresectable or metastatic melanoma who were determined to have tumors which tested positive for the BRAFV600E mutation as detected by the cobas[®] 2800 BRAF V600 mutation test were eligible for study.

Patients were stratified into two groups:

1. Vemurafenib- progressors (vemurafenib-PD), those who progressed while on Vemurafenib monotherapy immediately prior to enrollment on NO24595
2. BRAF inhibitor-naïve (BRAFi-naïve)
 - a. Patients who were previously untreated for metastatic disease
 - b. Patients who were previously treated but were naïve to BRAF- or MEK-inhibitor therapy

There were two stages in the trial: a multiple cohort, dose-escalation stage and a cohort expansion stage. Patients, primarily those unable to tolerate vemurafenib, were allowed to receive cobimetinib in a monotherapy cohort.

All patients in the dose-escalation stage received continuous twice daily (BID) vemurafenib at doses of either 720 mg or 960 mg BID. Cobimetinib was administered in combination with vemurafenib on one of three schedules in a 28-day treatment cycle:

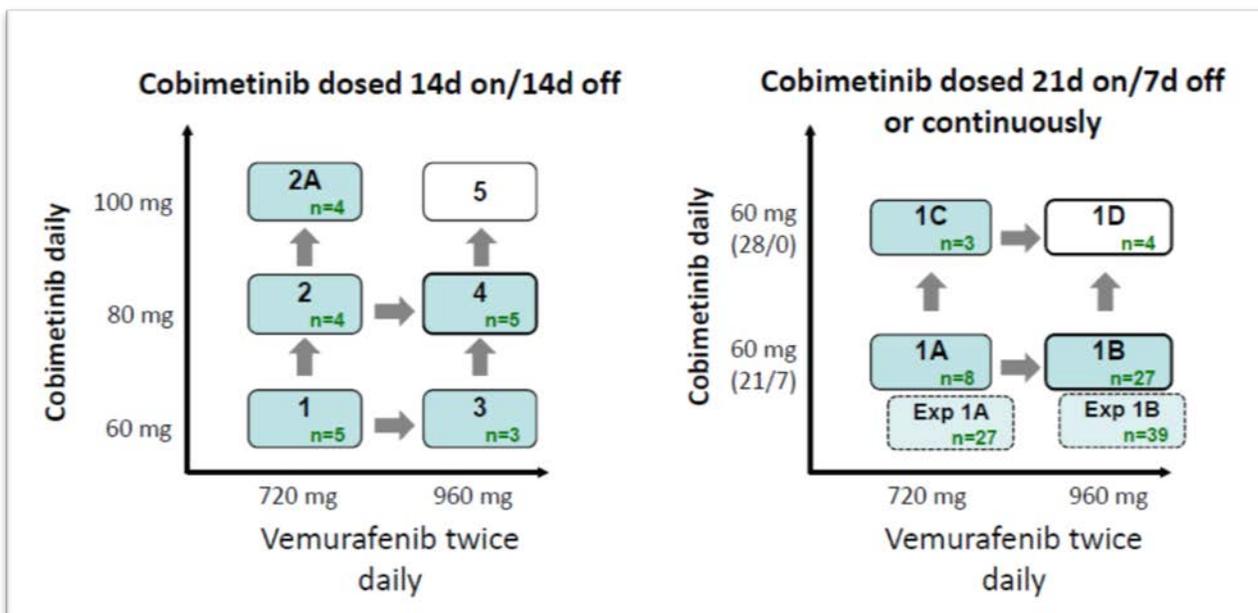
- 14 consecutive days followed by a 14-day treatment-free interval (14/14)
- 21 consecutive days followed by a 7-day treatment-free interval (21/7)
- Continuous daily dosing (28/0)

The dose-escalation stage consisted of 10 dose-escalation cohorts of 3 to 6 patients per cohort. Dose-escalation proceeded in a standard 3+3 design as shown below in Figure. Enrollment was staggered such that demonstration of safety and tolerability in cohort 2 and 3 was required prior to enrollment of cohort 4, demonstration of safety and tolerability in cohort 2A and 4 was required prior to enrollment of cohort 5, and demonstration of safety and tolerability in cohort 1B and 1C was required prior to enrollment of cohort 1D.

A selected cohort was expanded after that cohort was declared safe and tolerable. The selection of cohorts to be expanded was based on a review of the safety, activity and pharmacokinetics in patients treated in the dose-escalation stage. Approximately 20 vemurafenib-PD and twenty BRAFi-naïve patients were accrued into each expansion cohort.

Verbatim descriptions of adverse events were mapped to MedDRA (version 17.1) and graded according the NCI CTCAE version 4.0.

Figure 5: NO25395 Study Design



For purposes of this review the most relevant supportive data from the NO25395 trial are the 39 BRAF inhibitor-naïve patients from Cohort 1B (n=19) and the 1B expansion cohort (Exp 1B; n=20). These patients received the proposed dose and schedule of cobimetinib and vemurafenib.

MEK4592g: A Phase I Dose-Escalation Study of the Safety and Pharmacokinetics of GDC-0973/XL518 Administered Orally Daily to Subjects with Solid Tumors

First Patient Entered:	3MAY 2007
Last Patient Entered:	25MAY 2012
Data Cutoff Date:	25MAY2012
Number of Subjects	99
Trial Sites:	4 (U.S.)

MEK4592g Study Design

This was an open-label, nonrandomized safety and pharmacokinetic (PK) dose-escalation study of patients with histologically confirmed advanced solid tumors treated with cobimetinib monotherapy in 4 stages:

Stage I: Dose-escalation cohorts were treated on a 21-days-on, 7-days-off (21/7) schedule to determine the MTD.

Stage IA: Dose-escalation cohorts, starting at the MTD of the 21-days-on, 7-days-off (21/7) schedule, were treated on a 14-days-on, 14-days-off (14/14) schedule to determine the MTD on an alternate dosing regimen.

Stage II: Expansion cohort with the MTD determined in Stage I in approximately 20 patients with FDG-PET-avid tumors harboring a *BRAF*, *NRAS*, or *KRAS* mutation and with FDG-PET-avid disease.

Stage IIA: Expansion cohort with the MTD determined in Stage IA in approximately 20 patients with FDG-PET-avid tumors harboring a *BRAF*, *NRAS*, or *KRAS* mutation.

6 Review of Efficacy

Efficacy Summary

The NDA submission contained a single, randomized, controlled trial, GO28141, assessing the safety and efficacy of cobimetinib in support of the proposed indication. The submission was supported with data from the NO25395 (BRIM7) trial, an open-label, multicenter, dose-escalation trial to assess the safety, tolerability and pharmacokinetics of cobimetinib administered concurrently with vemurafenib.

The GO28141 trial demonstrated a statistically significant 50% improvement in investigator assessed progression-free survival in patients randomized to receive Vem/Cobi compared to patients randomized to receive Vem/Placebo [HR 0.50 (95% CI: 0.38, 0.67; $p < 0.0001$)]. The median PFS was estimated to be 9.9 months (95% CI: 9.0, NR) for patients randomized to the Vem/Cobi arm and 6.2 months (95% CI: 5.6, 7.4) in

patients randomized to the Vem/Placebo arm. Pre-specified secondary endpoints included progression-free survival as assessed by a blinded independent radiology committee (BIRC), overall survival (OS) and BIRC-confirmed overall response rate (ORR). PFS analysis based on BIRC review showed results consistent with the primary analysis [HR: 0.60 (95% CI: 0.45, 0.79); $p < 0.001$] and all secondary analyses showed consistent results across relevant subgroups. A statistically significant improvement in OS was observed for patients randomized to receive Vem/Cobi compared to those randomized to receive Vem/Placebo [HR: 0.63 (95% CI: 0.47, 0.85); stratified log-rank p -value=0.0019 is less than the nominal significance level of 0.019 based on the interim analysis]. The estimated median OS for patients randomized to receive Vem/Cobi was not reached (NR) at the time of the analysis (95% CI: 20.7, NR) and was 17.0 months (95% CI: 15.0, NR) for patients randomized to receive Vem/Placebo. The BIRC-confirmed ORR per RECIST v1.1 was significantly improved in patients randomized to receive Vem/Cobi compared to patients randomized to receive Vem/Placebo [67% (95% CI: 61%, 73%) vs. 45% (95% CI: 39%, 51%); Chi-Square test p -value < 0.0001]. Complete responses were reported in 10% of patients randomized to receive Vem/Cobi and in 5% of patients randomized to receive Vem/Placebo. The median duration of response among responders in the Vem/Cobi arm was not reached (NR) at the time of the analysis (range: 9.3, NA) and was 7.3 months (range: 5.8, NR) among responders in the Vem/Cobi arm. Responses lasting at least 6 months were seen in 25% of responders randomized to the Vem/Cobi arm and in 20% of responders randomized to the Vem/Placebo arm

An exploratory analyses of PFS and OS to assess the treatment effect by BRAF mutation subset (V600E and V600K retrospectively classified using Next Gen sequencing in patients pre-screened for study entry using the cobas[®] test) was conducted in 81% of patients in the ITT study population who had adequate tissue remaining for analysis. Three hundred forty-four patients (Vem/Cobi: $n=170$; Vem/Placebo: $n=172$) were identified as having BRAF V600E mutations and fifty-six (Vem/Cobi: $n=16$; Vem/Placebo: $n=10$). This analysis suggested a similar treatment effect on PFS in both mutation subtypes with no apparent decrement in OS [BRAV V600E: PFS: HR=0.56; 95%CI: 0.40, 0.79; OS: HR=0.76; 95% CI: 0.45, 1.26; BRAV V600K: PFS: HR: 0.25; 95% CI: 0.08, 0.81; OS: HR: 0.61; 95% CI: 0.16, 2.37]. Among patients with BRAF V600E mutations, confirmed objective responses were seen in 116 (68%) patients randomized to receive Vem/Cobi and in 83 (48%) patients randomized to receive Vem/Placebo. Among patients with BRAF V600K mutations, confirmed objective responses were seen in 16 (67%) patients randomized to receive Vem/Cobi and in 10 (31%) patients randomized to receive Vem/Placebo.

In summary, the GO28141 trial, the single randomized trial supporting efficacy in this NDA, demonstrated a robust, statistically significant and clinically relevant improvement in PFS, OS, and ORR with consistency across all secondary endpoints and relevant subgroups with the addition of cobimetinib to vemurafenib therapy. Within the limits of

the study design, patients with tumors harboring a BRAF V600E and those with a BRAF V600K appeared to derive a similar benefit with the addition of cobimetinib to vemurafenib therapy.

In the NO25395 trial, only 66 patients were BRAF-inhibitor naïve and received the proposed registrational dose and schedule. Of these, the investigator confirmed objective response rate was 87%, somewhat higher than that seen in the GO28141 trial, and of these, 10% were assessed by investigators to be complete responses.

6.1 Indication

Proposed Indication:

COTELLIC[®] is indicated for use in combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with the BRAF V600E and V600K mutations, (b) (4)

Proposed Dosage:

Cobimetinib: 60 mg po QD D1-21 administered in 28-day cycles

6.1.1 *Methods*

The Applicant submitted data from a single randomized trial (GO28141) which was adequately designed and conducted to test the hypothesis that in patients with previously untreated, unresectable or metastatic BRAF-mutated melanoma as detected by the cobas[®] 4800 BRAF V600 mutation test, the addition of cobimetinib to vemurafenib therapy results in an improvement in progression-free survival (PFS) compared to treatment with vemurafenib alone. As described in the protocol and in the statistical analysis plan, PFS was defined as the time from randomization to the first occurrence of disease progression, as determined by the study investigators using RECIST v 1.1, or death from any cause. The statistical analysis plan pre-specified a hierarchical order of analysis of the secondary endpoints to control Type 1 error at 0.05. Secondary endpoints were to be tested in the following order: confirmed best overall response rate as determined by investigator review and overall survival. No adjustment

to the α -level was made for the other analyses, including PFS based on the IRC-reviewed data. In addition to the data from GO28141, the Applicant provided results from one open-label, multicenter non-comparative trial, NO25395, as supportive information of a treatment effect of cobimetinib.

The review of efficacy is focused on the analysis of data provided for GO28141, including the CSR, the Applicant's presentation slides, case report forms, primary data sets submitted by the applicant. The review is focused on confirming the efficacy findings for GO28141 as presented by the Applicant and assessing in assessing whether sufficient evidence is provided to justify the broader indication sought for use in 1) BRAF-V600 mutation subsets, and 2) patient treated following vemurafenib progression. The justification for the former claim is based on a retrospective analysis of the GO28141 study population using Next Gen sequencing and is discussed in section 6.1.7 (page 85). The justification for the later claim is based on analysis of selected cohorts of study NO25395 and is discussed in section 6.1.10 (page 93).

6.1.2 *Demographics*

Overall, the treatment arms were well balanced with respect to demographic variables (Table 8) and with respect to tumor/prognostic factors (Table 9). The majority of patients enrolled were Caucasian and male. Most had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 at baseline. Approximately 60% of patients enrolled had distant metastatic disease (M1C) and 10% had received prior adjuvant therapy for resected melanoma.

Table 8: GO28141 - Demographic Characteristics (ITT* Population)

	Vem/Placebo (n=248)		Vem/Cobi (n=247)	
Age (years)				
Mean (SD)	55.3	(13.8)	54.9	(14.0)
Med (min, max)	55	(25,85)	56	(23,88)
≥ 65 years, n (%)	69	28%	64	26%
Sex - Male, n (%)	140	56%	146	59%
Race - White, n (%)	235	95%	227	92%
BMI (kg.m ²)				
Mean (SD)	27.1	(5.1)	27.7	5.9
Med (min, max)	26.6	(16.4,56.0)	27	(18.4,64.0)
Region – n (%)				
Europe	184	74%	182	74%
North America	26	10%	25	10%
Rest of World	38	15%	40	16%
ECOG PS				
0	164	67%	184	75%
1	80	33%	58	24%
2	0	-	1	<1%

*Abbreviation: ITT: Intent-to-Treat; Data cutoff date: May 9, 2014

Table 9: GO28141 - Prognostic and Tumor Characteristics (ITT Population)

	Vem/Placebo (n=248)		Vem/Cobi (n=247)	
Baseline LDH elevated n (%)	104	43%	112	46%
Baseline Tumor Burden (SLD ¹) (mm)				
Mean (SD)	76.4	(58.6)	73.8	(59.7)
Median (min,max)	59.5	(10, 366)	62	(10,398)
Time since initial diagnosis (mo.)				
Mean (SD)	41.0	(48.2)	53.4	(68.5)
Median (min,max)	25.1	(0.1,337.5)	28.1	(0.4,420.8)
AJCC Stage at enrollment – n (%)				
IIIc	13	5%	21	9%
M1a	40	16%	40	16%
M1b	42	17%	40	16%
M1c	153	62%	146	59%
Prior radiation for brain met n (%)	2	<1%	1	<1%
Prior adjuvant therapy n (%)	24	10%	24	10%

Source: adsl.xpt; Data cutoff date: May 9, 2014

¹Sum of the Longest Diameter, Target Lesions

Reviewer's comment:

- *There was a minor imbalance in the study arms in prognostic factors (e.g., the percentage of patients with a good performance status, and in the percentage of patients with Stage IIIc disease) which appear to favor the Vem/Cobi arm.*
- *The mean time since initial melanoma diagnosis was longer in the Vem/Cobi arm. However, since the median values are closer, the mean is likely skewed by outlying values. The time from diagnosis of metastatic disease would have been a more relevant comparison. However this data was not collected.*

Documentation of BRAFV600 mutation-positive melanoma in tumor tissue (archival or newly obtained) using the cobas[®] 4800 BRAF V600 mutation test was required for study entry. Testing could be performed at a local lab or at the central lab. Archival or newly obtained tumor specimens could be used for BRAF mutation testing. When a local lab BRAF mutation test results was used to determine eligibility, documentation confirming the result and use of the cobas[®] test was required. Patients in whom BRAF mutation status as assessed by the cobas test was not centrally verified were excluded from the analysis. If sufficient DNA remained, samples were retrospectively tested to further characterize the BRAF mutation subtype using Next Gen sequencing.

Overall, BRAF mutation subtype (V600E or V600K) was determined in 400 (81%) of the ITT population. Of these, 344 (86%) were found to have a BRAF V600E mutation and 56 (14%) were found to have a BRAF V600K mutation by Next Gen sequencing.

Reviewer's comment: In this study population pre-selected for BRAF V600 mutations using the cobas® 4800 BRAF V600 mutation test, the frequency of V600E and V600K mutations observed in the ITT population are consistent those reported in a population-based cohort of newly diagnosed Australian melanoma patients[13] which may or may not be representative of the U.S. population.

Seventeen percent of patients in the Vem/Placebo arm and twenty-one percent of patients in the Vem/Cobi arm had tumors which could not be further characterized as V600 E or V600 K due to insufficient remaining DNA or other reasons. Among participants who could be sequenced, the distribution of BRAF V600E and B600K mutations was similar between study arms (Table 10).

Table 10: GO28141 - BRAF Mutation Status as Retrospectively Assessed by Next Gen Sequencing (ITT Population)

BRAF mutation status	Vem/Placebo (n=248)		Vem/Cobi (n=247)	
	n	%	n	%
V600E	174	70%	170	69%
V600K	32	13%	24	10%
Unknown ¹	42	17%	53	21%

Source: adsl.xpt; Data cutoff date: May 9, 2014

¹Quantity not sufficient for testing; no tumor identified; outside detectable range.

Patients with active central nervous metastases were excluded from study. Data concerning the number and location of metastatic sites was not systematically collected in GO28141. However, investigators noted the location of target lesions. Overall, 72% of patients in the ITT population were noted to have a target lesion in one or more visceral site (brain, liver or lung metastases).

Reviewer's comment: In this GO28141, patients with active central nervous metastases were excluded from study. The proportion of patients with liver metastases appeared to be higher among patients testing positive for the BRAF V600K mutation. The proportion of patients with lung metastases appeared to be similar in both mutation subgroups (Table 11).

Table 11: GO28141 – Patients with a Visceral Target Lesion (Brain, Liver, Lung) by Study Arm and BRAF Mutation Status (ITT Population)

Patients with tumor at visceral site	All N=495 (100%)		BRAF V600E n=344 (100%)		BRAF V600K n=56 (100%)	
	n	%	n	%	n	%
Brain	13	(3 %)	8	(2 %)	0	-
Liver	191	(39 %)	127	(37 %)	28	(50 %)
Lung	289	(58 %)	206	(60 %)	35	(63 %)
≥ 1 site*	356	(72 %)	248	(72 %)	44	(79 %)

*Number of patients with at least one visceral site of melanoma involvement.; Data cutoff date: May 9, 2014

The number of patients with a target lesion in one or more visceral site was similar between study arms (Vem/Placebo: 73%; Vem/Cobi: 70%) (Table 12).

Table 12: GO28141 – Patients with a Visceral Target Lesion (Brain, Liver, Lung) by Study Arm and BRAF Mutation Status (ITT Population)

Patients with tumor at visceral site	Vem/Placebo						Vem/Cobi					
	All N=248 (100%)		BRAF V600E n=174 (100%)		BRAF V600K n=32 (100%)		All N=247 (100%)		BRAF V600E n=170 (100%)		BRAF V600K N=24 (100%)	
	n	%	n	%	n	%	n	%	n	%	n	%
Brain	7	(3%)	3	(2%)	0	-	6	(2%)	5	(3%)	0	-
Liver	94	(38%)	58	(33%)	18	(56%)	97	(39%)	69	(41%)	10	(42%)
Lung	150	(50%)	105	(60%)	21	(66%)	139	(56%)	101	(59%)	14	(58%)
≥ 1 site*	182	(73%)	125	(72%)	26	(81%)	174	(70%)	123	(72%)	18	(75%)

*Number of patients with at least one visceral site of melanoma involvement.; Data cutoff date: May 9, 2014

Reviewer's comment: It is this reviewer's assessment that the treatment arms were sufficiently similar with respect to key demographic, tumor and prognostic characteristics assessed as to make bias of study findings due to these factors unlikely. This suggests that randomization was effective in controlling for sources of bias.

6.1.3 Subject Disposition

Per the Applicant’s report, 1045 patients were screened at 133 study sites in 19 countries between January 8, 2013, and the data cutoff date of May 9, 2014. The applicant reports that 550 (53%) of patients screened were found to be ineligible for the trial. A line listing detailing the reason for screen failure is provided in the Clinical Study Report (page 7460). Among the 457(83%) patients for whom a cause of screening failure was reported, the most common reasons for screening failure are listed below. The single most common reason for screening failure was the absence of a confirmed BRAF V600 mutation as detected by the cobas[®] 4800 BRAF V600 mutation test, followed by active CNS disease.

Table 13: GO28141 - Most Common (≥1.5%) Reasons Provided for Screening Failure

	n	%
BRAF V600 mutation positive status not confirmed	247	54.0
Active CNS lesion	54	11.8
Not able/willing to give informed consent and comply with study protocol	24	5.3
Unwilling/unable to comply with study and follow-up procedures	16	3.5
Did not have measurable disease per RECIST v 1.1	16	3.5
ECOG performance status > 1	12	2.6
Did not meet criteria for hematologic/end organ function	10	2.2
Psych., familial, sociological or geographic condition hamper compliance	9	2.0
Radiotherapy/surgery within 14 days prior to first study treatment	8	1.8
Clinically significant cardiac dysfunction	7	1.5

Source: Patient line listing, CSR page7460, screen failure data not validated.; Data cutoff date: May 9, 2014

Reviewer’s comment: With the reason for screening failure missing in 17% of patients reported as screening failure, it is not possible to make a specific assessment of the generalizability of the ITT study population. However, the percentage of patients excluded because BRAF mutation positive status was not confirmed is approximately what would be expected in an unselected study population, 40% to 60%. The proportion of patients excluded for active CNS lesions and because they were unwilling/unable to comply with study procedures appear high. While this may reflect a study population selected for an optimized outcome, this fact is unlikely to impact the internal validity of the trial.

Based on the study dose modification guidelines (Section .3, page 201), patients with toxicity assessed as being related to cobimetinib/placebo could continue on study on vemurafenib alone in the absence of disease progression or other reason for study discontinuation. Patients with a toxicity assessed as related to vemurafenib could continue on study on cobimetinib/placebo alone in the absence of disease progression or other reason for study discontinuation. In both study arms, the most common reason for discontinuation from one or from both study drugs was disease progression. A higher proportion of patients on the Vem/Placebo arm than on the Vem/Cobi arm discontinued one or both study drugs due to disease progression. A higher proportion of patients on the Vem/Cobi arm than on the Vem/Placebo arm discontinued one or

both drugs due to an adverse event. Discontinuations for other reasons were infrequent and occurred at a similar rate on both arms (Table 14).

Table 14: GO28141 - Disposition of Intent-to-Treat (ITT)* Study Population

Disposition	Screened (N = 1045)			
	Randomized (N = 495)			
	Vem/Placebo n (%)		Vem/Cobi n (%)	
Randomized (ITT)	248	(100)	247	(100)
Randomized but not Treated	1	(< 1)	1	(< 1)
Treated	247	(99)	246	(99)
Patients Discontinued from Cobi/Placebo	189	(77)	150	(61)
Adverse event	23	(9)	42	(17)
Death	1	(< 1)	3	(1)
Loss to follow-up	1	(< 1)	1	(< 1)
Withdrawal by subject	4	(2)	3	(1)
Physician Decision	2	(1)	4	(2)
Progression	158	(64)	95	(39)
Patients Discontinued from Vemurafenib	188	(76)	149	(60)
Adverse event	23	(9)	37	(15)
Death	2	(1)	4	(2)
Loss to follow-up	1	(< 1)	1	(< 1)
Withdrawal by subject	4	(2)	3	(1)
Physician Decision	2	(1)	3	(1)
Progression	156	(63)	98	(40)
Patients Discontinued from Vem and Cobi/Placebo**	188	(76)	146	(59)
Adverse event	21	(9)	33	(13)
Death	2	(1)	4	(2)
Loss to follow-up	1	(< 1)	1	(< 1)
Withdrawal by subject	4	(2)	3	(1)
Physician Decision	2	(1)	4	(2)
Progression	157	(64)	98	(40)

Source: adsl.xpt, ds.xpt

*Data Cutoff Date: 15 Sept 2014; ** Patients shown as discontinued from Vem and Cobi/Placebo are also included as discontinued from Vem and as discontinued from Cobi/Placebo

Reviewer's comment: The above analysis does not suggest disproportionate loss in either study arm due to reasons other than adverse events or disease progression which might result in early study termination.

Overall, the median duration of follow-up in the trial was 7.3 months and was similar in both study arms.

Table 15: GO28141 - Duration of Follow-up (ITT Population)

Duration of follow-up (months)	Vem/Placebo (N=248)	Vem/Cobi (N=247)	Total (N=495)
Mean (SD)	7.4 (2.80)	7.66 (2.75)	7.51 (2.78)
Median (min, max)	7.02 (0.5, 16.5)	7.43 (1.4, 14.7)	7.29 (0.5, 16.5)

Source: adsl.xpt; Data cutoff date: May 9, 2014

The number of patients receiving post-trial treatment for melanoma was similar between arms.

Table 16: GO28141 – Proportion of Patients Progressed on Study Treatment Who Receiving Post-Trial Anti-Cancer Therapy (ITT Population)

Post-trial cancer treatment	Vem/Placebo (N=188)	Vem/Cobi (N=146)
2 nd line, n (%)	43 (23)	39 (27)
3 rd line, n (%)	7 (4)	7 (5)
4 th line, n (%)	0	1 (1)

Source: adsl.xpt; Data cutoff date: May 9, 2014

The type cancer treatment administered following trial discontinuation is shown below in Table. In both study arms, ipilimumab was the most commonly administered second line treatment followed by a BRAF inhibitor or chemotherapy. The percent of patients receiving ipilimumab, a BRAF inhibitor or chemotherapy was similar between study arms. Two patients on the Vem/Cobi arm and no patients on the Vem/Placebo arm received an anti-PD-1 antibody as second line treatment. The percent of patients receiving post-trial treatment over all lines of therapy with a BRAF-inhibitor, MEK-inhibitor or combined BRAF-, MEK- inhibitor therapy was the same between arms; 24 (10%) patients on the Vem/Placebo arm compared to 18 (7%) of patients received either an anti-PD-1 antibody or Ipilimumab as post-treatment therapy (any line).

Reviewer's comment: While the optimal sequencing of small molecule targeted therapy, biologic therapy and immunotherapy in the treatment of metastatic melanoma is not well understood, it does not appear likely that the small between arm differences in post-treatment anti-cancer therapy would confound the interpretation of the PFS and OS analyses given the small number of patients in the ITT study population who received these treatments.

Table 17: GO28141 - Post-Trial Treatment for Melanoma in Patients Progressing on Study Treatment (ITT Population)

Type of post-trial cancer treatment	Vem/Placebo (188)	Vem/Cobi (146)
2 nd line, n (%)	43	39
Anti PD-1 antibody	0	2
Ipilimumab, n (%)	20 (47%)	14 (36%)
RAFi/MEKi	3	1
MEKi	1	0
RAFi	7	10
Other investigational product	0	2
Chemotherapy	12	10
3 rd line, n	7	7
Anti PD-1 antibody	1*	0
Ipilimumab	4*	2
RAFi/MEKi	0	0
MEKi	0	2
RAFi	2	1
Other investigational product	0	0
Chemotherapy	1	2
4 th line, n	0	1
Chemotherapy	0	1
Any Line, n (%)		
Anti PD-1/Ipilimumab	24 (56%)	18 (46%)
RAFi/MEKi, RAFi or MEKi	13 (30%)	14 (36%)
Chemotherapy	13 (30%)	13 (33%)

*One patient received Anti PD-1 in combination with ipilimumab and is listed in both cells.

Abbreviations: RAFi – BRAF-inhibitor; MEKi – MEK-inhibitor; RAFi/MEKi – combined BRAF and MEK inhibitors

Source: suppcm.xpt, cm.xpt, dm.xpt; Data cutoff date: May 9, 2014

6.1.4 Analysis of Primary Endpoint(s)

Primary PFS Analysis (Data Cutoff Date: May 9, 2014)

The primary efficacy analysis of the GO28141 trial demonstrated a statistically significant improvement in progression-free survival (PFS) as assessed by study investigators with the addition of cobimetinib to vemurafenib [HR: 0.5 (95% CI: 0.4, 0.7); 2-sided p-value <0.0001]. The median PFS in the Vem/Cobi arm was 9.9 months (95%

CI: 9.0, NR) compared to 6.2 months (95% CI: 5.6, 7.4) in the Vem/Placebo arm (Table 18). The Kaplan-Meier curves of PFS as assessed by the investigator are shown in Figure.

Reviewer's comment:

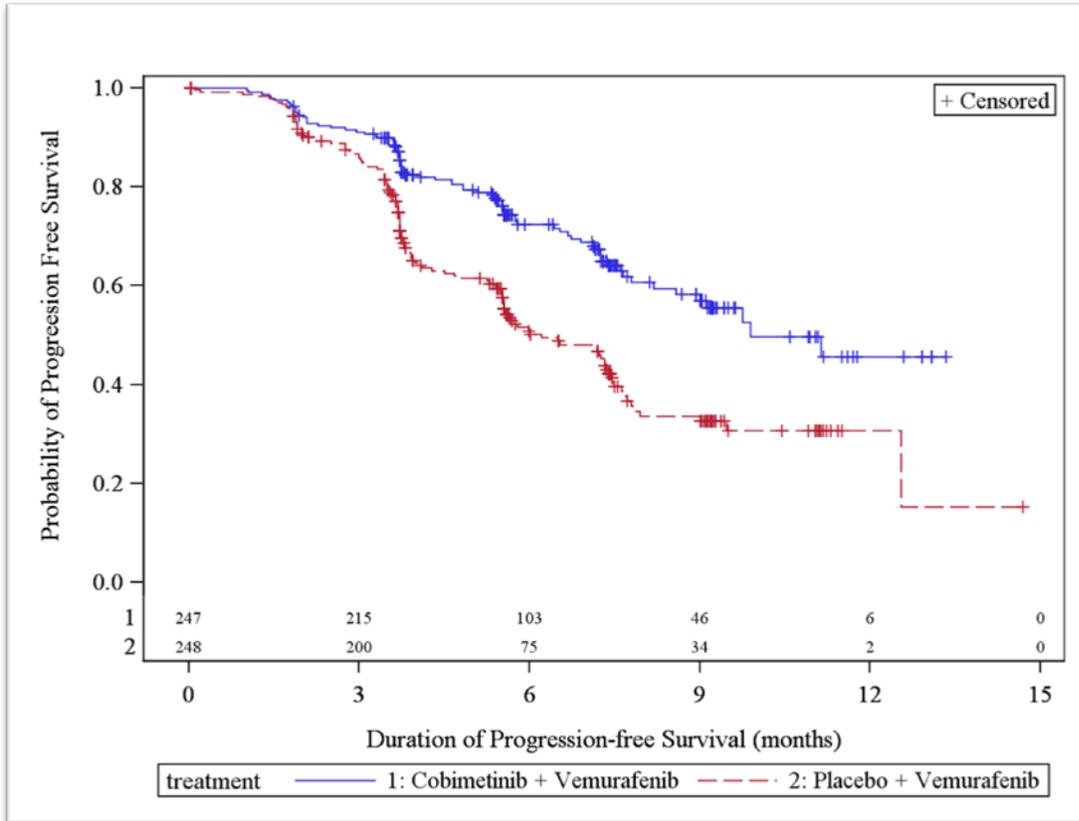
As detailed in Dr. Jiang's statistical review, the assessment based on treatment assignment derived from the interactive response system (IxRS) rather than on the treatment assignment based on the study case report forms (CRF) was viewed to be consistent with the intent-to-treat principal and was the FDA-preferred primary endpoint. Use of this endpoint differed only slightly from the Applicant's analysis using strata recorded from the CRF. Only the analyses using the FDA-preferred endpoints are shown in the time-to-event analyses in section 6.1 below. The FDA reviewer verified response data according to RECIST version 1.1 using raw datasets containing tumor measurements as documented by the study investigators in the case report forms.

Table 18: GO28141 - Progression-Free Survival (PFS) Analysis, Investigator Assessment (Data Cutoff Date: May 9, 2014) (ITT Population)

	Vem/Placebo (n=248)	Vem/Cobi (n=247)
Number of Event (%)	128 (52)	79 (32)
Progression	125	74
Death	3	5
Number of Censored (%)	120 (48)	168 (68)
Median PFS in months (95% CI)	6.2 (5.6, 7.4)	9.9 (9.0, NR*)
Strata Recorded from IxRS		
Hazard ratio** (95%CI)	0.5 (0.4, 0.7)	
p-value (stratified*** log-rank)	<0.0001	

NR=not reached due to small number of events occurred; **a hazard ratio of less than 1 indicates that treatment with combination of cobimetinib and vemurafenib is associated with lower risk of progression or death compared to treatment with combination of placebo and vemurafenib; *stratified by region and metastatic classification*
Source: FDA Statistical Review; Data cutoff date: May 9, 2014

Figure 6: Kaplan-Meier Curves of Progression-Free Survival Investigator Assessment (ITT Population)



Source: FDA Statistical Review; Data cutoff date: May 9, 2014

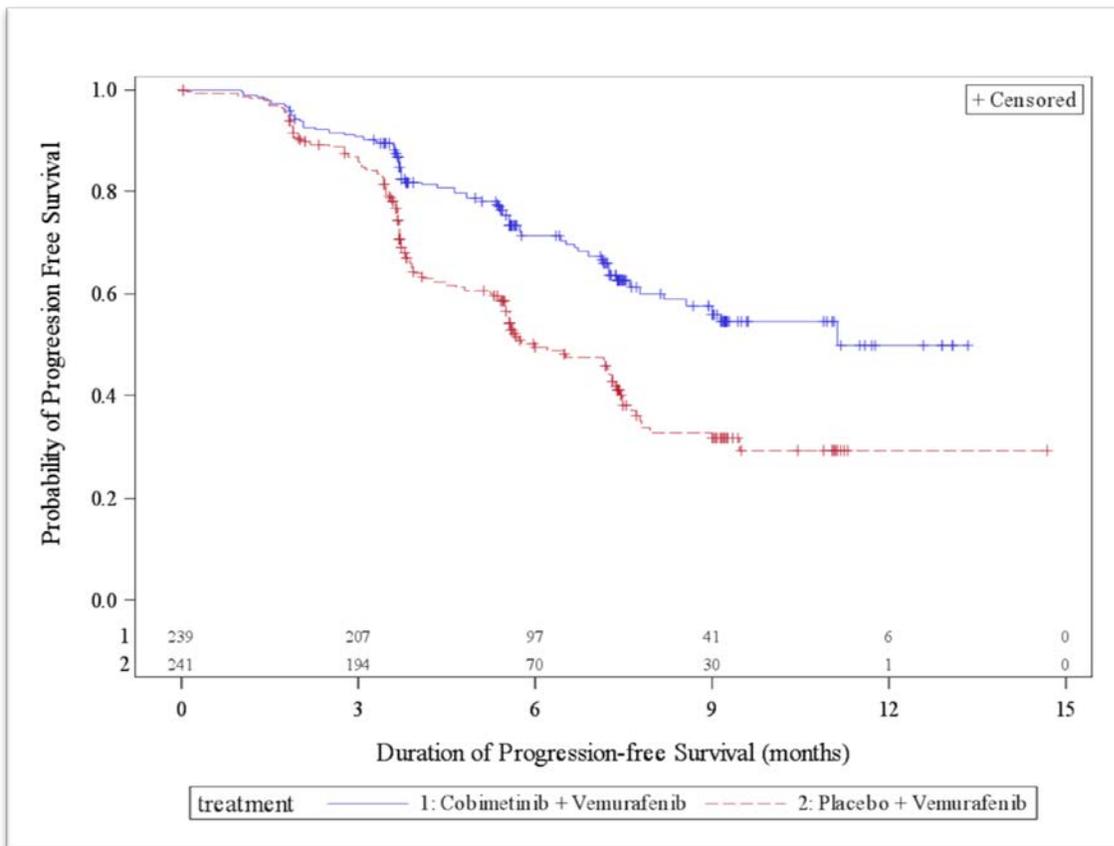
To assess whether inclusion of data from site #257793 (Dr. Virginia Ferraresi, Roma, Italy), which was judged by the OSI inspector to be unreliable, had an impact on the GO28141 study results, a subset analysis was performed eliminating data from this site. The results of these analyses are shown below. Elimination of this study site, which enrolled 15 patients, yielded results similar to that of the full ITT study population.

Table 19: GO28141 - Progression-Free Survival (PFS) Analysis, Investigator Assessment, Sensitivity Analysis Eliminating Site # 257793 (ITT Population)

	Placebo + Vemurafenib (N=241)	Cobimetinib + Vemurafenib (n=239)
Number of Event (%)	124 (51.4)	76 (31.8)
Number of Censored (%)	117 (48.6)	163 (68.2)
Median PFS in months (95% CI)	6.01 (5.52, 7.36)	11.14 (8.57, NR)
Strata Recorded from IxRS		
Hazard ratio* (95%CI)	0.50 (0.37, 0.67)	
p-value (stratified* log-rank)	<0.0001	

Source: FDA Statistical Review; Data cutoff date: May 9, 2014

Figure 7: GO28141 - Kaplan-Meier Curves of Progression - Free Survival Investigator Assessment, Sensitivity Analysis Eliminating Site # 257793 (ITT Population)



Source: FDA Statistical Review; Data cutoff date: May 9, 2014

Reviewer's comment: Three of 15 patients enrolled at Site # 257793 had assessments that were significantly delayed. However, elimination of this study site does not materially impact the overall study results. Inclusion of this study site in labeling is felt to be preferable by this reviewer than eliminating this study site from the final analysis which would result in reporting a subset analysis.

Post-Final Analysis of PFS (Data Cutoff Date: January 16, 2015)

As discussed during the Pre-NDA meeting (Table 3), Genentech submitted a protocol amendment to the IND on March 11, 2015 (Table 7) to revise the overall survival (OS) analyses plan for GO28141. After the primary PFS analysis was performed on July 10, 2014, and after enrollment to the study was completed, additional ad-hoc analyses of PFS and OS were conducted (b) (4)

(b) (4) The GO2811 efficacy update and supporting datasets with a data cutoff date of January 16, 2015 were submitted to the NDA on October 13, 2015. A total of 244 progression events were added with this update. However, only the final analysis file which contained the investigator’s final assessment of response (RECIST V1.1) at each time point was included. FDA was not able to verify this data against individual lesion measurements.

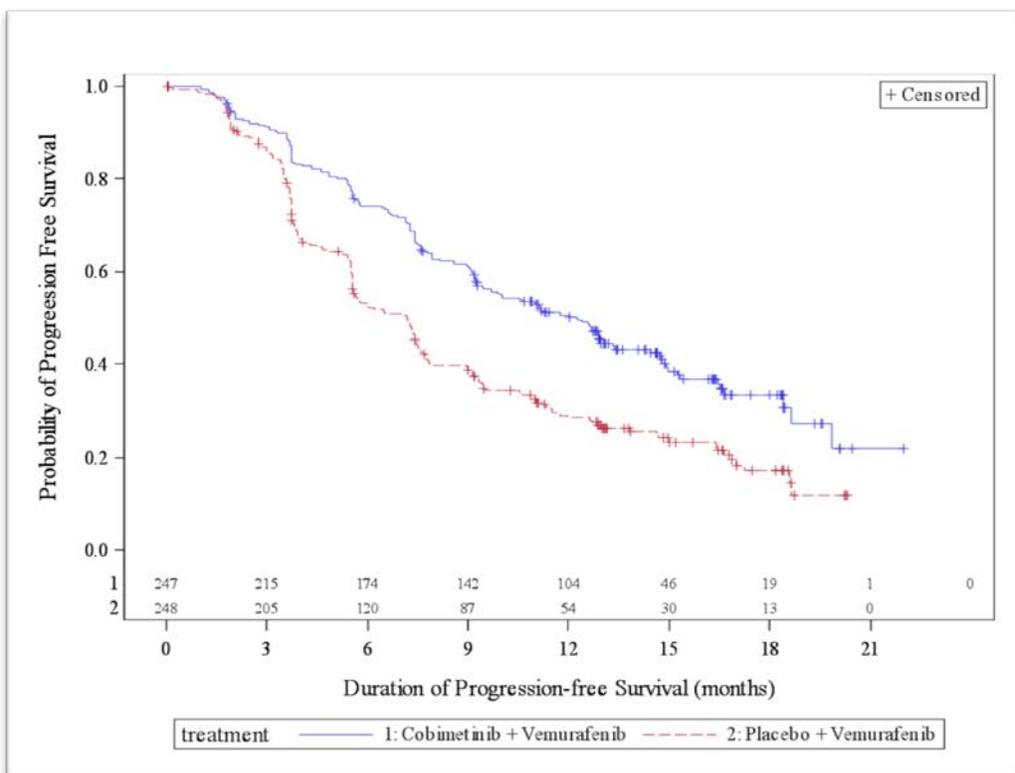
The results of the post-final PFS analysis (data cutoff date: Jan 16, 2015) and Kaplan-Meier curve for the second interim analysis as provided by the sponsor are shown below.

Table 20: GO28141 - Progression-Free Survival (PFS) Analysis, Investigator Assessment, Post-Final Assessment (Data Cutoff Date: May 9, 2014) (ITT Population)

Analysis of Progression-Free Survival with Stratifications Intent-to-Treat Population		
Earliest Contributing Event to Investigator PFS		
	Vemurafenib + Placebo (N=248)	Vemurafenib + Cobimetinib (N=247)
Patients included in analysis	248 (100.0%)	247 (100.0%)
Patients with event (%)	180 (72.6%)	143 (57.9%)
Patients without event (%)	68 (27.4%)	104 (42.1%)
Time to events (Months)*		
Median (a)	7.20	12.25
95%CI for Median(b)	(5.55, 7.49)	(9.46, 13.37)
25% and 75% Percentile	3.71, 14.65	5.75, 19.84
Range	0.03 to 20.34	0.03 to 21.98
Stratified Analysis by geographic region and metastasis classification		
Hazard Ratio	0.575	
95% CI	(0.460, 0.719)	

Source: GO28141: Efficacy Update Report (12October2015)

Figure 8: GO28141 - Kaplan-Meier Curves of Progression - Free Survival, Investigator Assessment, Post-Final Assessment (Data Cutoff Date: January 16, 2015) (ITT Population)



Source: FDA Statistical Review, Addendum

Reviewer's comment: At the time of finalization of this review, the review team is in discussion as to whether to include this updated data in labeling. Median PFS for the Vem/Cobi arm would change from 9.9 (9.0, NR) months based on the May9, 2014 cutoff date to 12.3 (9.46, 13.4) months based on the January 16, 2015 data cutoff dates. The dates for the Vem/Placebo arm would be 6.2 (5.6, 7.4) months and 7.2 (5.6, 7.5) months for the two data cutoff dates, respectively.

6.1.5 Analysis of Secondary Endpoints(s)

Key secondary endpoints for the trial included an analysis of PFS as assessed by a blinded independent review committee (BIRC), analysis of confirmed objective response rate and duration of response as assessed by study investigators, and analysis of the

overall survival (OS). In addition, a number of sensitivity analyses were conducted to assess the treatment effect across relevant demographic and prognostic subgroups.

Progression-Free Survival

The findings of the pre-specified secondary analysis of PFS as assessed by the BIRC are shown below in Table 21. The results of this secondary analysis were consistent with the analysis of PFS as assessed by the study investigators.

Table 21: GO28141 - Progression-Free Survival Analysis, Blinded Independent Review Committee Assessment (ITT Population)

	Vem/Placebo (n=248)	Vem/Cobi (n=247)
Number of Event (%)	117 (47)	82(33)
Number of Censored (%)	131(53)	165 (67)
Median PFS in months (95% CI)	6.0 (5.6, 7.5)	11.33 (8.5, NR*)
Strata Recorded from IxRS		
Hazard ratio** (95%CI)	0.60 (0.45,0.79)	
p-value (stratified*** log-rank)	0.0003	

NR=not reached due to small number of events occurred; **a hazard ratio of less than 1 indicates that treatment with combination of cobimetinib and vemurafenib is associated with lower risk of progression or death compared to treatment with combination of placebo and vemurafenib; *stratified by region and metastatic classification.*

Source: FDA Statistical Review; Data cutoff date: May 9, 2014

There was a high level of concordance between PFS as assessment by the investigators and by the BIRC (Table 22). Overall, there was concordance between the PFS assessed by the investigators and by the blinded IRF in 84% of the ITT study population (Vem/Placebo – 81%; Vem/Cobi – 84%).

Table 22: GO28141 - Concordance of Investigator and Blinded Independent Review Committee Assessments of Progression-Free Survival (ITT Population)

INV Assessment, n (%)	BIRC Assessment, n (%)			
	Vem/Placebo (n=248)		Vem/Cobi (n=247)	
	Event	No Event	Event	No Event
Event	98 (39.5)	27 (10.9)	62 (25.1)	12 (4.9)
No Event	16 (6.5)	104 (41.9)	15 (6.1)	153 (61.9)

Source: FDA Statistical Review; Data cutoff date: May 9, 2014

The results of a series of pre-specified sensitivity analyses of PFS and of the Statistical Reviewer's confirmation of PFS are shown in below.

Table 23: GO28141 - Sensitivity Analyses of Progression-Free Survival (ITT Population)

	Number of Events (%)		HR (95%CI)
	Vem/Placebo (n=248)	Vem/Cobi (n=247)	
Applicant's Analyses			
Unstratified analysis	128 (52)	79 (32)	0.5 (0.4, 0.7)
PFS, censored for non-protocol anti-cancer therapy	126 (51)	77 (31)	0.5 (0.4, 0.7)
PFS assessed by BIRC	117 (47)	82 (33)	0.6 (0.5, 0.8)
Reviewer's Analysis			
Using the INV and BIRC assessment	144 (58)	94 (38)	0.6 (0.4,0.7)

Source: FDA Statistical Review; Data cutoff date: May 9, 2014

Reviewer's comments: The estimate of the hazard ratio is robust and is consistent with that observed in the primary analysis over all pre-planned sensitivity analyses suggesting a low potential for bias or uncertainty in the potentially subjective assessment of PFS.

Overall Response:

The BIRC-confirmed overall objective response rate (ORR) defined as the percent of patients with a complete or partial response using RECIST v. 1.1, and the duration of response were key secondary endpoints for GO28141. A hierarchical test order was pre-specified for the secondary endpoints to adjust for multiplicity such that the ORR

would be tested first at the 0.05 level after the primary analysis of PFS showed statistical significance.

The ORR was 68% on the Vem/Cobi arm (95% CI: 61%, 73%) and 45% in the Vem/Placebo arm (95% CI: 39%, 51%). This difference was highly statistically significant (p-value, $X^2 < 0.0001$). The median duration of response was 7.3 months in the Vem/Placebo arm and was not reached in the Vem/Cobi arm. Twenty-two patients (20%) of responders in the Vem/Placebo arm and 41 patients (25%) of responders in the Vem/Cobi arm had responses with duration of six months or more.

Table 24: GO28141 - Objective Response and Duration of Response (ITT Population)

	Vem/Placebo (n=248)	Vem/Cobi (n=247)
Response (CR+PR), n (%)	111 (45)	167 (68)
(95%CI)	(39, 51)	(61, 73)
Complete response, n (%)	11 (5)	25 (10)
Partial response, n (%)	100 (40)	142 (57)
P-value (χ^2 -test)	<0.0001	
Median of Duration of Response (months)	7.3 (5.8, NA)	NA (9.3, NA)
Responses lasting \geq 6 months, n (%)	22(20)	41(25)

Source: FDA Statistical Review; Data cutoff date: May 9, 2014

Overall Survival

Interim Analysis: Data Cutoff Date May 9, 2014

The interim analysis for overall survival (OS) was conducted at the time of the final PFS analysis and was conducted in hierarchical order once the primary PFS analysis was determined to demonstrate statistical significance. Based on strata recorded from IxRS, the stratified log-rank test $p = 0.0273$, but the result did not cross the pre-specified boundary for statistical significance ($\alpha = 0.0000037$) according to pre-specified O'Brien/Flemming method (based on 22% of planned events). Median OS had not yet been reached for either of the treatment arms at this pre-specified interim analysis. The Kaplan-Meier curve for OS is shown in Figure 9 below.

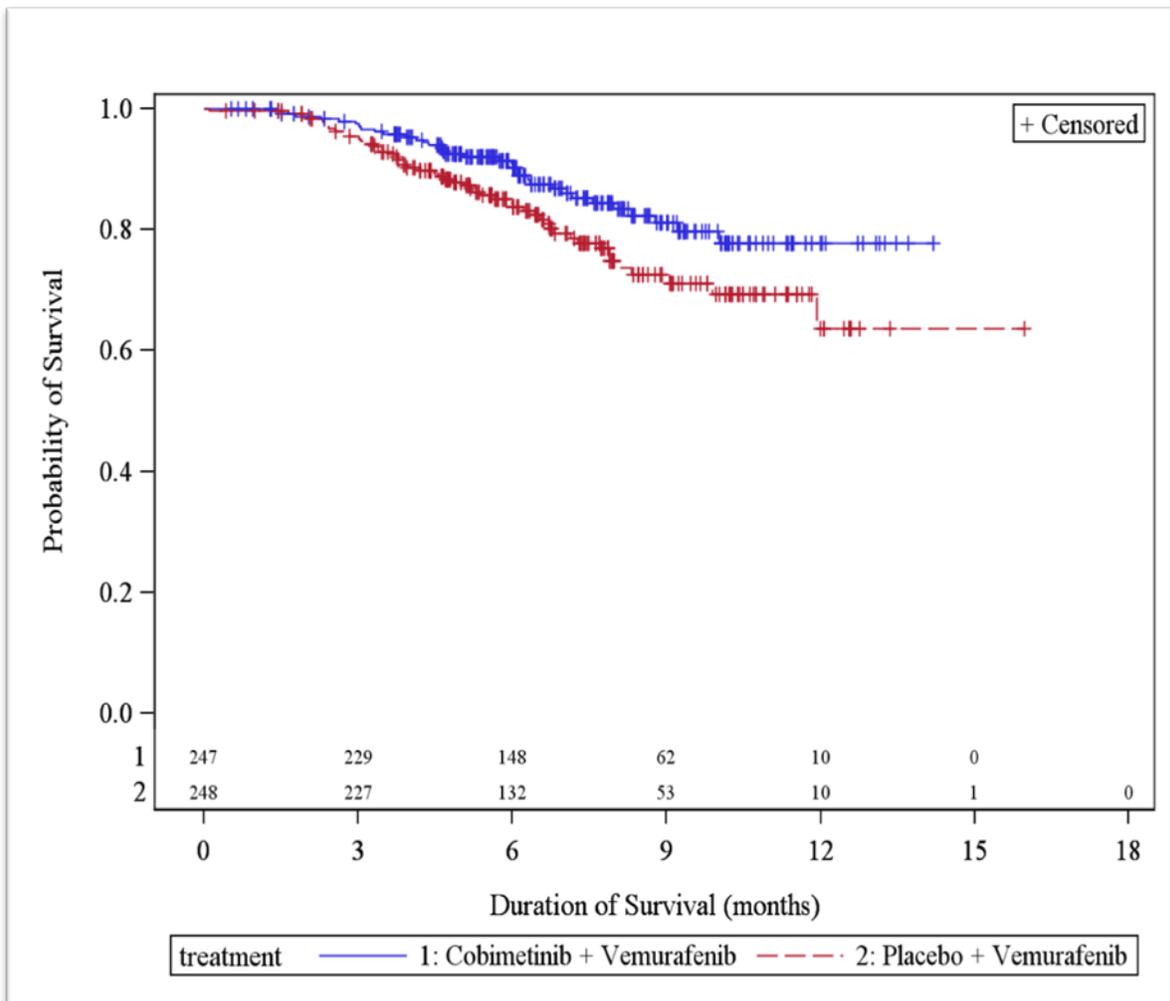
Table 25: GO28141 - Overall Survival (ITT Population), Interim Analysis (Data Cutoff Date: May 9, 2014)

	VEM/Placebo (n=248)	VEM/Cobi (n=247)
Number of Event (%)	51 (20.6)	34 (13.8)
Number of Censored (%)	197 (79.4)	213 (86.2)
Median OS in Months (95% CI)	NR*(11.9, NR*)	NR*(NR*, NR*)
Strata Recorded from IxRS		
Hazard ratio** (95%CI)	0.62 (0.40, 0.95)	
p-value (stratified*** log-rank)	0.0273	

NR=Not reached due to small number of events occurred; **a hazard ratio of less than 1 indicates that treatment with combination of cobimetinib and vemurafenib is associated with lower risk of progression or death compared to treatment with combination of placebo and vemurafenib; *stratified by region and metastatic classification.*

Source: FDA Statistical Review; Data cutoff date: May 9, 2014

Figure 9: GO28141 - Overall Survival (ITT Population) (Interim Analysis, Data Cutoff Date: May 9, 2014)



Source: FDA Statistical Review; Data cutoff date: May 9, 2014

Reviewer's comment: Based on this interim analysis of OS with 85 OS events reported, the Kaplan-Meier curves show a trend toward an improvement in OS in the Vem/Cobi arm.

Interim Analysis: Data Cutoff Date Jan 16, 2014

As discussed during the Pre-NDA meeting (Table 3), Genentech submitted a protocol amendment to the IND on March 11, 2015 (Table 7) to revise the overall survival (OS) analyses plan for GO28141. After the primary PFS analysis was performed on July 10,

2014, and after enrollment to the study was completed, additional ad-hoc analyses of PFS and OS were conducted (b) (4)

The revised analysis plan submitted to the IND reduced the events required for the final analysis from 385 to 250 events, the Type-I error rate (2-sided) was defined at 0.05 with a power of 80% to detect an HR= 0.70 (median 15 vs. 21.4 months). On October 8, 2015, FDA held an informal teleconference with Genentech to discuss the results of the updated analyses. The GO2811 efficacy update and supporting datasets with a data cutoff date of January 16, 2015 were submitted to the NDA on October 13, 2015. FDA's verification of this data (using IxRS) indicates that the efficacy boundary for the O'Brien-Flemming boundary for OS was crossed. Since the study met its primary endpoint, and pursuant to the agreement made at the pre-NDA meeting, the FDA statistical team recommends inclusion of data from the second interim OS analysis in final labeling. The second interim analysis demonstrated a significant improvement in overall survival among patients randomized to receive Vem/Cobi compared to patients randomized to receive Vem/Placebo. The median OS for the Vem/Cobi treatment arm was not reached at the time of the second interim analysis. Please see the addendum to Dr. Jiang's statistical review for additional details.

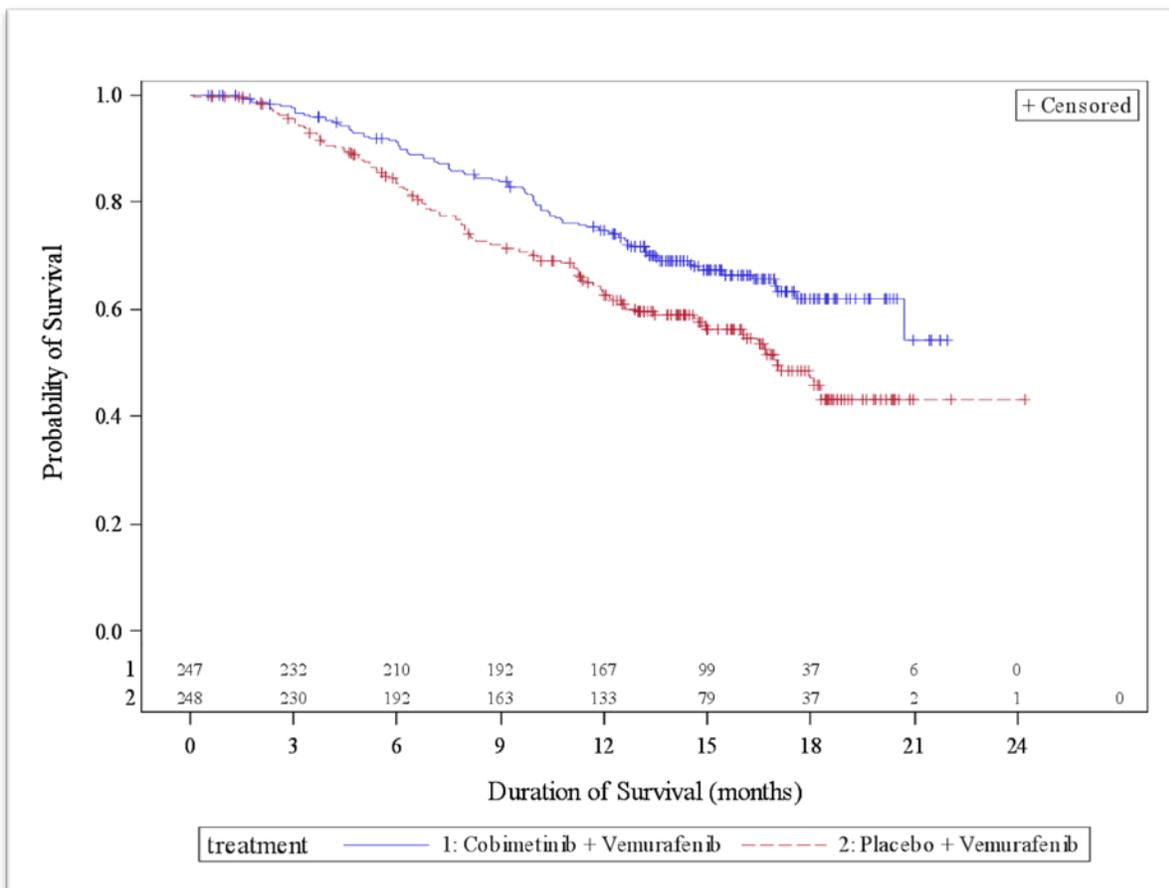
The analysis and Kaplan-Meier curve for the second interim analysis are shown below.

Table 26: GO28141 - Overall Survival (ITT Population), Interim Analysis (Data Cutoff Date: Jan 16, 2014)

	Vem/Placebo (n=248)	Vem/Cobi (n=247)
Number of Event (%)	109 (43.9)	79 (32.0)
Number of Censored (%)	139 (56.1)	168 (68.0)
Median OS in months (95% CI)	17.0 (15.0, NA)	NA(20.7, NA)
Strata Recorded from IxRS		
Hazard ratio* (95%CI)	0.63 (0.47, 0.85)	
p-value (stratified* log-rank)	0.0019	

*NR=Not reached due to small number of events occurred; **a hazard ratio of less than 1 indicates that treatment with combination of cobimetinib and vemurafenib is associated with lower risk of progression or death compared to treatment with combination of placebo and vemurafenib; ***stratified by region and metastatic classification.
Source: FDA Statistical Review; Data cutoff date: Jan 16, 2015

Figure 10: GO28141 - Overall Survival (ITT Population) (Interim Analysis, Data Cutoff Date: January 16, 2014)



Source: FDA Statistical Review; Data cutoff date: Jan 16, 2015

6.1.6 Other Endpoints

Global health/health-related quality of life, symptom severity, and functional interference of symptoms as reported by patients were assessed for each treatment arm using the EORTC QLQ-C30 questionnaire. As reported by Genentech, patient completion rates were in excess of %96% at baseline and were in excess of 88% overall.

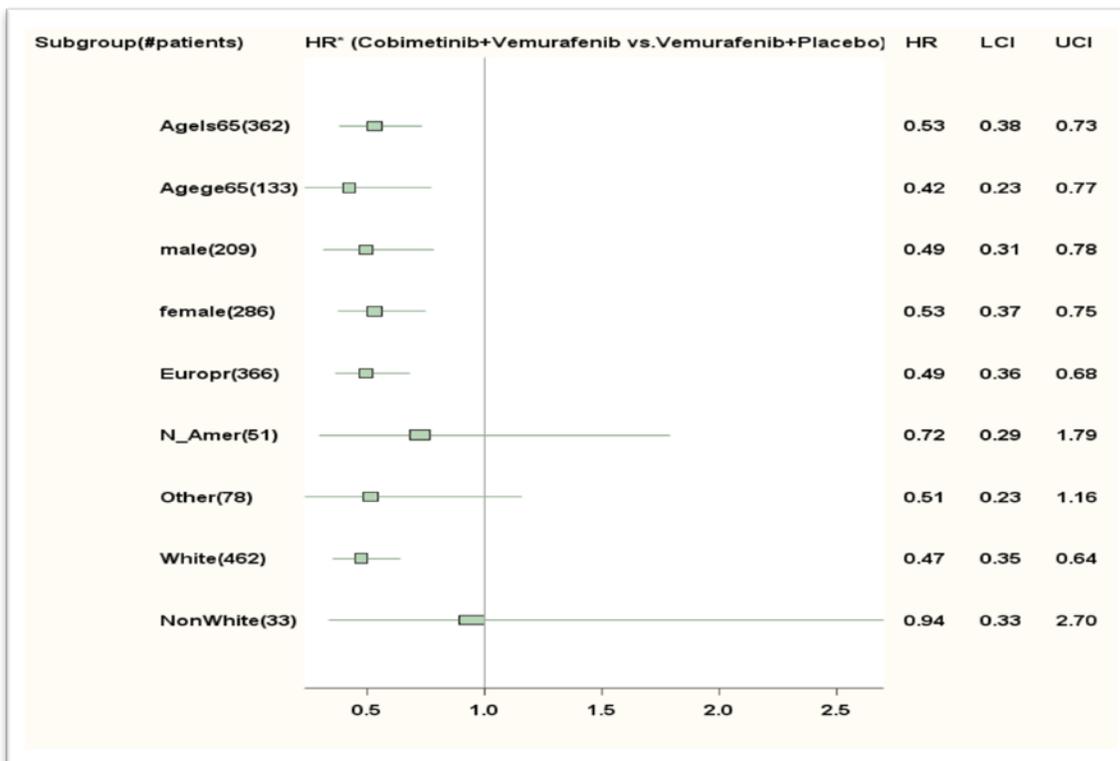
Genentech conducted an assessment of the EORTC QLQ-C30 scales and change from baseline at Days 1 and 15 in Cycles 1 and 2 and every other cycle thereafter until patient withdrawal or end of study.

Genentech reports that across all functioning domains (cognitive, emotional, social, role, and physical) and across most symptoms (appetite loss, constipation, nausea and vomiting, dyspnea, pain, fatigue) of the EORTC ALQ-C30, patients in the cobimetinib plus vemurafenib arm reported better scores at most of the post-baseline time points evaluated. However, the differences from baseline in function and symptoms did not constitute a clinically meaningful change (≥ 10 point increase or decrease from baseline). Genentech reported that patients randomized to receive Vem/Cobi experienced clinically meaningful worsening of diarrhea from baseline at Cycle 1 Day 15 and Cycle 2 Day 15. These claims were not verified by because the Applicant's analysis did not suggest a negative impact of treatment based on patient reported outcomes, the event of diarrhea as reported by providers could be assessed in the safety database, and because Genentech did not propose to include the results of these analysis in labeling or as supportive evidence of the efficacy of cobimetinib.

6.1.7 Subpopulations

The FDA statistical reviewer conducted exploratory PFS analyses in subgroups defined by age, gender, race and geographic region. The results of these exploratory analyses are shown below in Figure. The forest plot of the analyses shows consistent treatment effects favoring the Vem/Cobi arm in demographic subgroups and shows no outliers.

Figure 11: GO28141 - PFS Results in Demographic Subgroups, Assessed by Investigator (ITT Population)



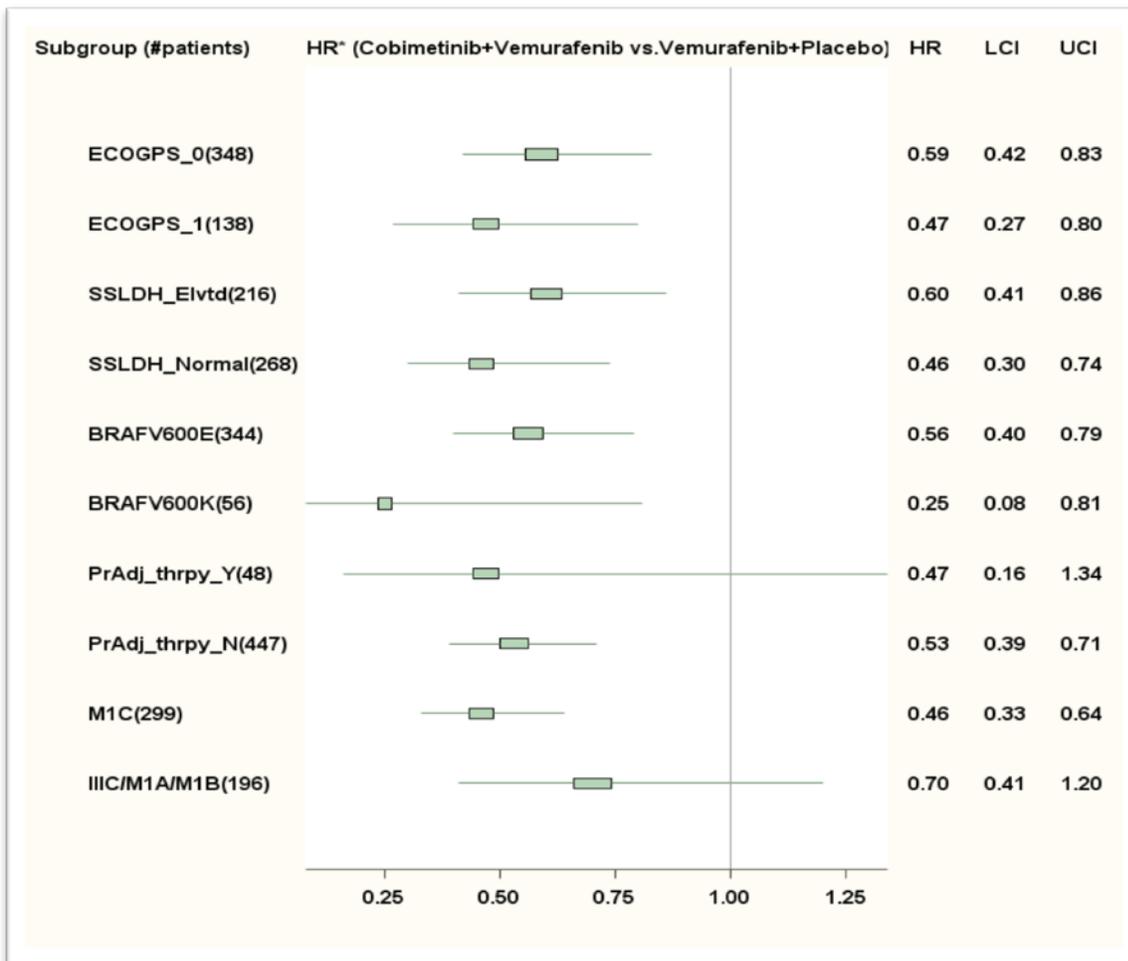
*hazard ratio of less than 1 indicates that treatment with combination of cobimetinib and vemurafenib is associated with lower risk of progression or death compared to treatment with combination of placebo and vemurafenib.

Source: FDA Statistical Review

Reviewer comment: The non-white subgroup appeared to be comparable to the White subgroup in each treatment arm with respect to the baseline ECOG status, metastatic stage, and the proportion of patients with elevated LDH at baseline. Differences in the estimate of the HR for the non-white subgroup appear to be due to variation within the small sample.

The FDA statistical reviewer conducted PFS analyses in subgroups defined by tumor characteristics and prognostic factors. The results of these exploratory analyses are shown below in Figure. The forest plot of the analyses shows consistent benefit in demographic subgroups and shows no outliers.

Figure 12: GO28141 - PFS in Major Characteristics Subgroups, Investigator Assessed (ITT Population)



* hazard ratio of less than 1 indicates that treatment with combination of cobimetinib and vemurafenib is associated with lower risk of progression or death compared to treatment with combination of placebo and vemurafenib.

Abbreviations: ECOGPS_0/1= subgroup of patients whose Eastern Cooperative Oncology Group performance status=0/1; SSLDH_Elvtd/Normal=subgroups of patients with elevated/normal screening serum LDH level; BRAFV600E/K = subgroup of patients with BRAF V600 mutation status (V600E, V600K); PrAdj_thrpy_Y/N=subgroup of patients with/without prior adjuvant therapy; M1C= subgroup of patients with disease stage M1C; IIIC/M1A/M1B= subgroup of patients with disease stage IIIC, M1a, M1b.

Source: FDA Statistical Review

Reviewer's comment: The above subgroup analyses show consistent evidence of benefit across all relevant demographic and prognostic subgroups.

BRAF V600 Subsets:

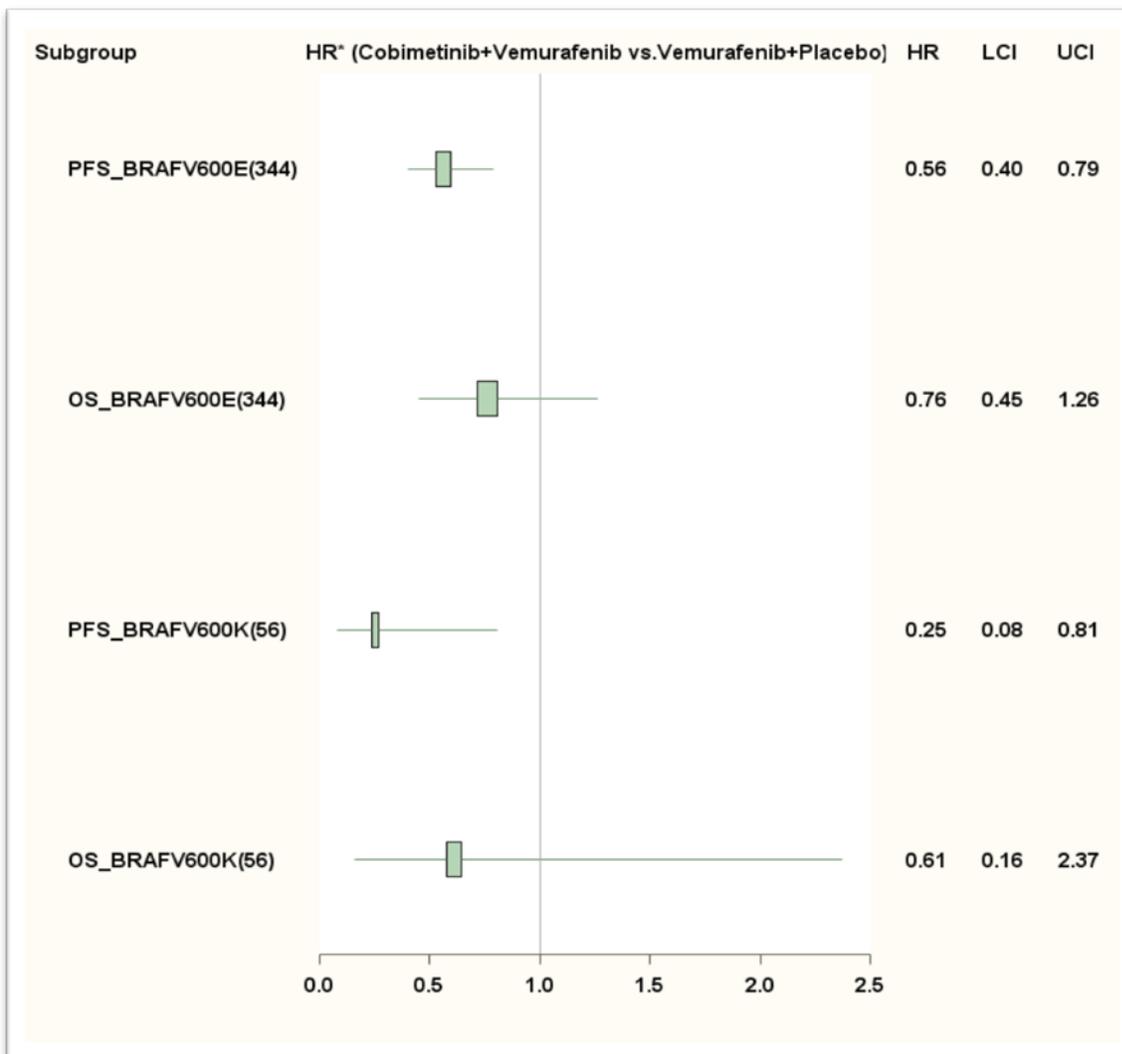
The estimates of the prevalence of BRAF codon 600 mutations occurring in patients with metastatic melanoma range from 40% to 60%. The most prevalent mutations in BRAF mutation-positive melanoma are BRAF V600E (about 80%) and BRAF V600K (5-30%). Other mutations are rare. The frequency of BRAFV600K mutation has been reported to increase with age, and to be associated with cumulative sun induced skin damage [13], and may be associated with brain and lung metastases and a shorter time from diagnosis to metastasis and death [14]. The ability to detect the BRAF V600K mutation also varies with the characteristics of the test kit. The cobas 4800 BRAF V600 mutation Test is an in vitro diagnostic that was specifically designed to detect the BRAF V600E mutation in DNA extracted from formalin-fixed, paraffin-embedded melanoma tissue and is FDA-approved as an aid in selecting melanoma patients for treatment with vemurafenib. However, the cobas test will read a “positive” result for approximately 70% of tumors with BRAF V600K mutations [15].

The statistical reviewer conducted exploratory PFS and OS analyses in patients with BRAF V600 mutation status V600E or V600K. The results of these analyses are displayed in Figure – 15 below. The analysis of ORR and DoR by BRAF mutation subset is shown below in Table 27.

The results of these analyses suggest an improvement in PFS in both the V600E and V600K subgroups with the addition of cobimetinib to vemurafenib therapy as well as a trend towards improvement in OS in both mutation subgroups.

Reviewer’s comment: Since the GO28141 trial pre-screened patients using the cobas 4800 BRAF V600 mutation test which would exclude approximately 1/3 of patients with BRAF V600K mutations. Based on a discussion with CDRH, it is not clear that these patients differ in any systematic way from tumors detected. Lack of detection was felt to be related to DNA quality. It is strictly speaking, unclear how the subset analysis relates to patients not detected by Cobas who may be detected using other testing methods. There However, within the limits of the selection criteria, the retrospective subset analysis by mutation subsets shows a consistent benefit across both mutation subsets and across primary and secondary endpoints. It is therefore likely but not certain that the effect in patients with V600K mutations excluded from the analysis would be similar. Post-marketing confirmation is recommended

Figure 13: Frost Plot of PFS/OS Results in Subgroups of BRAF V600 Mutation Status



* hazard ratio of less than 1 indicates that treatment with combination of cobimetinib and Vemurafenib is associated with lower risk of progression or death compared to treatment with combination of placebo and Vemurafenib.

Abbreviations: PFS_BRAFV600E/K = PFS result in the subgroup of patients with BRAF V600 mutation status (V600E, V600K); OS_BRAFV600E/K = OS result in the subgroup of patients with BRAF V600 mutation status (V600E, V600K).

Source: FDA Statistical Review

The Kaplan-Meier curves for the exploratory analyses of PFS and OS by BRAF mutation subgroups are shown below.

Figure 14: GO28141: Kaplan-Meier Curves of Progression-Free Survival by Treatment Group for BRAF V600E and BRAF V600K Subtypes (ITT Population)

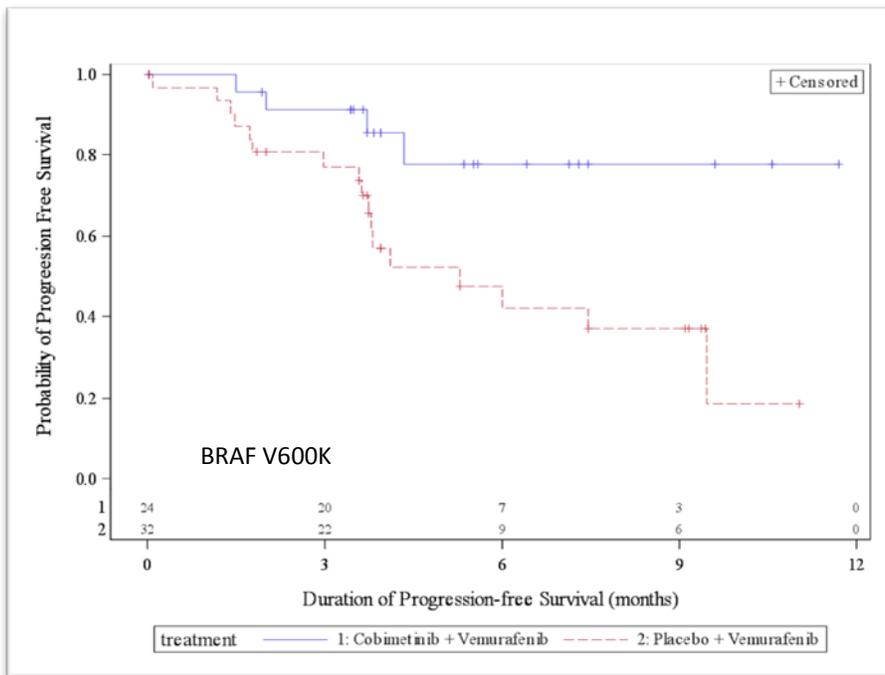
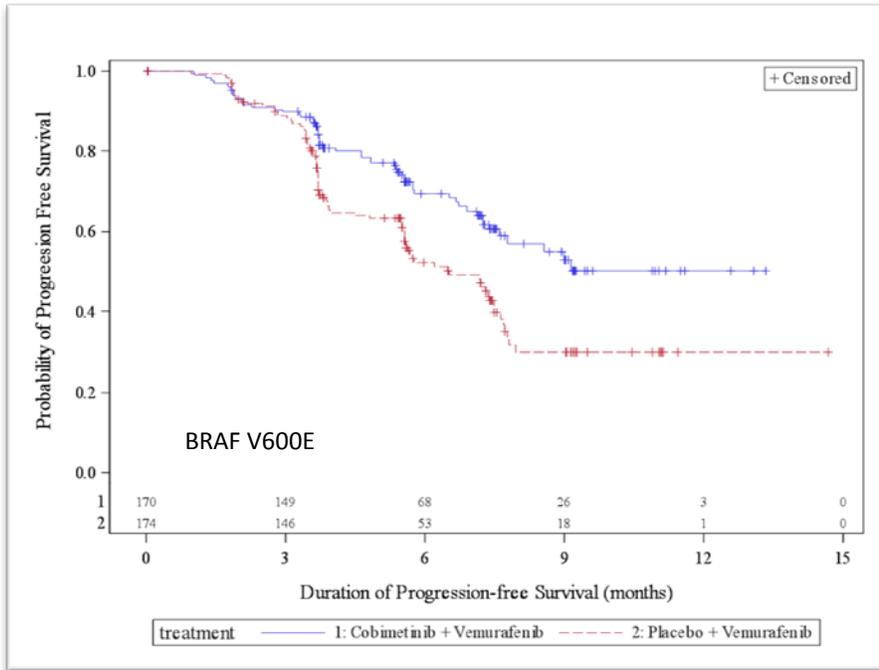


Figure 15: GO28141: Kaplan-Meier Curves of Overall Survival by Treatment Group for BRAF V600E and BRAF V600K Subtypes (ITT Population)

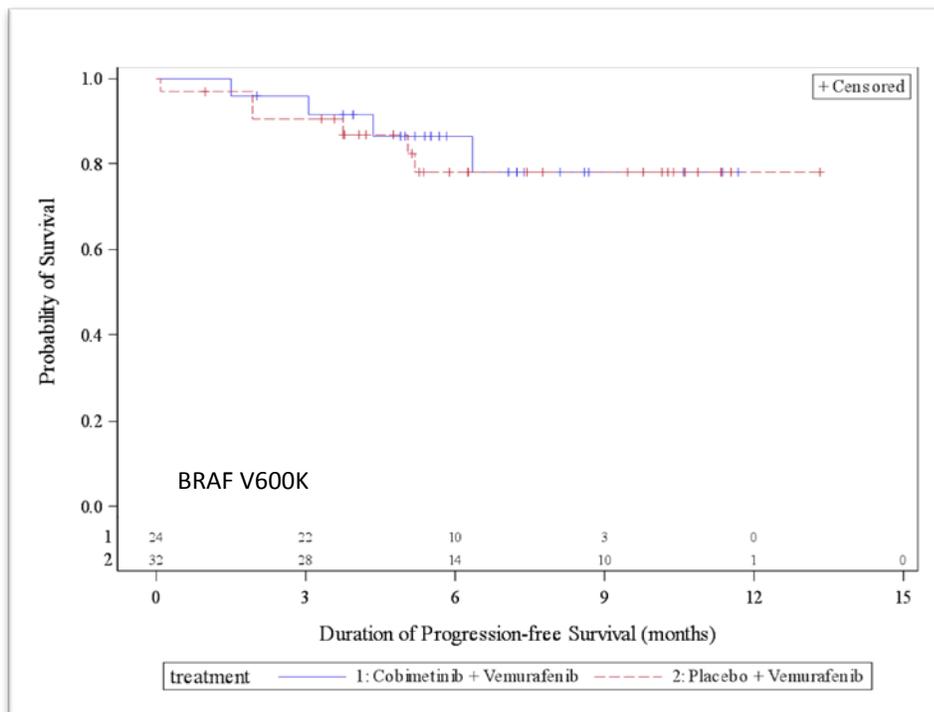
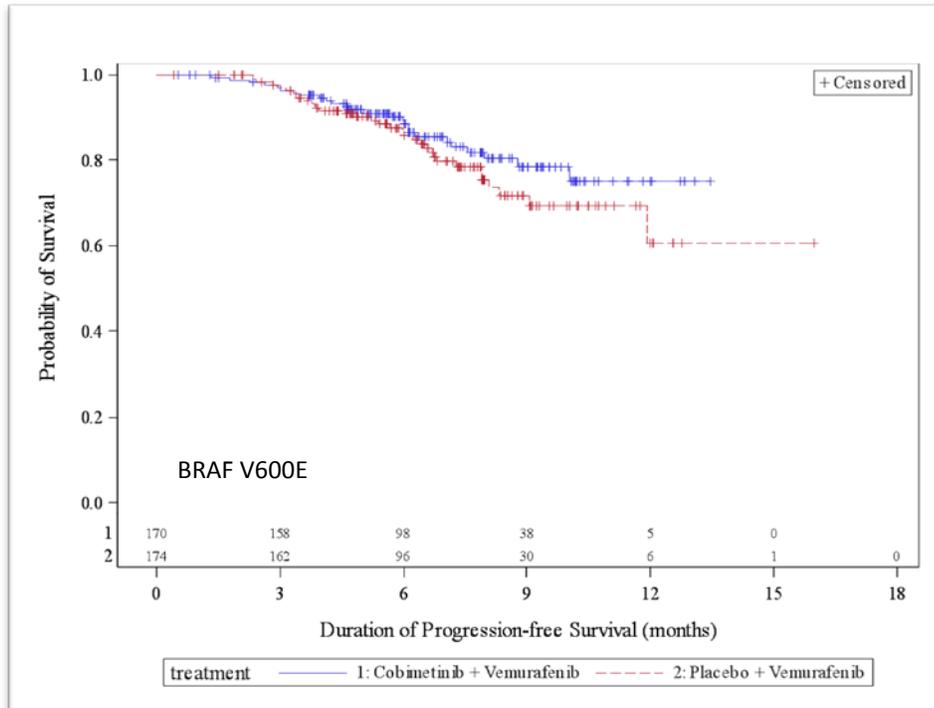


Table 27: GO28141 - Objective Response and Duration of Response by V600 Mutation Subset (ITT Population)

	Vemurafenib +Placebo	Cobimetinib + Vemurafenib
BRAF V600E	n=174	n= 170
Responders, n (%)	83 (48)	116 (68)
Duration of response>=6 months	12 (14.5%=12/83)	24 (20.7%=24/116)
BRAF V600K	n= 32	n=24
Responders, n (%)	10 (31)	16 (67)
Duration of response>=6 months	3 (30%=3/10)	2 (12.5%=2/16)

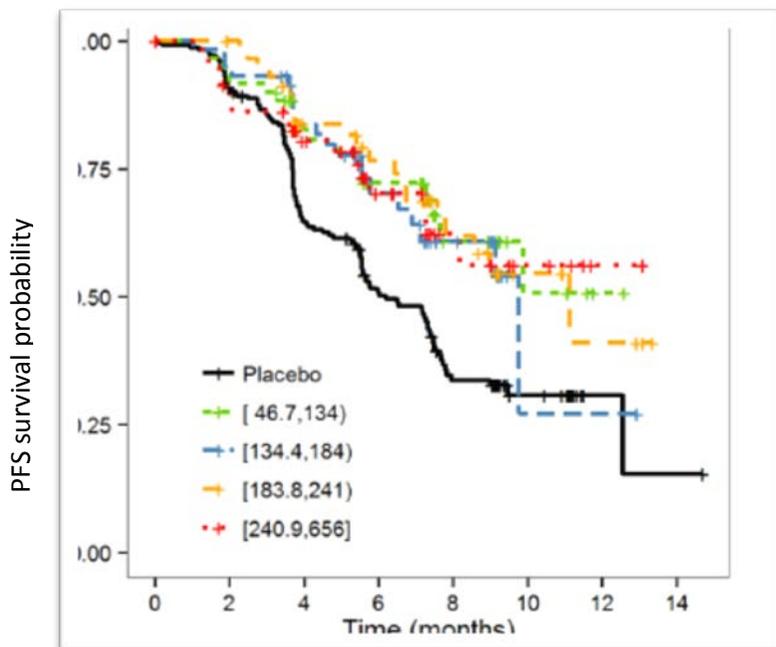
Source: FDA Statistical Review

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Exploration for exposure-response relationships was limited to the GO28141. Within the narrow range of exposure to cobimetinib, no exposure-response relationship was observed (Figure 16). Please see the FDA Clinical Pharmacology NDA Review for further details.

Figure 16: GO28141 – Cobimetinib Exposure – Response Relationship

Cobimetinib AUCss (day.ug/L)



Source: FDA Clinical Pharmacology Review

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

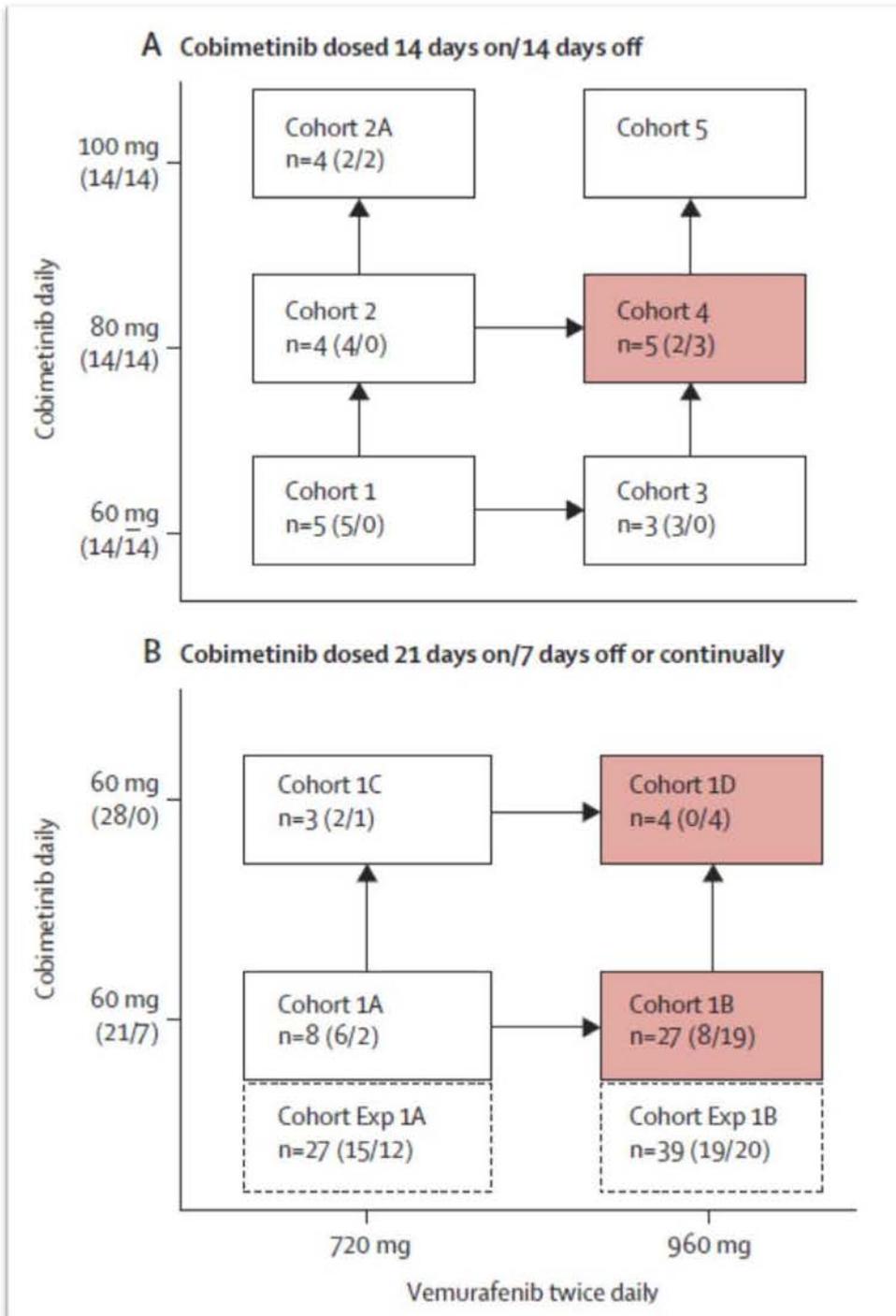
In the GO28141 trial, the median duration of response was 7.3 months in the Vem/Placebo arm and was not reached in the Vem/Cobi arm (Section 6.1.5). These results suggest that the benefit related to the addition of cobimetinib to vemurafenib is durable.

6.1.10 Additional Efficacy Issues/Analyses

The Applicant's development program for cobimetinib administered in combination with vemurafenib contained limited assessment of dose-response. The Applicant conducted one dose-escalation study, NO25395 which is described in section 5.3.1.2. In this trial of 129 patients with BRAF-mutated melanoma as detected by the cobas 4800 BRAF V600 mutation test who were either BRAF inhibitor naive or had recently progressed on a BRAF inhibitor were enrolled onto ten dosing cohorts which explored three

cobimetinib dosing schedules, 14 days on/14 days off (14/14), 21 days on and 7 days off (21/7) and continuous cobimetinib dosing (28/0). Within each cobimetinib dosing schedule, two continuous twice daily vemurafenib doses were explored (720mg or 960 mg PO QD). Within each vemurafenib dose, the cobimetinib dose was escalated. Cohort enrollment was staggered to allow for demonstration at a lower dose before either escalation of cobimetinib or vemurafenib was allowed. The distribution of patients entered into each cohort and the numbers of patients who had progressed following BRAF inhibitor therapy in each cohort is shown below in Figure.

Figure 17: NO25395 – Cohort Enrollment



Notes: Dose escalation scheme for cobimetinib 21 days on/7 days off (21/7) and continuous (28/0) dosing.

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Numbers (n) indicate patients assigned to each cohort and numbers in parentheses are patients who progressed on vemurafenib/patients who had never received a BRAF inhibitor. Red boxes show cohorts in which dose-limiting toxicities were identified. Dotted outlines indicate cohorts that were expanded.

Source: Ribas A, et. al. Lancet Oncology 2014;15:953-65[26]

The efficacy endpoint for the NO25395 trial was confirmed overall response rate as assessed by study investigators using RECIST v. 1.1. Responses were not independently reviewed. Response rates for patients in all cohorts combined by prior BRAF inhibitor exposure is shown below in Table 28. The confirmed overall response rate (ORR) among BRAF inhibitor naïve patients was 87% (95% CI: 77%, 94%) with complete responses observed in 6 (10%) patients. The median duration of response was 12.5 months (95% CI: 9.7, NE months). The ORR among patients who had progressed following treatment with a BRAF inhibitor was 15% (95% CI: 8%, 26%). All responses were partial responses. In the 10 patients who had an objective response, the median time duration of response was 6.7 months (95% CI: 4.9, NE months).

Reviewer's comment: Data from the NO25395 suggests that the combination of vemurafenib plus cobimetinib has little activity in patients who have progressed following treatment with a BRAF inhibitor

Table 28: NO25395 – Objective Responses as Assessed by Study Investigators

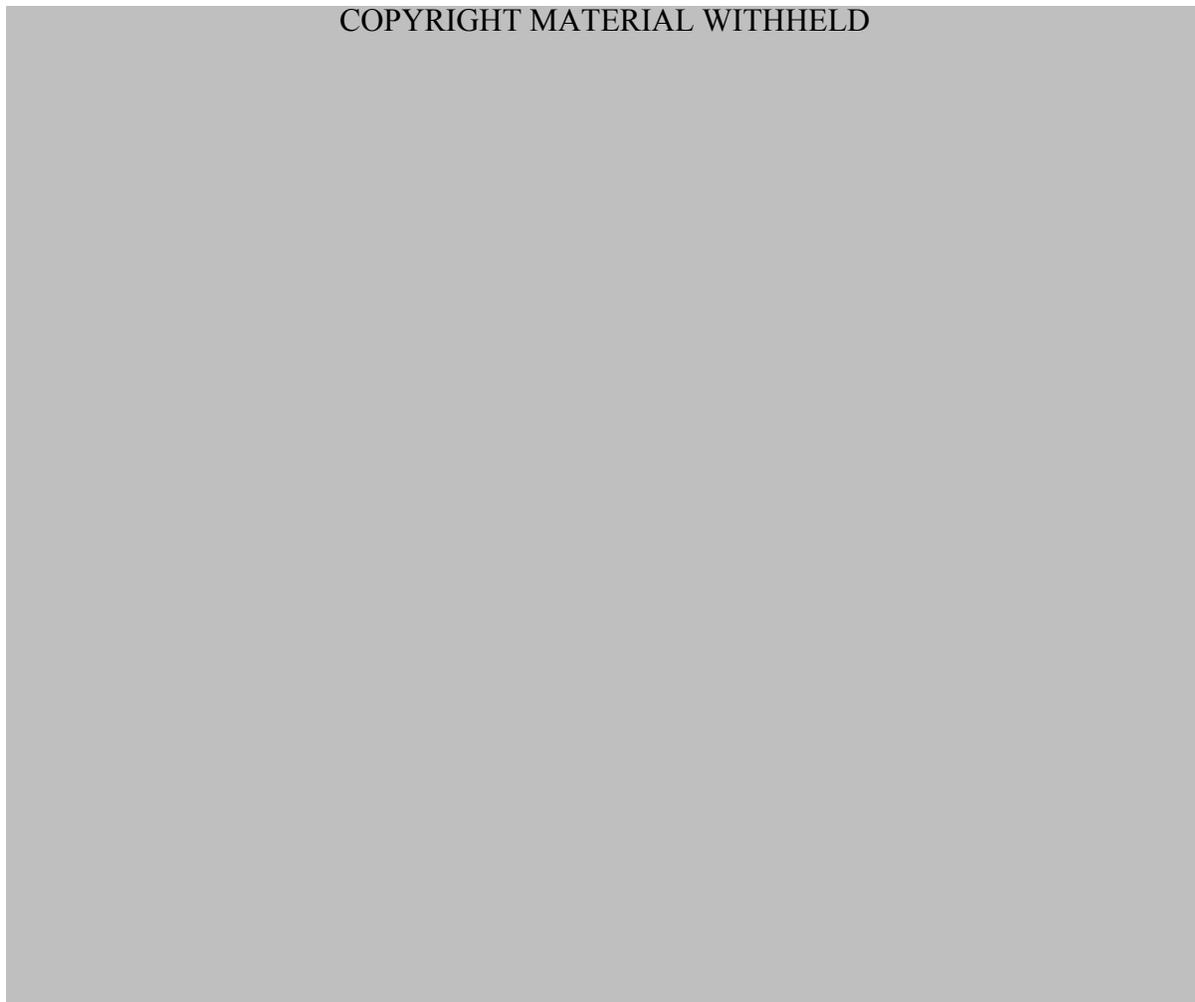
	Prior BRAFi (N=66)		BRAFi Naïve (N=63)	
	n	%	n	%
Patients with objective response	10	15%	55	87%
95% Confidence Interval				
Complete response	0	-	6	10%
Partial response	10	15%	49	78%
Stable disease	28	42%	6	10%
Progressive Disease	24	36%	2	3%
Not assessable	4	6%	0	-

*Source: NO25395 Clinical Study Report, page 168

^a95% DI for response rate was computed using Blyth-Still-Casella method.

^bPost-baseline tumor assessment was performed prior to the minimum required 6-week interval .

Figure 18: NO25395 – Best Change from Baseline in Target Lesions in Patients with Prior BRAF Inhibitor Therapy (A) and BRAF Inhibitor Naïve Patients (B)



Source: Ribas A, et. al. Lancet Oncology 2014;15:953-65[26] and NO25395 Clinical Study Report, page 169-170

Reviewer's comment: While the waterfall plot shows an interesting response, FDA considers this type of analysis to be exploratory in assessing anti-tumor activity as only target lesions are considered in the assessment and a minimum durability of response is not required.

7 Review of Safety

Safety Summary

This review of safety focused primarily on assessing the safety of cobimetinib when administered with vemurafenib and in defining the safety profile of cobimetinib. The review focused on data from the GO28141 trial, the single randomized trial submitted by the Applicant to support the safety of cobimetinib in combination with vemurafenib which composed 80% of the Integrated Summary of Safety (ISS) and represented 88% of patients treated with the proposed dose and schedule. The size of the safety data base was sufficient to characterize the safety profile of cobimetinib when used in combination with vemurafenib and was sufficient to isolate the effect of cobimetinib when added to vemurafenib. The GO28141 was a multicenter, international, randomized (1:1) active treatment, placebo-controlled trial of 495 patients with previously untreated, unresectable or metastatic BRAF V600 mutation-positive melanoma, as identified by the cobas 4800 BRAF V600 mutation test. Patients received vemurafenib 960 mg PO BID on Days 1-28 in combination with cobimetinib 60 mg PO QD (Vem/Cobi; N= 246) or a matched placebo (Vem/Placebo; N=247). Cobimetinib/Placebo was administered on Days 1-21 of each 28 day cycle (i.e., with 7 days off therapy).

The median duration of exposure to cobimetinib/placebo was 267 days (range 4-563 days) in the Vem/Cobi treatment group and 173 days (range: 5-515 days) in the Vem/Placebo treatment group. The median duration of exposure to vemurafenib was 279 days (range 4-563 days) in the Vem/Cobi treatment group and 175 days (range 5-516 days) in the Vem/Placebo arm. The most common reason for treatment discontinuation in both study arms was disease progression. Forty-five percent of Vem/Cobi treated patients and 35% of Vem/Placebo treated patients required a dose modification or interruption during treatment due to an adverse event. The AEs which most commonly resulted in a reduction/interruption of cobimetinib/placebo were: gastrointestinal disorders (diarrhea: 9% vs. 4%; vomiting: 6% vs. 5%; and nausea: 5% vs. 4%), rash (rash, unspecified: 5% vs. 6%; and rash, maculo-papular: 5% vs. 4%), pyrexia (6% vs. 3%), increased blood CPK (5% vs. 1%), and chorioretinopathy (7% vs. 0%). Fifteen percent of Vem/Cobi treated patients and 8% of Vem/Placebo treated patients discontinued both study drugs due to an adverse event (AE). The most common adverse events leading to discontinuation of both study drugs included: liver function test abnormalities (AST: 2% vs <1%; ALT: 2% vs. < 1%, and GGT: 2% vs. 1%), rash (2% vs <1%), pyrexia (1% vs 0), and retinal detachment (1% vs. 0).

Overall, the most frequent ($\geq 20\%$) adverse reactions among patients who received cobimetinib with vemurafenib were: gastrointestinal [diarrhea (60%), nausea (41%) vomiting (24%), rash (rash, unspecified, generalized, macular, maculo-papular and morbilliform) (55%) photosensitivity reaction (46%), arthralgia (36%), fatigue (34%), increased blood creatinine phosphokinase (32%), pyrexia (28%), and elevated alanine aminotransferase (25%) and aspartate aminotransferase (23%).

Adverse reactions which occurred in $\geq 20\%$ of patients with a higher frequency (between arm difference $\geq 5\%$, all CTCAE grades or $\geq 2\%$ CTCAE grades 3-4) in patients treated with cobimetinib in addition to vemurafenib compared to vemurafenib alone included: diarrhea (60% vs. 31%), nausea (41% vs. 25%), vomiting (24% vs. 13%), photosensitivity reaction (45% vs. 35%), increased blood creatinine phosphokinase (32% vs. 3%), pyrexia (28% vs. 23%), elevated alanine aminotransferase (25% vs. 18%) and aspartate aminotransferase (23% vs. 18%).

Serious adverse events (SAEs) were more common among patients who received vemurafenib with cobimetinib than among patients who received vemurafenib alone (35% vs. 26%) as were CTCAE Grade 3-4 AEs (28% vs. 22%). The most common ($\geq 5\%$) Grade 3-4 adverse reactions among patients receiving cobimetinib with vemurafenib included diarrhea (7% vs. 1%), increased blood creatinine phosphokinase (11% vs. 0%), elevated alanine aminotransferase (11% vs. 6%) and aspartate aminotransferase (9% vs. 2%), and basal cell carcinoma (5% vs. 2%).

The following were adverse events of special interest:

New Primary Malignancies:

- c. Cutaneous Malignancies: A lower rate of cutaneous squamous cell carcinoma (cusCC)/keratoacanthoma (KA) (6% and 19%) and of second primary melanoma (1% and 2%) were seen among patients treated with Vem/Cobi compared to patients treated with Vem/Placebo. A higher rate of basal cell carcinoma was seen in the Vem/Cobi treatment group compared to the Vem/Placebo group (4% and 2%). The median time to detection of basal cell carcinoma was 4 months (range: less than 1 to 13 months), the median time to detection of first cusCC/KA was 3 months (range 1-8 months), and the median time to detection of second melanoma was 9.4 months (range: 7-12 months).
- d. Non-Cutaneous Malignancies: there were two patients with non-cutaneous malignancies in the COTELLIC plus vemurafenib arm (transitional cell carcinoma: n=2) and 4 patients with non-cutaneous malignancies in the vemurafenib arm (mucinous breast carcinoma: n=1; adenocarcinoma of the colon: n=1; Genitourinary tract neoplasm: n=1; Kaposi's sarcoma: n=1).

Hemorrhage: The incidence of hemorrhage (all grades) was 10% in patients receiving Vem/Cobi and was 6% in patients receiving Vem/Placebo. Grade 3-5 hemorrhages occurred in 1% of patients receiving Vem/Cobi and in 0.4% of patients receiving Vem/Placebo. Cerebral hemorrhage occurred in 1% of patients receiving Vem/Cobi and in none of the patients receiving Vem/Placebo. GI tract hemorrhage (3% vs 1%), reproductive system hemorrhage (2% vs 1%), and hematuria (2% vs 1%) also occurred at a higher incidence in patients receiving Vem/Cobi compared to

patients receiving Vem/Placebo. However, there were no CTCAE Grade 4 or 5 hemorrhagic events in either arm.

Cardiomyopathy: Decreased left ventricular ejection fraction (LVEF) of Grade 2 or 3 detected by serial assessment using ECHO/MUGA was reported in 64 (26%) patients receiving Vem/Cobi and in 47 (19%) patients receiving Vem/Placebo. No Grade 4 or 5 events were reported. Median time to first onset of LVEF decrease was 4 months (range 1 to 7 months) in patients receiving Vem/Cobi. Two patients with symptomatic LVEF decrease required permanent discontinuation of cobimetinib; the remaining patients required dosing interruption or decrease.

Serious Skin Toxicity: The overall incidence of skin and subcutaneous tissue disorders was 85% among patients treated with Vem/Cobi and 87% among patients treated with Vem/Placebo. Grade 3-4 skin and subcutaneous tissue adverse reactions occurred in 60 (24%) patients treated with Vem/Cobi and in 47 (19%) patients treated with Vem/Placebo. Photosensitivity reactions (46% vs. 35%) and acneiform dermatitis (16% vs. 11%) were more common among patients in the Vem/Cobi treatment group. Rash (rash, unspecified, generalized, macular, maculopapular and morbilliform) (55% vs. 53%), pruritis (19% vs. 19%), and erythema (10% vs. 13%) occurred with a similar frequency in both arms. The median time to onset of Grade \geq 3 skin rash was 15 days (range: 3 to 125 days). Skin and subcutaneous adverse reactions resulted in hospitalization in 10 (4%) patients treated with Vem/Cobi and included one patient diagnosed with DRESS and one patient thought to have early Steven's Johnson Syndrome.

Ocular toxicity: Chorioretinopathy (13% vs. <1%), retinal detachment (9% vs. <1%), and blurred vision (10% vs. 2%) occurred more frequently among patients treated with Vem/Cobi than in patients treated with Vem/Placebo. Median time to first onset of serous retinopathy events was 1 month (range 0-9 months). The median duration of serious retinopathy was 5.7 months (range .2 to 16.4). Serous retinal events were reported as resolved in 41% patients following cobimetinib dose interruption or reduction. One patient in each arm developed retinal vein occlusion.

Hepatotoxicity: The incidences of Grade 3 or 4 liver test abnormalities among patients receiving Vem/Cobi compared to patients receiving Vem/Placebo were: alanine aminotransferase (11% vs. 6%), aspartate aminotransferase (7% vs 3%), total bilirubin (2% vs. 1%) and alkaline phosphatase (7% vs 3). One patient treated with Vem/Cobi met Hy's Law criteria. One additional patient met the criteria for Hy's Law but interpretation of the event was confounded by concomitant medications rarely causing hepatotoxicity.

Serum Creatinine Kinase (CK) Elevations/Musculoskeletal Adverse Reactions: CK elevation over baseline occurred in 59% of patients treated with Vem/Cobi and in 9%

of patients treated with Vem/Placebo and Grade 3-4 CK elevation over baseline occurred in 10% of patients treated with Vem/Cobi and in <1% of patients treated with Vem/Placebo. Rhabdomyolysis (defined as serum CK increase of more than 10 times the baseline value with a concurrent 1.5 –fold or greater increase in serum creatinine above baseline value) occurred in eight (3%) patients treated with Vem/Cobi and in one (<1%) patient treated with Vem/Placebo. Two additional patients (one in each treatment arm) were reported to have rhabdomyolysis but did not meet this definition. However, musculoskeletal adverse reactions occurred less frequently among patients treated with Vem/Cobi than among patients treated with Vem/Placebo (All Grades: 51% vs. 61%; Grade 3-4 6% vs.10%) and resulted in hospitalization in 2% of patients in each study arm. Arthralgias (36% vs. 40%), myalgias (11% vs. 12%), and extremity pain (10% vs. 14%) occurred less commonly among patients treated with Vem/Cobi than with Vem/Placebo.

Photosensitivity: Photosensitivity was reported in 47% of patients receiving COTELLIC plus vemurafenib: Grades 1 or 2 events occurred in 43% and the remaining 4% were Grade 3 events. Median time to first onset of photosensitivity events of any grade was 1 month (range 0-14 months). Ninety-five percent of patients with photosensitivity adverse reactions were managed without a change in cobimetinib or vemurafenib.

No differences were noted in the safety profile of vemurafenib used in combination with cobimetinib in patient subsets defined by age, gender or BRAF V600 mutation subset.

Ocular toxicities were inadequately assessed in the GO28141 (see the FDA ophthalmology consult review for details). Post-marketing trials to delineate the risk are recommended. The reviewer concurs with the recommendation of the FDA Clinical Pharmacology reviewer that drug-drug interaction studies be conducted post-marketing.

This reviewer does not recommend a REMS based on the information provided in the submission

7.1 Methods

The ISS database is comprised of safety data from two trials:

- GO28141 (n=495 patients) is a multicenter, international, double-blind, randomized active-controlled trial of previously untreated patients with BRAF V600 mutated, unresectable Stage IIIc/IV melanoma. All patients from this trial received the proposed marketed dose of vemurafenib 960 mg po BID D 1-28

either with cobimetinib 60 mg po QD or matched placebo on Days 1-21 of a 28-day cycle (i.e., 21 days on and 7 days off schedule). The clinical study report, case report forms, clinical narratives concerning patients experiencing death on study, serious or Grade 3 or 4 adverse events, raw safety data sets and safety analysis datasets were submitted with the application for review. Patients from the GO28141 represented 80% of the ISS.

- NO25395 (n= 129 patients) is an open-label, dose-escalation/expansion trial of patients with BRAF V600-mutated unresectable Stage IIIc/IV melanoma. Patients could have been previously untreated or could have progressed recently following treatment with a BRAF inhibitor. Patients were treated at cobimetinib doses ranging from 60 to 100 mg in combination with doses of vemurafenib of 720 and 960 mg and with three different dosing schedules (21 days on/7 days off therapy; 28 days on/0 days off therapy; 14 days on/14 days off therapy) (Figure 17). Of the 129 patients enrolled on the trial, 66 patients (39 BRAF inhibitor naïve; 27 patients who had progressed on a BRAF inhibitor) were treated with the proposed marketed dosage of the combination. The clinical study report, case report forms, clinical narratives concerning patients experiencing death on study, serious or Grade 3 or 4 adverse events, raw safety data sets and safety analysis datasets were submitted with the application for review.

Data from a third trial, MEK4952g (n=115 patients) an open-label, dose escalation/expansion trial enrolled patients with advanced solid malignancies who were treated with cobimetinib as a single agent. This is the only trial exploring the safety of cobimetinib as a single agent. The clinical study report and safety narratives concerning patients experiencing death on study, serious or Grade 3 or 4 adverse events were submitted with the application. Data sets from this trial were not provided.

The review of safety is focused primarily on the GO28141 trial as this is the only trial which is blinded and has a comparator arm submitted by the Applicant to support the safety of cobimetinib used in combination with vemurafenib. Data from the NO25395 is not pooled because of the variation in the dose and schedule of Vem/Cobi administered, and because of differences in the definition of adverse events of special interest. An analysis of common adverse events reported in the NO25395 is presented separately for comparison and deaths and serious adverse events from this trial are reviewed with reference to the subset of 39 BRAF-inhibitor naïve patients who received the proposed dose and schedule of Vem/Cobi. Relevant findings are reported in the relevant sections of the review.

Assessment of Data Quality for Safety Analysis in GO28141

As noted in section 3.1, the overall quality of the submission was judged to be adequate for review. The Study Data Tabulation Model (SDTM) datasets (i.e., raw datasets) were used as sources for the analysis datasets. The following data cutoff dates were agreed to during the pre-submission negotiations:

Analysis	Data cut-off date	Database lock
Primary analysis	May 9, 2014	July 10, 2014
90-day safety update	September 19,2014	November 20, 2014

For the original submission (NDA 206192/001, December 11, 2014), the DM, DS, EX, AE, LB and VS SDTM datasets were compared to the corresponding analysis datasets. Only minor discrepancies were noted reflecting data excluded based on the May 9, 2014 data cutoff date.

The FDA clinical review of safety included an audit of AE case report forms as well as an assessment of the coding of AE verbatim terms to MedDRA preferred terms (PT) to assess the completeness and verify the accuracy of the raw AE datasets. In an audit of 5% of the GO28141 trial population, minor differences between the information captured on the case report forms and that included in the AE datasets. These were primarily due to the occurrence of the event after the data cutoff date of May 9, 2014. In addition, the review audit included an assessment of the Applicant's mapping of AE verbatim terms to MedDRA PTs for all 3314 verbatim terms in the GO28141 raw AE dataset. A manual assessment of 371 verbatim terms which could not be matched to MedDRA preferred terms was conducted. This manual assessment revealed that the MedDRA preferred terms captured in the analysis datasets adequately represent the verbatim terms in the case report forms in nearly all cases

Safety Analysis Population in GO28141

As detailed in Section 3.1 of this review, in the original NDA submission, Genentech reported that 10 patients in the ITT study population did not receive the randomized treatment. Two patients, one in each treatment group, received no study treatment. Eight patients randomized to receive Vem/Placebo were identified as having received one or more doses of cobimetinib and were therefore included in the Vem/Cobi group for the safety analysis. These patients were enrolled at seven different study sites. At the time of the 90-day Safety update, Genentech reported that as a result of further on-site monitoring and drug kit reconciliation at the time of the data lock, it was subsequently determined only one of these eight patients did, in fact, receive cobimetinib. This exposure resulted from a drug dosing error. This patient remained with the Vem/Cobi group for the safety analysis. In the remaining seven patients errors in data transcription resulted in an incorrect test kit number being entered into the electronic case report form. None of these seven patients received cobimetinib. For the safety analysis, these misclassified patients were returned to the Vem/Placebo group.

In a May 22, 2015 response to FDA's information request dated May 19, 2015, Genentech further reported that an additional 11 patients randomized to receive Vem/Cobi had received one or more doses of placebo. As a result of further site monitoring and drug kit reconciliation at the time of the data lock, it was subsequently determined that four of these patients had received placebo due to a pharmacy error. However, since these four patients had also received one or more doses of cobimetinib, these four patients remained in the Vem/Cobi group for the safety analysis. The misclassification of the remaining seven patients resulted from a transcription error of the test kit number into the electronic case report form. None of these patients had actually received placebo. As a result, they remained classified with the Vem/Cobi group for the safety analysis. The reclassification of these patients is summarized in Figure 19 below. FDA requested that Genentech submit the data sets used to generate the 90-day Safety Update report (90D Safety Update) in order to verify that data in the original submission had not undergone substantial change after the data lock in response to data queries.

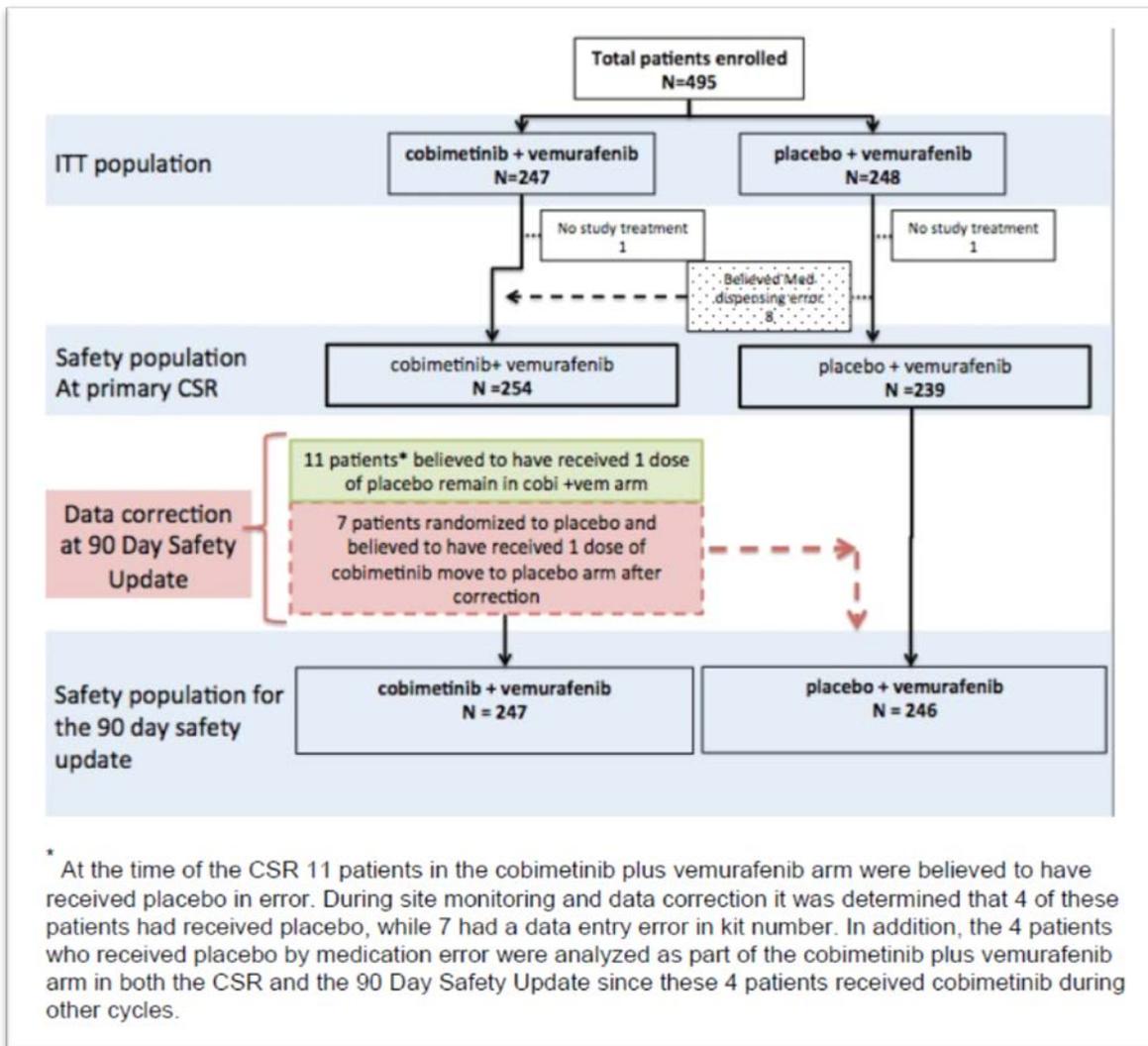
On June 15, 2015, Genentech submitted an amendment to the NDA (NDA 206192/0036) which contained the following analysis datasets used to generate the 90-D Safety Update: adae.xpt, adeg.xpt, adex.xpt, adlb.xpt, adv.xpt, and adsl.xpt as well as the corresponding SDTM datasets. It is noted that updates were not provided for all datasets in the original submission. Based on a comparison between the original datasets and the datasets used to generate the 90-D Safety Update, the FDA reviewer was able to: 1) verify that there were no systematic changes made to data in the 90-D Safety Update and 2) verify the Applicant's claim that changes in group assignment at the time of the 90-D Safety Update did not materially change the reported safety findings.

Reviewer comment: Submission of the SDTM and ADaM datasets for verification of data in the 90D Safety Update was considered a major amendment to this application and the goal date was extended by three months to provide time for a full review of the submission. The revised goal date was extended to November 11, 2015.

Since the 90-D Safety Update provided approximately 3 months of additional follow-up for this relatively small safety population which was felt to be advantageous, FDA decided to base the safety evaluation on the data from the 90D Safety Update, where data was available, and to incorporate this data into labeling. The 90D safety update increased the median durations of exposure to both cobimetinib and vemurafenib by approximately 90 days in the cobimetinib plus vemurafenib group and by 20 days in the placebo plus vemurafenib group.

Reviewer comment: For all tables and figures below, analyses based on data from the 90-D Safety Update reflect a cutoff date of September 19, 2014. All tables and figures based on data from the original submission reflect a cutoff date of May 9, 2014.

Figure 19: GO28242 - A Schematic Summary of Reclassifications Within the Safety Analysis Population Reflecting Correction of Data Entry Errors at the 90 Day Safety Update



Source: NDA 206191/0032(33) 5/22/2015; Response to Request for Information dated 5/22/2015

The number of patients in the intent-to-treat population, the safety population and in the EKG evaluable analysis population is shown in below.

Table 29: GO28141 - Analysis Populations (Data Cutoff Date: 19 SEP 2014)

Analysis Population	Vem/Placebo	Vem/Cobi	All Patients
Intent-to-treat (ITT)	248	247	495
Safety evaluable patients, Original Submission*	239	253	493
Safety evaluable patients, Corrected for Actual Treatment Status**	246	247	493
EKG Evaluable	238	230	468

*One patient in each group received no treatment; eight patients in Vem/Placebo group classed as Vem/Cobi

**One patient in each group received no treatment; only one Vem/Placebo patient actually received Vem/Cobi
NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adsl.xpt

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

See section 7.1 above.

7.1.2 Categorization of Adverse Events

The Applicant mapped and coded verbatim adverse event terms for the GO28141 trial using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.0. Adverse events were characterized using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0. Adverse events of special interest were defined in the individual study protocols as shown below in Table 30.

Table 30: Adverse Events of Special Interest as Defined by the Applicant in Individual Study Protocols

Pivotal Study GO28141 ^a	Study NO25395 ^a	Study MEK4592g ^b
Any RVO	Grade ≥ 1 RVO	Grade ≥ 1 RVO
Any retinal detachment, retinal pigment epithelium detachment, neurosensory retinal detachment, or CSCR	Grade ≥ 2 visual disturbances (including serous retinopathy)	Grade ≥ 2 visual disturbances (including serous retinopathy)
Any cutaneous primary malignancy, including SCC, KA, BCC, or new primary melanoma	cuSCC of any grade	SCC of the skin of any grade
Grade ≥ 3 QTc interval prolongation	Grade ≥ 3 QTc interval prolongation	Grade ≥ 3 QTc interval prolongation
Grade ≥ 3 photosensitivity	Grade ≥ 3 photosensitivity	Grade ≥ 3 photosensitivity
Grade ≥ 3 elevations in AST, ALT, serum bilirubin, GGT, or cases of elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Section 5.3.5.6 in Protocol version 4	Grade 4 elevations in liver laboratory tests ^c (serum ALT, AST, and/or bilirubin)	Grade 4 elevations in liver laboratory tests ^c (serum ALT, AST, and/or bilirubin)
Grade ≥ 3 rash	N/A	Grade ≥ 3 rash
Cardiac events/Grade ≥ 2 LVEF reduction	N/A	N/A

ALT = alanine transaminase; AST = aspartate transaminase; BCC = basal cell carcinoma; CSCR = central serous chorioretinopathy; CPK = creatine phosphokinase; cuSCC = cutaneous squamous cell carcinoma; GGT = gamma-glutamyltransferase; KA = keratoacanthoma; LVEF = left ventricular ejection fraction; QTc = QT interval corrected; RVO = retinal vein occlusion; SCC = squamous cell carcinoma. N/A = not defined.

^a MedDRA 16.1 AEGTs were utilized to capture potential events for each event category for the pivotal Study GO28141 and Study NO25395, and MedDRA 16.0 AEGTs were used capture potential events for Study MEK4592g.

^b AESI category was not pre-defined in the protocol for Study MEK4592g. AESIs were defined differently across the study protocols of NO25395 and MEK4592g. In order to perform a consistent evaluation of AESI across both studies, standardized MedDRA 16.0 adverse event preferred terms (group terms) were utilized to capture potential events for each event category based on Study NO25395.

^c Elevation in liver laboratory tests was listed as elevation in liver function tests in the original data outputs.

*Provided by the Applicant as Table 5, Section 2.7.4 Summary of Clinical Safety Section 1.1.2.4 p.29

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The pooled ISS dataset including all patients exposed to cobimetinib (any dose and schedule) in combination with vemurafenib (any dose and schedule) is used only to compare common adverse events between the GO29141 and the ISS

For purposes of all other safety analyses, data from the NO25395 is not pooled with data from the GO29141 because of the open-label nature of the NO25395 trial, the variation in the dose and schedule of Vem/Cobi administered in the two trials, and because of differences between these trials in the definition of adverse events of special interest. An analysis of common adverse events reported in the NO25395 is presented separately for comparison and deaths and serious adverse events from this trial are reviewed with reference to the subset of 39 BRAF-inhibitor naïve patients who received the proposed dose and schedule of Vem/Cobi. Relevant findings are reported in the relevant sections of the review.

The per-patient incidence of treatment emergent adverse events (TEAE) reported (all NCI CTCAE Grades combined) that occurred in $\geq 10\%$ of patients in either database regardless of assessed relationship to the study drugs is shown below in Table. Overall, the incidences of the most common TEAEs occurring on the GO28141 and in the ISS database were similar suggesting that common TEAEs are reflected in the safety database of the GO28141.

Table 31: Per-Patient Incidence of Common Adverse Events (All Grades) Regardless of Relationship to Study Drug That Occurred in $\geq 10\%$ of Patients in the Integrated Safety Population (Data Cutoff Date: 19 SEP 2014)

MedDRA SOC/PT	Vem/Cobi Group	
	GO28141 (n=247) (%)	ISS (n=376) (%)
GASTROINTESTINAL DISORDERS		
DIARRHEA	60%	60%
NAUSEA	41%	41%
VOMITING	24%	25%
ABDOMINAL PAIN	10%	13%
CONSTIPATION	10%	11%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
RASH	40%	39%
PHOTOSENSITIVITY REACTION	33%	32%
PRURITUS	20%	19%
ALOPECIA	15%	13%
RASH MACULO-PAPULAR	15%	15%
DERMATITIS ACNEIFORM	14%	15%
DRY SKIN	14%	13%
HYPERKERATOSIS	11%	9%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
ARTHRALGIA	36%	31%
MYALGIA	11%	12%
METABOLISM AND NUTRITION DISORDERS		
DECREASED APPETITE	19%	20%
GEN DISORDERS AND ADMIN SITE CONDITIONS		
FATIGUE	35%	39%
PYREXIA	28%	27%
ASTHENIA	17%	13%
EDEMA PERIPHERAL	13%	17%
CHILLS	10%	13%
INVESTIGATIONS		
BLOOD CREATINE PHOSPHOKINASE INCREASED	33%	30%
ALANINE AMINOTRANSFERASE INCREASED	25%	23%
ASPARTATE AMINOTRANSFERASE INCREASED	24%	22%
GAMMA-GLUTAMYLTRANSFERASE INCREASED	19%	14%
BLOOD ALKALINE PHOSPHATASE INCREASED	15%	18%
BLOOD CREATININE INCREASED	14%	15%
INJURY, POISONING AND PROCEDURAL COMPL		
SUNBURN	14%	18%
NERVOUS SYSTEM DISORDERS		
HEADACHE	17%	17%
DYSGEUSIA	15%	11%
VASCULAR DISORDERS		

HYPERTENSION	15%	16%
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
ANAEMIA	13%	16%
EYE DISORDERS		
CHORIORETINOPATHY	13%	9%
BLURRED VISION	10%	-

Source: NDA206192/001(2)12/11/2014: 5.3.5.3:ISS adae.xpt; NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adae.xpt

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Among the 247 patients treated on the Vem/Cobi group, the median number of cobimetinib cycles received was 10 (range 1- 27 cycles), the median duration of cobimetinib exposure was 267 days (range: 4 to 563 days), and the median dose intensity of cobimetinib was 97% (range 25% to 108.2%) (Table 32). Among patients treated with Vem/Cobi, the median number of vemurafenib cycles received was 10 (range 1-21 cycles), the median duration of vemurafenib exposure was 279 days (range 9-563 days), and the median dose intensity of vemurafenib was 94% (range 23% - 103%). Among the 246 patients in the Vem/Placebo group, the median number of vemurafenib cycles received was 7 (range 1-18 cycles), the median duration of vemurafenib exposure was 175 days (range 5-516), and the median dose intensity of vemurafenib as 97% (range 39% - 114%) (Table 33).

Reviewer's comment: The addition of cobimetinib to vemurafenib did not appear to negatively impact the number of vemurafenib cycles or the duration of vemurafenib therapy. However, the addition of vemurafenib required a reduction in median dose intensity of vemurafenib delivered.

Table 32: GO28141 - Exposure to Cobimetinib or Placebo (Safety Population; Data Cutoff Date: 19 SEP 2014)

	GO28141 placebo + vemurafenib n=246	GO28141 cobimetinib + vemurafenib n=247	NO25395 cobimetinib + vemurafenib n=129	Integrated Safety Population n=376
Duration of Treatment Period (Days)				
Mean (SD)	205.8 (130.1)	243.4 (140.2)	312.9 (269.3)	267.3 (196.8)
Median	172.5	267	211	251.5
Min, Max	5 - 515	4 - 563	14 - 998	4 - 998
Number of Cycles Received				
Mean (SD)	7.7 (4.7)	9.1 (5.0)	11.5 (9.5)	9.9 (7.0)
Median	6.0	10.0	8.0	9.0
Min, Max	1 - 18	1 - 21	1 - 32	1 - 32
Average Dose Taken Per Day (mg/day)				
Mean (SD)	43.56 (7.17)	41.43 (9.30)	43.75 (7.78)	42.23 (8.86)
Median	45.21	44.06	44.89	44.47
Min, Max	18.2 - 64.0	11.6 - 60.0	17.3 - 68.3	11.6 - 68.3
Percent Dose Intensity				
Mean (SD)	92.62 (13.70)	87.12 (16.74)	92.78 (13.80)	89.07 (16.01)
Median	99	96.6	98.76	97.61
Min, Max	39.7 - 110.5	25.0 - 108.2	34.5 - 109.6	25.0 - 109.6

SD = standard deviation; Min = minimum; Max = maximum.

The safety update data cut-off dates for each study are: GO28141, 19 September 2014;
NO25395, 5 September 2014.

[1] Includes Partial or full cycles. A cycle is counted as long as a patient takes any amount of the study drug on Day 1 of a planned cycle.

Source: NDA206192/0036(37); 3/10/2015; Safety Update Report; page 25.

Table 33: GO28141 – Summary of Patient Exposure to Vemurafenib (Safety Population; Data Cutoff Date: 19 SEP 2014)

	GO28141 placebo + vemurafenib n=246	GO28141 cobimetinib + vemurafenib n=247	NO25395 cobimetinib + vemurafenib n=129	Integrated Safety Population n=376
Duration of Treatment Period (Days)				
Mean (SD)	210.3 (127.6)	253.1 (138.3)	312.0 (267.9)	273.3 (194.5)
Median	175.0	279	201	266.5
Min, Max	5 - 516	9 - 563	14 - 998	9 - 998
Number of Cycles Received				
Mean (SD)	7.7 (4.6)	9.3 (5.0)	11.3 (9.4)	10.0 (6.9)
Median	7.0	10.0	8.0	9.5
Min, Max	1 - 18	1 - 21	1 - 32	1 - 32
Average Dose Taken Per Day (mg/day)				
Mean (SD)	1638.23 (349.98)	1642.74 (329.37)	1570.85 (298.80)	1618.07 (320.64)
Median	1856.33	1813.33	1463.41	1750.99
Min, Max	746.6 - 2194.4	445.6 - 1981.1	727.9 - 1920.0	445.6 - 1981.1
Percent Dose Intensity				
Mean (SD)	85.32 (18.23)	85.56 (17.16)	91.05 (13.52)	87.44 (16.19)
Median	96.69	94.44	97.3	95.7
Min, Max	38.9 - 114.3	23.2 - 103.2	47.9 - 123.3	23.2 - 123.3

SD = standard deviation; Min = minimum; Max = maximum.

The safety update data cut-off dates for each study are: GO28141, 19 September 2014; NO25395, 5 September 2014.

Source: [Integrated safety population/t_ex_vem.](#)

Source: NDA206192/0036(37); 3/10/2015; Safety Update Report; page 26.

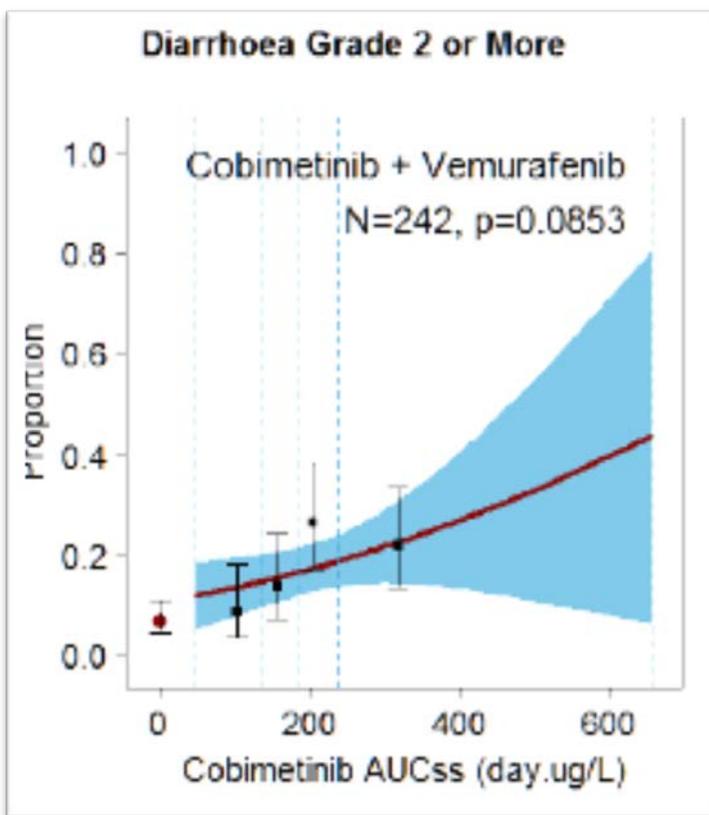
[1] Includes Partial or full cycles. A cycle is counted as long as a patient takes any amount of the study drug on Day 1 of a planned cycle.

7.2.2 Explorations for Dose Response

A trend for an increase in diarrhea with higher cobimetinib exposure was noted in the GO28141 trial (Figure 20). No other exposure – dose relationships were observed for

other safety endpoints. Please see the Clinical Pharmacology review for additional details.

Figure 20: GO28141 – Exposure - Dose Exploration for Diarrhea



Source: NDA 206192, FDA Clinical Pharmacology Review

7.2.3 Special Animal and/or In Vitro Testing

Please refer to the summary of pharmacology/toxicology in Section 4.3.

7.2.4 Routine Clinical Testing

Routine clinical monitoring of patients included monitoring of laboratory parameters, vital signs, and ECGs as detailed in Section 7.4.4. Based on a review of the safety findings the monitoring plan appears to be adequate.

7.2.5 *Metabolic, Clearance, and Interaction Workup*

See the summary of clinical pharmacology in Section 4.4.

7.2.6 *Evaluation for Potential Adverse Events for Similar Drugs in Drug Class*

As discussed in Section 2.4, based on prior safety experience with BRAF inhibitors, MEK inhibitors, and the combined use of BRAF and MEK inhibitors, the following adverse events were anticipated with the combination of cobimetinib and vemurafenib:

- Major hemorrhagic events
- Venous thrombosis and pulmonary embolism
- Cardiomyopathy, LVEF reduction
- Ocular toxicities: RPED, uveitis, iritis
- Serious febrile reactions, pyrexia
- New primary malignancies, cutaneous and non-cutaneous, new primary melanoma
- Hyperglycemia

Adverse events of special interest were defined for each study as described in Table. Routine monitoring included periodic physical exam with recording of vital signs, routine laboratory exams and monitoring for adverse events as described in Table. Intensified monitoring was conducted to screen for 1) the development of cutaneous and non-cutaneous malignancies, 2) cardiomyopathy/left ventricular dysfunction and 3) ocular toxicities.

Monitoring for Cutaneous and Non-cutaneous Malignancies

Screening for Dermatologic Malignancies

A complete history of prior dermatologic interventions and cutaneous squamous cell carcinoma risk factors were collected at baseline. Complete evaluation of the skin by a dermatologist was conducted at baseline and at every third treatment cycle thereafter. The dermatologic evaluation included:

- Assessment of dermatologic medications and cusCC risk factors (i.e., radiation therapy, sun exposure, immunosuppression, prior cusCC, use of tanning beds, precursor lesions and phototherapy for psoriasis)
- Skin examination for cusCC, BCC, actinic keratosis, KA, and/or second primary melanoma.
- Mapping of any suspicious lesions that may represent cusCC, BCC, actinic keratosis, KA, and/or second primary melanoma.
- Biopsy and/or excision of any suspicious lesions identified at baseline and while on study. Available specimen block/sections were centrally reviewed for confirmation of diagnosis and further molecular characterization.

- Treatment of identified skin neoplasms or conditions per local standards of care
- A final dermatologic examination was performed 6 months after discontinuation of study treatment.

Screening for Non-Cutaneous Primary Malignancies

Head and Neck Examination

The complete physical examination performed at the beginning of every cycle included examination of HEENT and neck (including lymph nodes) by the investigator to monitor for the occurrence of SCC in the upper aerodigestive tract.

Lung Examination

The routinely scheduled chest CT/MRI scan performed as part of the tumor assessment was used for lung SCC surveillance while on study treatment and 6 months after end-of-study-treatment visit.

Anal Examination

Visual inspection and digital examination of the anus and anal canal was performed at screening, discontinuation of study treatment, 6 months after study treatment discontinuation, and at other times as clinically indicated to monitor for anal SCC.

Gynecological Examination

All female patients received a pelvic examination including visual inspection of the uterine cervix and Pap smear at screening, discontinuation of study treatment, 6 months after study treatment discontinuation, and at other times as clinically indicated to monitor for the occurrence of cervical carcinoma.

Monitoring of Cardiac Function

Because vemurafenib is associated with concentration-dependent QTc prolongation, all patients received ECG monitoring at study prescribed time points (Table 67). Triplicate digital ECG recordings were obtained within approximately 2–5 minutes at each specified time point. The average of the three readings was used to determine ECG intervals (e.g., PR, QT).

All patients underwent evaluation of left ventricular ejection function (LVEF) either by echocardiography (ECHO) or multiple gated ejection acquisition scan MUGA. Assessments were done at baseline and every three cycles thereafter. Any patient who developed clinical signs or symptoms suspicious of cardiac failure underwent an LVEF assessment.

Screening for Ocular toxicity

All patients underwent a baseline ophthalmologic examination to evaluate for evidence of retinal pathology that is considered a risk factor for neurosensory retinal detachment, RVO or neovascular macular degeneration. Patients with risk factors for RVO (elevated serum cholesterol, hypertriglyceridemia, hyperglycemia, hypertension, and glaucoma) were excluded from study. Ophthalmologic examinations were performed by a qualified ophthalmologist at baseline and every three cycles thereafter, more frequently if clinically indicated. No post-study follow-up exam was performed if the most recent prior exam was normal and there were no clinical signs/symptoms. Baseline and surveillance ophthalmologic examinations included visual acuity testing, intraocular pressure measurements by tonometry, slit lamp ophthalmoscopy, indirect ophthalmoscopy, and spectral domain optical coherence tomography, or if not available, time-domain OCT.

Following an ophthalmologic evaluation, a report was prepared by the ophthalmologist in his or her local language which was submitted to the study investigator. Data from this report were transcribed into the CRF by study site staff and the reports were retained within the patients study records at the local site. OCT scans were not retained for primary review and were not retrievable in all but a small subset of patients in the GO28141.

Reviewer's comment: During the development of cobimetinib, ophthalmic examinations were not performed in a uniform manner, and the terminology used to describe clinical findings was inconsistent. Please see the FDA ophthalmologist consult review for details.

7.3 Major Safety Results

In the 90D Safety Update for the GO28141, 7738 adverse events were reported in 484 patients, 3515 events among 240/246 (98%) Vem/Placebo treated patients and 4223 events among 244/247(99%) Vem/Cobi treated patients.

7.3.1 Deaths

Deaths reported on the GO28141 trial as of the cut-off date of September 19, 2014 are shown below in Table. In both study groups the primary cause of death was reported to be disease progression.

Table 34: GO28141 - Subject Follow-up Status and Cause of Death (Safety Population/Data Cutoff Date: 19 SEP 2014)

Number of Patients	Vem/Placebo (n=246)		Vem/Cobi (n=247)	
	n	%	n	%
All Deaths	80	(32)	62	(25)
Primary cause of death				
Disease progression	76	(31)	54	(22)
SAE	2	(1)	5	(2)
Other	2	(1)	3	(1)
Time to death from last dose				
≤ 30 days	26	(11)	13	(5)
> 30 Days	54	(22)	49	(20)

Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adae.xpt, adsl.xpt, clinical narratives

In the GO28141, Grade 5 adverse events were reported in 3 patients in the Vem/Placebo group and in 5 patients on the Vem/Cobi group at the time of the September 19, 2014 data cutoff date. These are shown below.

Table 35: GO28141 – Grade 5 Adverse Events (Safety Population, Data Cutoff Date: 19 SEP 2014)

MedDRA SOC/PT	Vem/Placebo (n=246)		Vem/Cobi (n=247)	
	n	%	n	%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
DEATH (Unspecified)	0	-	1	(< 1) ²
CARDIAC DISORDERS				
CARDIAC ARREST	0	-	1	(< 1)
CARDIAC FAILURE	1	(< 1)	0	-
NERVOUS SYSTEM DISORDERS				
COMA	-	-	1	(< 1)
INFECTIONS AND INFESTATION				
PNEUMONIA	0	-	1	(< 1)
CLOSTRIDIUM DIFFICILE COLITIS	-	-	1	(< 1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
PULMONARY EMBOLISM	1 ¹	(< 1)	0	-
ATELECTASIS	1	(< 1)	-	-

Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adae.xpt, adsl.xpt, clinical narratives

¹Disease progression was the likely cause of death.

²The primary cause of death was reported as “Other”

The safety update (data cut-of date: September 19, 2014) reflected the following changes:

- Vem/Placebo: One patient originally classed as having Grade 5 Fatigue was reclassified as having progressive disease. One new Grade 5 adverse event of atelectasis was reported (patient 2400). The total number of patient deaths due to Grade 5 AEs in the Vem/Placebo group remained constant at 3 patients.
- Vem/Cobi: Three patients previously reported to have Grade 5 adverse events (2447: asthenia and fatigue, 2107: hemiparesis, and 2335: cerebral hemorrhage) were re-assessed. In patient 2447, the cause of death was originally reported as “Other”. Upon review, the two Grade 5 adverse events for patient 2447 were re-classified as Grade 3 asthenia and Grade 2 fatigue and not as reportable Grade 5 adverse events. The cause of death in this patient was assessed as likely related to disease progression. The cause of death for patients 2107 and 2335 were also reclassified as PD and not as reportable Grade 5 adverse events. At the time of the safety update, two new patients were reported to have experienced Grade 5 AEs (2376: coma and 2118: clostridium difficile colitis). Thus, after the safety update, 5 Grade 5 adverse events were reported in 5 patients in the Vem/Cobi group. These 5 patients are listed along with the FDA assessment in Table 36 below.

Reviewer’s comment: Patient 2335 was a 43year-old female patient diagnosed with Stage M1b with an ECOG performance status of short spindle cell melanoma of the lower extremity approximately 17 years prior to enrollment. The patient developed a Grade 3 retinal detachment on Study Day 5 which was confirmed by an ophthalmological exam. On this day, treatment with cobimetinib was permanently discontinued due to this event. Due to ongoing and worsening ocular findings, treatment with vemurafenib was discontinued on study day 47. No post-baseline assessments were performed. On study day 141, the patient was reported to have died possibly due to a cerebral hemorrhage. No autopsy was performed and no further details were provided. The cause of death was attributed to disease progression. Reviewer’s assessment: While the contribution of cobimetinib to the presumed event of cerebral hemorrhage cannot be ruled out, the onset of the event and subsequent death 136 days following the discontinuation of cobimetinib makes a causal association less likely.

Table 36: GO28141 – Grade 5 Adverse Events in Patients Treated with Vem/Cobi (Safety Update: Data Cutoff Date: 19 SEP 2014)

Patient ID	Age/Sex	COD	Last dose day	AE Onset Date	Death Day	Investigator’s Assessment	FDA Assessment
2025	74/M	Cardiac arrest	Cobi: 21 Vem: 100	100	100	Unrelated	Possibly Related

							confounders
2034	88/F	Pneumonia	50	57	68	Unrelated	Unrelated
2069	58/M	Unexplained Death	90	90	90	Unrelated	Possibly Related
2376	36/F	Coma	252	289	289	Unrelated	Possibly Related
2118	53/M	Clostridium difficile colitis	347	343	437	Related	Related

These 5 patients are further described in the narrative summaries below.

- 2025, a 74-year-old male patient diagnosed with M1c nodular melanoma on the back on 31-May-2012. The patient was randomized to study GO28141 on (b) (6) with an ECOG performance status of 0. Previous diagnostic procedures and treatment for melanoma included excisional, wide local excision, sentinel lymph node biopsy and lymphadenectomy of the left upper extremity. Concurrent conditions included hypertensive heart disease, depression/anxiety (since 2006), diabetes mellitus (since 2009), binocular mild lenticular opacity and palpable left axillary lymph node (both since 18-Apr-2013). Concomitant medications included nicergoline (since 2004), escitalopram oxalate (since 2006), insulin aspart, insulin (suspension), protamine zinc/insulin aspart (both since 2009), alprazolam (since 2010), naloxone hydrochloride/oxycodone hydrochloride (since 28-Mar-2013), aspirin and carvedilol (both since 19-Apr-2013). Treatment with vemurafenib 960 mg twice daily and cobimetinib 60 mg daily 21/7 schedule was started on (b) (6) (Study Day 1).

The patient's baseline LVEF as assessed by ECHO was 50%. On (b) (6) (Study Day 27), the patient's LVEF assessed by echocardiogram was 40%. The patient was diagnosed with Grade 2 decreased ejection fraction (non-serious). His blood pressure was 110/70 mmHg and pulse was 90 bpm. ECG revealed sinus rhythm and ventricular repolarization abnormalities.

Treatment with cobimetinib was permanently discontinued in response to a worsening (Grade 3) ejection fraction. The last dose of cobimetinib was administered on (b) (6) (Study Day 21). On (b) (6) (Study Day 56), treatment with vemurafenib was interrupted. On (b) (6) (Study Day 66), treatment with vemurafenib was resumed at the same dose of 960 mg. On (b) (6) (Study Day 70), the patient underwent a coronary angiography which showed triple vessel atherosclerotic obstructive disease and he was diagnosed with Grade 3 arteriosclerosis (non-serious). On (b) (6) (Study Day 74), the patient was started on treatment with clopidogrel, pantoprazole, atorvastatin, carvedilol, and nitroglycerin after the coronary angiography. Treatment with ongoing ramipril was maintained.

The investigator considered decreased ejection fraction to be related to cobimetinib and unrelated to vemurafenib. Concurrent illness was considered a possible etiological factor for the event of ejection fraction decreased. On (b) (6) (Study Day 111), the patient's wife reported that the patient died, probably due to cardiac arrest, on (b) (6) (Study Day 100). The investigator considered cardiac arrest to be unrelated to vemurafenib and cobimetinib.

Reviewer's comment: Despite significant underlying cardiac risk factors, the decrease in

LVEF is temporally related to the administration of cobimetinib/vemurafenib. The reviewer assesses the event to be possibly related to study drug.

- 2034, an 88-year-old female patients diagnosed with M1c nodular melanoma of the lower extremity on 16-May-2012 and randomized to study GO28141 on (b) (6). At screening, the patient's disease stage was M1c with an ECOG performance status of 0. Previous diagnostic procedures and treatment for melanoma included excisional biopsy of right lower extremity, wide local excision of right upper and lower extremity, lymphadenectomy of right pelvis and sentinel lymph node biopsy of right chest. Concurrent conditions included hypertension (since 12-Dec-1990) and retinal pigment epithelial atrophy (since 24-Apr-2013). Her concomitant medications included aspirin and verapamil hydrochloride (both since 12-Dec-1990). Treatment with vemurafenib 960 mg twice daily and cobimetinib 60 mg daily 21/7 schedule was started on (b) (6) (Study Day 1).

On (b) (6) (Study Day 56), the patient experienced Grade 2 asthenia, Grade 1, and Grade 1 pyrexia. She was treated with paracetamol for fever. On (b) (6) (Study Day 57), the patient was diagnosed with serious Grade 1 pneumonia, leading to hospitalization (diagnostic details were not provided). She received treatment with an unspecified medication and oxygen therapy at high pressure for pneumonia. Treatment with vemurafenib and cobimetinib was not changed as a result of this event. On (b) (6) (Study Day 68), the patient died due to pneumonia. It was reported that the patient had developed cardio-respiratory failure. It was unknown whether an autopsy was performed. The patient received last dose of cobimetinib (60 mg) on (b) (6) (Study Day 50) and vemurafenib (960 mg) on (b) (6) (Study Day 57). The investigator considered pneumonia to be unrelated to study medication.

Reviewer's comment: Based on the information provided in the CRF and narrative, the reviewer concurs that the event is likely a community acquired pneumonia and unlikely related to study drug.

- 2069, a 58-year-old male patient was diagnosed with M1c melanoma of the head on 08-May-2003 and was to study GO28141 on (b) (6). At screening, the patient's ECOG performance status was 0. Previous diagnostic procedures and treatment for melanoma included resection from right ear and right wide local excision (× 3), punch biopsy (× 2) and fine needle aspiration (sites unspecified). The patient also adjuvant received radiotherapy to the right ear canal (48 cGy; 20 fractions) from 24-Oct-2012 to 21-Nov-2012. Surgical history included surgery for kidney stones (date unknown). Concurrent conditions included diabetes, hypertension, hyperlipidemia (dates unknown), dry mouth and anorexia (both since 13-Nov-2012) and pain in left shoulder (since Jan-2013). His concomitant medications included pioglitazone, metformin, simvastatin and enalapril (start dates unknown) and omeprazole (since 03-Apr-2012) and glipizide (since Jun-2012). Treatment with vemurafenib 960 mg twice daily and cobimetinib 60 mg daily 21/7 schedule was started on (b) (6) (Study Day 1). On (b) (6) (Study Day 90), the patient was found dead. Reportedly, no crime or suicide was suspected. No autopsy was performed. The investigator considered death to be unrelated to vemurafenib and cobimetinib

Reviewer's comment: The patient was seen on D 86 for Cycle 4 D1 and was well at that time. Cobimetinib dosing was off from D 80 to D 86. When seen on D 86, pulse rate was 95 bpm, BP was 143/77, and ECOG PS was graded as 0. LVEF was reported to be 60% with no segmental wall motion abnormalities on the (b) (6) screening exam, 60% on (b) (6). The most recent QTcF was reported to be 383 msec on C3D15. Laboratory values were WNL. Underlying cardiac risk factors confound the assessment, however a possible association with study drug cannot be ruled out.

- 2376, a 36-year-old female patient who was diagnosed with M1c melanoma of the chest on 04-Mar-2013 and was enrolled on study GO28141 on (b) (6). At screening, the patient's ECOG performance status was 1. Previous diagnostic procedures and treatments for melanoma included excisional biopsy on the left side of chest. No other past medical/surgical history was reported. No concomitant medications were reported. Treatment with vemurafenib 960 mg twice daily and cobimetinib 60 mg daily 21/7 schedule was started on (b) (6) the last dose of cobimetinib (60 mg) and vemurafenib (960 mg) was administered on (b) (6) (Study Day 245) and (b) (6) (Study Day 252) respectively. Adverse events on study included weakness and retinal pigment epithelium changes without detachment or atrophy. On (b) (6) (Study Day 289), the patient was hospitalized with Grade 4 coma (serious). The patient was reported to have taken 26 drops of homeopathy medication Aconitum. No further details were reported. On (b) (6) (Study Day 289), the patient died due to coma (Grade 5). The investigator considered coma to be unrelated to vemurafenib and cobimetinib.

Reviewer's comment: This death occurred 44D after disease progression was assessed and the patient was taken off study. While Aconitum has been associated with induced QT prolongation mediated through inhibition of hERG channels [27], an interaction between Vem/Cobi seems unlikely. Acute toxic herbal intake of Aconitum has been reported [28].

- 2118, 53-year-old male patient diagnosed with M1c abdominal melanoma on 25-Nov-2012 who was enrolled on Study GO28141 on (b) (6). At screening, the patient's ECOG performance status was 0. Previous diagnostic procedures and treatment for melanoma included lymphadenectomy of abdomen and radiotherapy to inguinal region (4000 cGy; 20 fractions) from 25-Feb-2013 to 22-Mar-2013. No past medical and surgical history was otherwise. Concurrent conditions included hypertension and anemia. Concomitant medications included ramipril and amlodipine (since Aug-2012), temazepam (Oct-2012 to Sep-2013), and gabapentin (25-Nov-2012 to Dec-2013). Treatment with vemurafenib 960 mg twice daily and cobimetinib 60 mg daily 21/7 schedule was started on (b) (6) (Study Day 1). Adverse events included Grade 1 bilateral chorioretinopathy and grade 2 pyrexia. On (b) (6) (Study Day 343), the patient was hospitalized with pyrexia, diarrhea and vomiting. Subsequently, he was diagnosed with Grade 2 Clostridium difficile infection (serious; diagnostic details not reported). On the same day (b) (6), treatment with vemurafenib and cobimetinib was interrupted. He received treatment with metronidazole, metoclopramide and ondansetron. On (b) (6) (Study Day 347), the event of Clostridium difficile infection was considered resolved and the patient was discharged from the hospital. Reportedly, it was planned to re-start the study treatment on (b) (6) (Study Day 348) or (b) (6) (Study Day 349)

however; on (b) (6) (Study Day 350), the patient again experienced diarrhea and vomiting resulting in hospitalization. A chest X-ray was normal however; an abdominal X-ray showed Grade 2 colitis (serious). The causal organism was *Clostridium difficile*. He received treatment with paracetamol, morphine sulfate, domperidone, cyclizine, metronidazole, ranitidine and calcium carbonate/sodium alginate/sodium bicarbonate. On (b) (6) (Study Day 353), the event of *Clostridium difficile* colitis was considered resolved and the patient was discharged from the hospital. On (b) (6) (Study Day 365), treatment with vemurafenib (960 mg) and cobimetinib (60 mg) was resumed. On (b) (6) (Study Day 369), the patient again experienced diarrhea and vomiting. On (b) (6) (Study Day 371), treatment with vemurafenib and cobimetinib was again interrupted. On (b) (6) (Study Day 373), the patient's condition worsened and he was hospitalized. Subsequently, he was diagnosed with Grade 2 *Clostridium difficile*-infection (serious; diagnostic details not reported). Reportedly, his *Clostridium difficile* Ribotype was 078 while norovirus was negative. Treatment with metronidazole was maintained. On (b) (6) (Study Day 385), the event of *Clostridium difficile* infection was considered resolved and he was discharged from the hospital. On (b) (6) (Study Day 392), the patient's ECOG performance status was 2. On (b) (6) (Study Day 421), treatment with vemurafenib (960 mg) and cobimetinib (60 mg) was resumed. The investigator considered the events of *Clostridium difficile* infection and *Clostridium difficile* colitis to be unrelated to vemurafenib and cobimetinib. Other unspecified cause was considered a possible etiological factor for these events.

On (b) (6) (Study Day 435), the patient presented to the hospital with nausea, vomiting and diarrhea. An unspecified test was positive for *Clostridium difficile*. Subsequently, the patient was hospitalized with the admitting diagnosis of Grade 3 *Clostridium difficile* colitis (serious; diagnostic details not reported). Reportedly, the patient had renal failure. His creatinine was 324 (units and normal range not reported). He was treated with paracetamol, vancomycin, metronidazole, piperacillin sodium/tazobactam sodium, metaraminol, noradrenaline, propofol, remifentanyl, dalteparin and ranitidine.

Treatment with vemurafenib and cobimetinib was not changed as a result of this event.

On (b) (6) (Study Day 437), a CT scan showed ischemic colon and small bowel mesenteric and portal vein thrombus. On the same day (b) (6), the patient died due to the *Clostridium difficile* colitis. It was unknown whether an autopsy was performed. The investigator considered the event of *Clostridium difficile* colitis to be related to vemurafenib and cobimetinib.

<p>Reviewer's comment: The reviewer concurs with the investigator's assessment of causality in this case.</p>

Among patients treated on the NO 25395, deaths as of the May 9, 2014 cut-off date are shown below in Table.

Table 37: NO25395 - Subject Follow-up Status and Cause of Death (Data Cut-off Date: May 9, 2014)

Number of Patients	BRAFi-naïve (n=63)		Vem Progressors (n=66)	
	n	%	n	%
Primary cause of death ¹				
Disease progression	12	(19)	43	(43)
SAE	0	(0)	0	(0)
Other	-	-	2	(3)
All Deaths	12	(19)	45	(68)
Time to death from last dose				
≤ 30 days	4	(6)	15	(23)
> 30 Days	8	(13)	30	(46)

¹The cause of death was reported as “unknown” for 2 patients who were vemurafenib progressors.
Source: NO25393: adsl.xpt, adae.xpt, clinical narratives

Reviewer’s comment: Narratives for deaths occurring on NO25395 were reviewed. The reviewer concurred that the underlying cause of death was likely attributable to disease progression for these cases. However, narratives were of a poor quality and failed to integrate collaborating clinical data.

Reported in the safety update (data cut-of date: September 19, 2014), for the NO25395 one additional non-progression event was reported in a BRAFi-naïve patient. This death was attributed to staphylococcal sepsis.

7.3.2 Nonfatal Serious Adverse Events

Section 5.2.2 of the GO28141 protocol defined serious adverse events (SAE) as an adverse event AE that meets any of the following criteria:

- Any non-cutaneous primary malignancy (related or unrelated to study treatment) that develop during or up to 12 months after study treatment completion must be reported as a serious adverse event
- Fatal (i.e., the AE actually causes or leads to death)
- Life threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death). This does not include any AE that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient’s ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

Non-fatal serious adverse events occurred in 64 (26%) patients on the Vem/Placebo group and in 85 (35%) patients on the Vem/Cobi group. Table 38 summarizes non-fatal SAEs that occurred in 1% or more of the Vem/Cobi treatment group.

The frequency of reported SAEs was low, but pyrexia, ocular toxicities, rash, and dehydration were more common among patients on the Vem/Cobi group.

Table 38: GO28141 – Per-Patient Incidence of Non-Fatal Serious Adverse Events Occurring in at Least 1% of the Vem/Cobi Treatment Group (Safety Population; Data Cutoff Date: 19 SEP 2014)

	Vem/Placebo (n=246)		Vem/Cobi (n=247)	
	n	%	N	%
CARDIAC DISORDERS				
ATRIAL FIBRILLATION	1	(0)	3	(1)
EYE DISORDERS				
CHORIORETINOPATHY	0	(0)	3	(1)
RETINAL DETACHMENT	0	(0)	4	(2)
GASTROINTESTINAL DISORDERS				
DIARRHOEA	0	(0)	3	(1)
SMALL INTESTINAL OBSTRUCTION	0	(0)	3	(1)
GENERAL DISORDERS AND ADMIN. SITE COND.				
PYREXIA	3	(1)	7	(3)
IMMUNE SYSTEM DISORDERS				
HYPERSENSITIVITY	0	(0)	3	(1)
INFECTIONS AND INFESTATIONS				
PNEUMONIA	3	(1)	4	(2)
INVESTIGATIONS				
ALANINE AMINOTRANSFERASE INCREASED	2	(1)	3	(1)
ASPARTATE AMINOTRANSFERASE INCREASED	2	(1)	3	(1)
METABOLISM AND NUTRITION DISORDERS				
DEHYDRATION	0	(0)	5	(2)
NERVOUS SYSTEM DISORDERS				
CONVULSION	0	(0)	3	(1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
RASH	1	(0)	4	(2)
RASH MACULO-PAPULAR	2	(1)	3	(1)

Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adae.xpt

In the NO25395, serious adverse events were reported in 11 (28%) patients. The distribution of these events by MedDRA SOC and PT is shown below.

Table 39: NO25395 - Per-Patient Incidence of Non-Fatal Serious Adverse Events (Safety Population; Data Cutoff Date: 19 SEP 2014)

SOC/PT	n (%)
INFECTIONS AND INFESTATIONS	
CELLULITIS	1 (3)
OPHTHALMIC HERPES ZOSTER	1(3)
PNEUMONIA CHLAMYDIAL	1(3)
SEPSIS	1(3)
STREPTOCOCCAL BACTERAEMIA	1(3)
URINARY TRACT INFECTION	2(5)
DEHYDRATION	1(3)
METABOLISM AND NUTRITION DISORDERS	
HYPONATRAEMIA	1(3)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
BACK PAIN	1(3)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED	
BASAL CELL CARCINOMA	1(3)
SQUAMOUS CELL CARCINOMA OF SKIN	3(8)
PSYCHIATRIC DISORDERS	
SUICIDAL IDEATION	1(3)
RENAL AND URINARY DISORDERS	
RENAL FAILURE	1(3)
VASCULAR DISORDERS	
HYPERTENSION	1(3)

Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: NO25395:adae.xpt

7.3.3 Dropouts and/or Discontinuations

At the time of the 90D Safety Update, 57 (23%) of patients on the Vem/Placebo group and 95 (38%) of patients on the Vem/Cobi were still receiving cobimetinib or placebo treatment. The most common reason for discontinuation of cobimetinib or placebo treatment in both study groups was disease progression. More patients on the Vem/Cobi group than on the Vem/Placebo group discontinued cobimetinib or placebo due to an adverse event. There appeared to be little difference between groups in other reasons for cobimetinib or placebo discontinuation (Table 40).

Table 40: GO28141 – Patients Discontinuing Cobimetinib or Placebo by Study Group (Safety Population; Data Cutoff Date: 19 SEP 2014)

Patients Discontinued from Cobi/Placebo	Vem/Placebo		Vem/Cobi	
	(n)	%	(n)	%
Treated	246	(100)	247	(100)
Still on Treatment	57	(23)	95	(38)
Discontinued from Treatment	189	(77)	152	(62)
Adverse Event	23	(9)	42	(17)
Pregnancy	1	(<1)	-	-
Death	1	(<1)	3	(1)
Loss to Follow-up	1	(<1)	1	(<1)
Protocol Violation	-	-	-	-
Non-compliance with Study Drug	-	-	1	(<1)
Non-compliance	-	-	2	(1)
Withdrawal by Subject	4	(2)	3	(1)
Physician Decision	2	(1)	4	(1)
Progression of Disease	157	(64)	96	(39)
Other	-	-	-	-

Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adsl.xpt; Clinical Study Report

At the time of the 90D Safety Update, the discontinuation rates for adverse events for both study treatments were higher for the Vem/Cobi treatment group than in the Vem/Placebo treatment group (15% vs. 8%). Discontinuation rates for cobimetinib/placebo were higher in the Vem/Cobi arm than in the Vem/Placebo arm (19% vs 10%). For discontinuation of vemurafenib, the rates were 16% in the Vem/Cobi arm and 10% in the Vem/Placebo arm. Most patients who discontinued study treatment for an AE had both study drugs withdrawn. The most common reason for discontinuation of cobimetinib/placebo treatment in both study groups was disease progression. There appeared to be little difference between groups in other reasons for vemurafenib discontinuation ().

Table 41: GO28141 – Patients Discontinuing Treatment: Overview of Adverse Events by Study Group (Safety Population; Data Cutoff Date: 19 SEP 2014)

	Vem/Placebo		Vem/Cobi	
	(n)	%	(n)	%
Total number (%) of patients with ≥ 1 AE	240	98	244	99
Total number of patients (%) with ≥ 1:				
Grade ≥ 3 AEs	146	59	176	71
Grade 5 AEs ^a	3	1	5	2
SAEs	64	26	85	34
AEs leading to discontinuation of cobimetinib/Placebo	24	10	47	19
AEs leading to discontinuation of vemurafenib	24	10	39	16
AEs leading to discontinuation of cobimetinib and vemurafenib	20	8	37	15

AE-adverse event; SAE- serious adverse event

^aFor details of patients reported as having experienced Grade 5 SAEs see Section 7.3.1.

^bPatients who discontinued both drugs are also represented in the rows for discontinuation from each individual drug.

Source: Reproduced from Table 2, page 22 NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141Clinical Study Report

Discontinuation rates for both study drugs were higher for patients receiving Vem/Cobi (15%) than for patients receiving Vem/Placebo (8%). Discontinuation rates for the individual drugs were also higher among patients receiving Vem/Cobi (discontinued Cobi: 19%; discontinued Vem: 16%) than among patients receiving Vem/Placebo (discontinued Placebo: 10%; discontinued Vem: 10%). Increased liver function tests, rash, retinal detachment and pyrexia most commonly led to study drug discontinuation among patients treated with Vem/Cobi group. Liver function elevations and rash most commonly led to study drug discontinuation among patients treated with Vem/Placebo (Table 42).

Table 42: GO28141 – Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment in at Least 1% of Patients in Either Group (Safety Population: Data Cutoff Date: 19 SEP 2014)

Patients experiencing event, n(%)	Vem/Placebo (n=246)		Vem/Cobi (n=247)	
	n	(%)	n	(%)
Withdrawal of cobimetinib/placebo				
Increased AST	1	(0.4)	6	(2.4)
Increased GGT	3	(1.2)	4	(1.6)
Increased ALT	1	(0.4)	4	(1.6)
Rash	1	(0.4)	4	(1.6)
Retinal detachment	0	0	5	(2.0)
Pyrexia	0	0	3	(1.2)
Withdrawal of vemurafenib				
Increased ALT	3	(1.2)	5	(2.0)
Increased AST	2	(0.8)	6	(2.4)
Increased GGT	4	(1.6)	4	(2.0)
Rash	1	(0.4)	4	(1.6)
Pyrexia	1	(0.4)	3	(1.2)
Retinal detachment	0	0	3	(1.2)
Withdrawal of cobimetinib/placebo and vemurafenib				
Increased AST	1	(0.4)	5	(2.0)
Increased GGT	3	(1.2)	4	(1.6)
Increased ALT	1	(0.4)	4	(1.6)
Rash	1	(0.4)	4	(1.6)
Pyrexia	0	0	3	(1.2)
Retinal detachment	0	0	3	(1.2)

ALT-alanine aminotransferase; AST-aspartate aminotransferase; GGT-gamma-glutamyltransferase
Source: NDA206192/0036(37); 3/10/2015: 2.4.5, Table 10, page 44: GO28141:adae.xpt

The percentage of patients requiring a dosing modification or dosing interruption of one or both study drugs was higher among patients receiving Vem/Cobi than for patients receiving Vem/Placebo (Table 43).

Table 43: GO28141 – Percentage of Patients Requiring Dose Modification or Interruption of One or Both Study Drugs by Study Group (Safety Population: Data Cutoff Date: 19 SEP 2014)

	Vem/Placebo (n=246)	Vem/Cobi (n=247)
Dose modification/interruption	%	%
Cobi/Placebo	37	55
Vem	49	58
Cobi/Placebo and Vem	35	45

Source: NDA206192/0036(37); 3/10/2015: 2.4.5, page 45

The most common AEs that resulted in dose interruption or reduction of cobimetinib in the cobimetinib plus vemurafenib arm, compared with the placebo plus vemurafenib arm, 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%).

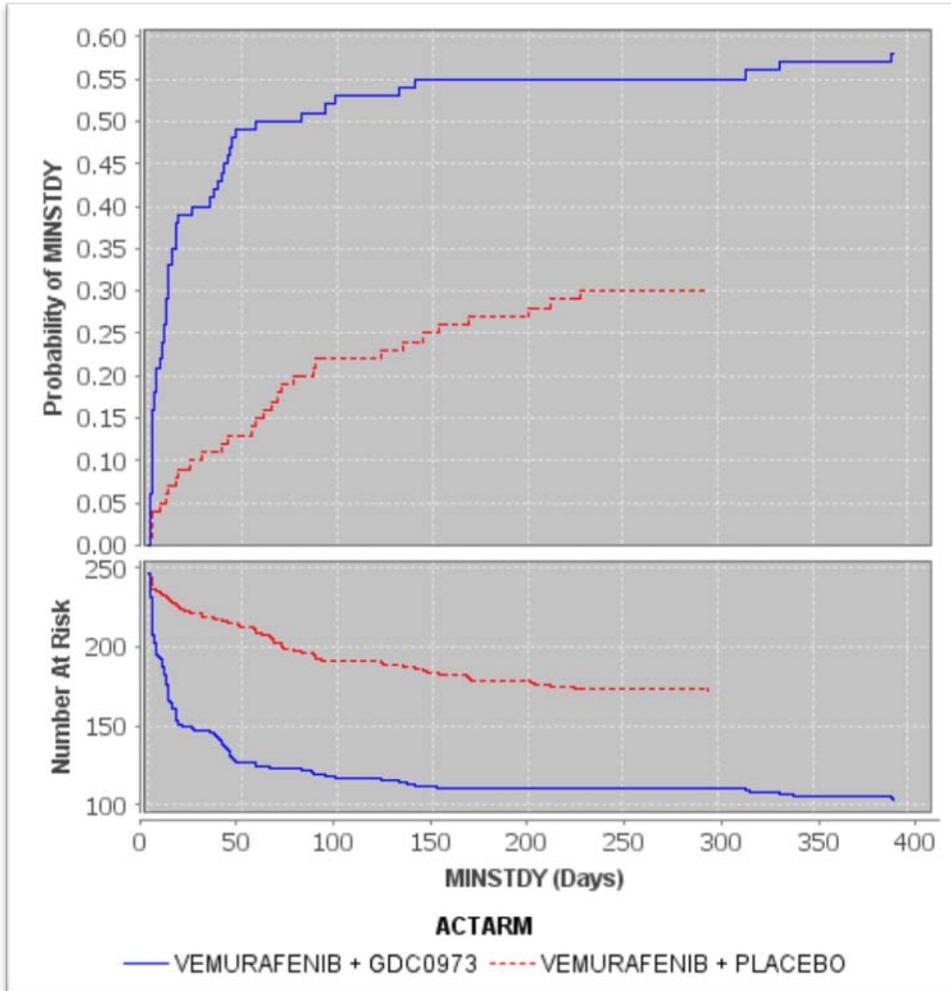
7.3.4 Significant Adverse Events

CTCAE Grade 3 and 4 adverse events are discussed under section 7.4.1.

7.3.5 Submission Specific Primary Safety Concerns

The most common adverse event among patients treated with Vem/Cobi was diarrhea. Sixty percent of patients in the Vem/Cobi treatment group experienced diarrhea. The median time to onset among of diarrhea in the Vem/Cobi group was 11 days (range 1 to 392 days). Despite the frequency of this event, it was not listed as a cause for treatment discontinuation (Table 42). Diarrhea was reported to have resulted in hospitalization in three Vem/Cobi treated patients.

Figure 21: GO28141 - Cumulative Per-Patient Incidence of Diarrhea (All Grades) by Study Day of Onset and Treatment Group (Safety Population; Data Cutoff Date: 19 SEP 2014)



Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adae.xpt

Adverse events of special interest were pre-defined in the study protocol (Table 30). The per-patient incidence of these pre-specified adverse events of interest by study arm is summarized below.

Table 44: GO28141 – Per-Patient Incidence of Adverse Events of Special Interest (Safety Population; Data Cutoff Date: 19 SEP 2014)

Adverse Event of Special Interest	Vem/Placebo (n=246)		Vem/Cobi (N=247)	
	(n)	%	(n)	%
Ocular events				
Retinal vein occlusion, all grades	1	(<1)	1	(<1)
RPED, Serous retinopathy, all grades	7	(3)	63	(26)
Visual disturbances (≥ Grade 2)(not RVO/Serous retinopathy)	73	(30)	93	(38)
Photosensitivity (≥ Grade 3)	0	0	9	(4)
LVEF reduction (≥ Grade 2)*	9	(4)	21	(9)
QTc interval prolongation (≥ Grade 3)	4	(2)	4	(2)
Liver function tests increased (≥ Grade 3)	36	(15)	53	(22)
CPK elevation (≥ Grade 3)	8	(3)	80	(33)
Primary cutaneous malignancy	48	(19)	14	(6)
Secondary non-cutaneous primary malignancies	10	(4)	2	(1)
Rash (≥ Grade 3)				
Acneiform	3	(1)	6	(2)
Non-acneiform	38	(15)	36	(15)

Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adae.xpt

*This rate is based upon events reported in the adae.xpt. The rate is somewhat higher when the actual LVEF assessments are considered. See Section 7.4.5 for additional information.

Adverse events of special interest which occurred in excess in either arm are discussed in further detail below and in subsequent sections as indicated. See Section 7.4.2 for a discussion of elevations in liver function tests and CPK. See section 7.4.4 for a further discussion of QTc interval prolongation, and Section 7.4.5 for a discussion of LVEF reduction.

Ocular Toxicities:

Ocular toxicities of special interest included retinal vein occlusion, serous retinopathy/retinal pigment epithelial detachment (RPED) and other visual disturbances. These events were defined using the following lists of MedDRA preferred terms:

Table 45: GO28141 – MedDRA Preferred Terms Used to Identify Patients Ocular Toxicity of Special Interest

Retinal Vein Occlusion (RVO)	Serous Retinopathy (RPED)	Visual Disturbances
Angiogram retina abnormal	Chorioretinal disorder	All other preferred terms within the Eye Disorders System Organ Class not included in RVO or serous retinopathy
Blindness unilateral	Chorioretinopathy	
Macular ischemia	Detachment of macular retinal pigment epithelium	
Retinal infarction	Detachment of retinal pigment epithelium	
Retinal ischemia	Macular fibrosis	
Retinal edema	Macular edema	
Retinal toxicity	Retinal detachment	
Retinal vascular disorder	Retinal disorder	
Retinal vascular occlusion	Retinal pigment epithelial tear	
Retinal vascular thrombosis	Retinal tear	
Retinal vein occlusion	Retinopathy	
Retinal vein thrombosis	Scleral buckling surgery	
Retinogram abnormal		
Venous stasis retinopathy		

Source: NDA206192/001(2); 12/11/2014: 2.7.4 Summary of Clinical Safety: page 125.

Serous retinopathy/RPED (all grades) and visual disturbances (\geq Grade 2 and not reported as either RVO or serous retinopathy) were reported with a higher incidence among patients treated with Vem/Cobi than among patients treated with Vem/Placebo. Only two patients (one in each treatment group) were reported to have had retinal vein occlusion.

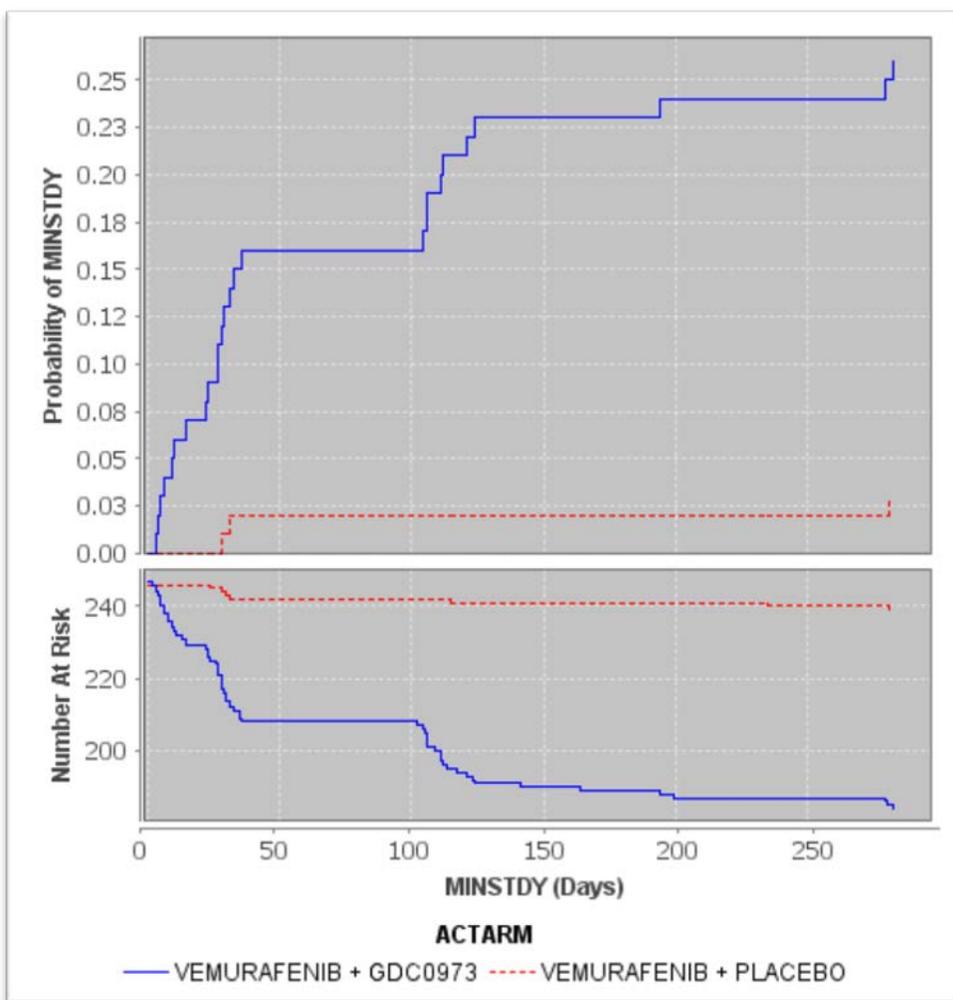
Reviewer's comment: It is noteworthy that these events were not uniformly recorded over the course of the trial. Nor were retinal scans available for review and verification. The ophthalmology consult has noted the poor quality of the ophthalmologic data submitted in the application. Thus, the rate reported by the applicant cannot be confirmed by FDA. Please see the FDA ophthalmology consult review for further details.

Serous Retinopathy/Retinal Pigment Epithelial Detachment (RPED):

Most events were Grade 1 or Grade 2. The median time of onset of serous retinopathy/RPED among the seven (3%) patients treated with Vem/Placebo was 31 days (range: 24 to 281 days); the median time to onset of serous retinopathy/RPED among 63 (26%) patients treated with Vem/Cobi was similar, 30 days (range: 2 to 282

days). The cumulative per-patient incidence of serous retinopathy/RPED by study day of onset and treatment group is shown below.

Figure 22: GO28141 – Cumulative Per-Patient Incidence of Serous Retinopathy/RPED by Study Day of Onset and Treatment Group (Safety Population; Data Cutoff Date: 19 SEP 2014)



Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adae.xpt

Patients with multiple events of serous retinopathy/RPED were assumed to have a data of onset at the onset date of the earliest occurring event and were assumed to have an ongoing event with the end date assigned as the date of the outcome of the latest

occurring event. Patients reported to have an ongoing event of serous retinopathy/RPED at the time of the data cutoff date were censored at this date for purposes of the duration analysis. As can be seen in Table, 43% of patients treated with Vem/Cobi who developed serous retinopathy/RPED had events that were ongoing at the time of the 19 SEP 2014 data cutoff date.

Table 46: GO28141 – Patients with Event of Serous Retinopathy/RPED by Resolution of Latest Occurring Event (Safety Population; Data Cutoff Date: 19 SEP 2014)

Event Resolution	Treatment Group	
	Vem/Placebo N=7 N (%)	Vem/Cobi N=63 N (%)
Recovered/Resolved	2 (29)	26 (41)
Recovered/Resolved with Sequelae	-	2 (3)
Recovering/Resolving	1 (14)	4 (6)
Not Recovered/Not Resolved	4 (57)	27 (43)
Unknown	-	4 (6)

Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adae.xpt

The median duration of serous retinopathy/RPED events among the 7 patients treated in the Vem/Placebo group was 137 days (range: 16 to 296 days). The median duration of serous retinopathy/RPED events among the 63 patients treated in the Vem/Cobi group was 171 days (range: 5-491 days).

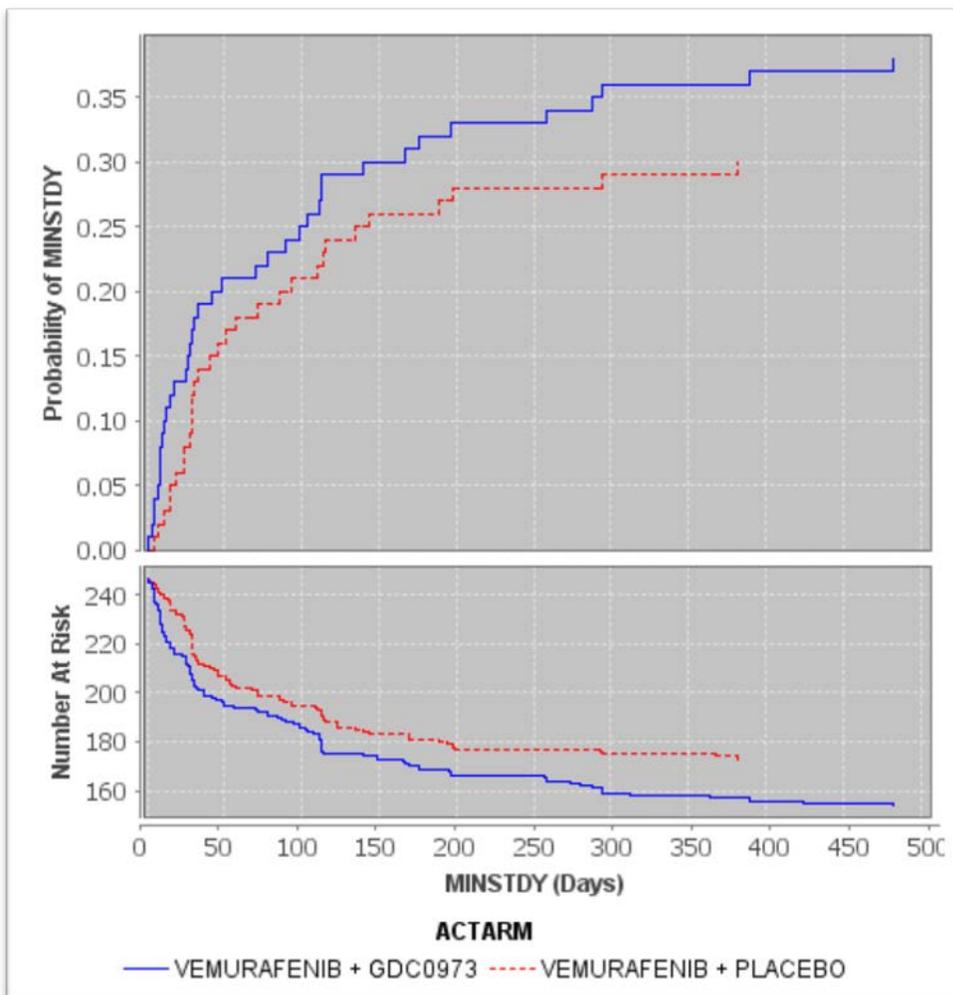
Reviewer's comment: Adverse events of serous retinopathy/RPED were common among patients treated with Vem/Cobi. This incidence of these events appeared to continue throughout the exposure period and a number of patients were reported to have had multiple events. When they occurred, these events were of long duration. As 43% of patients with serous retinopathy/RPED had events that were ongoing at the time of the data cutoff date, there is insufficient information to assess whether this event is reversible. See Dr. Chamber's ophthalmology consult for his recommendations concerning a post-marketing requirement for monitoring of this event.

Visual Disturbances:

The median time of onset of visual disturbances among the 73 (30%) patients treated with Vem/Placebo was 43 days (range: 2 to 382 days); the median time to onset of visual disturbances among the 93 (38%) patients treated with Vem/Cobi was 36 days

(range: 1 to 482 days). The cumulative per-patient incidence of visual disturbances by study day of onset and treatment group is shown below.

Figure 23: GO28141 - Cumulative Per-Patient Incidence of Visual Disturbances by Study Day of Onset and Treatment Group (Safety Population; Data Cutoff Date: 19 SEP 2014)



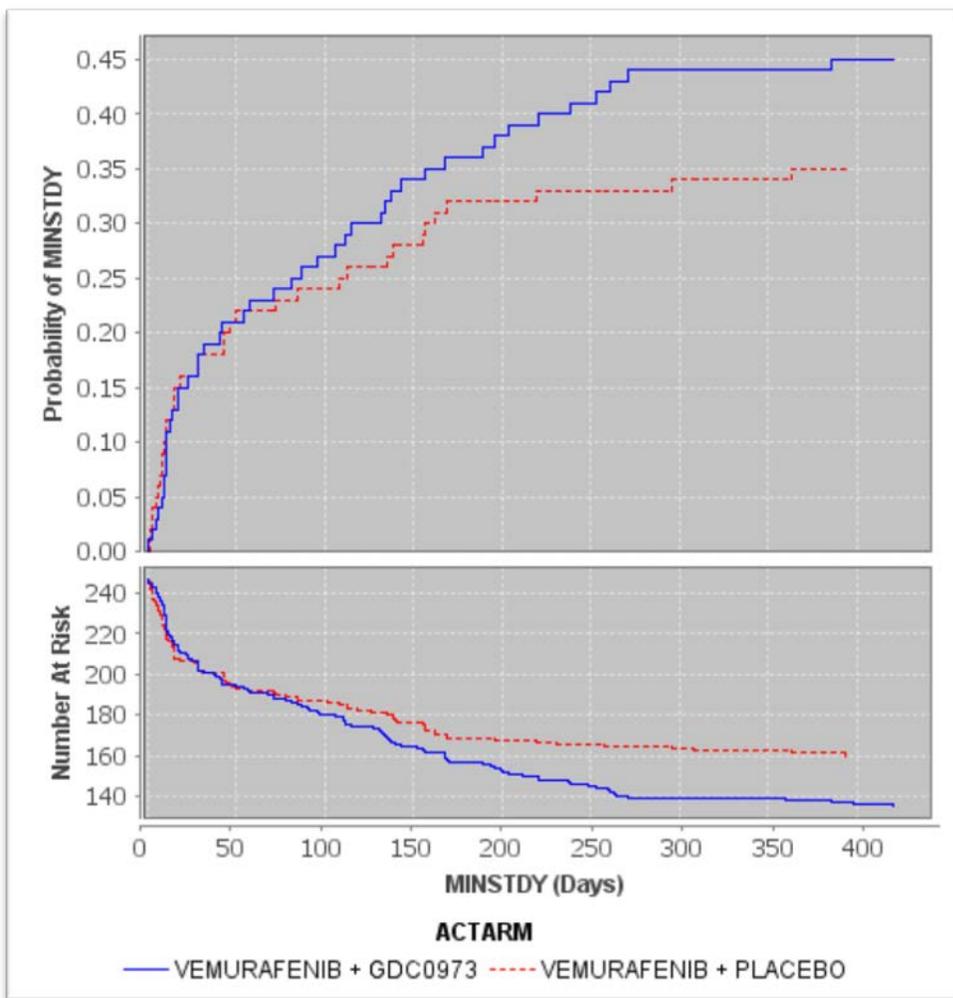
Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adae.xpt

Photosensitivity:

Grade ≥ 3 photosensitivity was rare, occurring in no patients treated with Vem/Placebo and in 9 (4%) of patients treated with Vem/Cobi. However photosensitivity (all Grades)

was common, occurring in 86 (35%) patients treated with Vem/Placebo and 112 (45%) patients treated with Vem/Cobi. The median time of onset of photosensitivity among the 86 patients treated with Vem/Placebo was 29 days (range: 2 to 393 days); the median time to onset of photosensitivity reactions among the 112 patients treated with Vem/Cobi was 63 days (range: 1 to 420 days). The cumulative per-patient incidence of photosensitivity reactions by study day of onset and treatment group is shown below.

Figure 24: GO28141 – Cumulative Per-Patient Incidence of Photosensitivity (Any Grade) by Study Day of Onset and Treatment Group (Safety Population; Data Cutoff Date: 19 SEP 2014)



Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adae.xpt

QTc Interval Prolongation and Decrease in Left Ventricular Ejection Fraction:

These events are discussed in Sections 7.4.4 and 7.4.5, respectively.

Increases in Blood Creatinine Phosphokinase and Liver Enzyme:

These adverse events of special interest are discussed in more detail in Section 7.4.2.

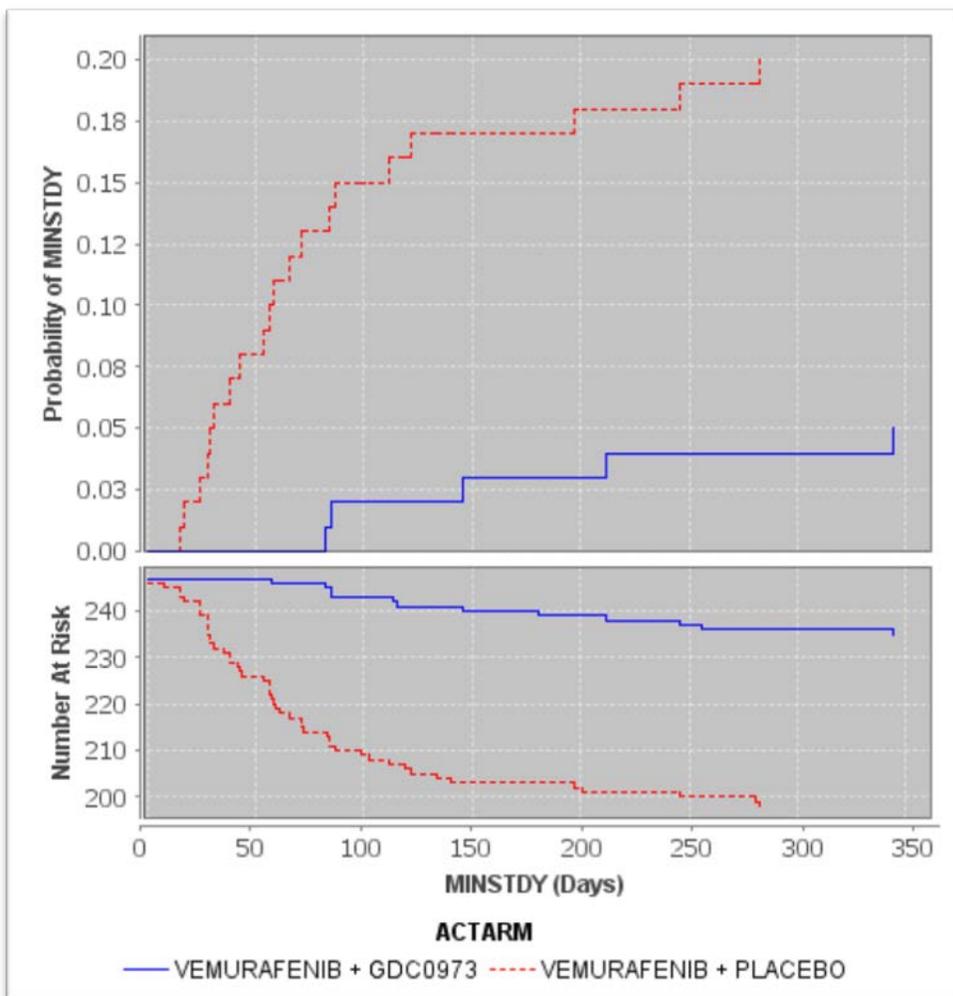
Primary Cutaneous Malignancies:

Primary cutaneous malignancies included primary cutaneous squamous cell carcinoma and keratoacanthomas, basal cell carcinomas and second primary malignant melanomas. These events are discussed below.

Primary Cutaneous Squamous Cell Carcinoma (cusCC) and Keratoacanthoma (KA):

Primary cutaneous squamous cell carcinoma (cusCC) and keratoacanthoma (KA) were reported at a much lower frequency among patients in the Vem/Cobi treatment group than in the Vem/Placebo treatment group. The median time of onset of cusCC/ KA malignancies among the 48 (19%) patients treated with Vem/Placebo was 57 days (range: 8 to 283 days); the median time to onset of cusCC/KA among the 14 (6%) patients treated with Vem/Cobi was 131 days (range: 57 to 344 days). The cumulative per-patient incidence of cusCC/KA by study day of onset and treatment group is shown below.

Figure 25: GO28141 – Cumulative Per-Patient Incidence of Cutaneous Squamous Cell Carcinoma (cusCC) and Keratoacanthoma (KA) by Study Day of Onset and Treatment Group (Safety Population; Data Cutoff Date: 19 SEP 2014)



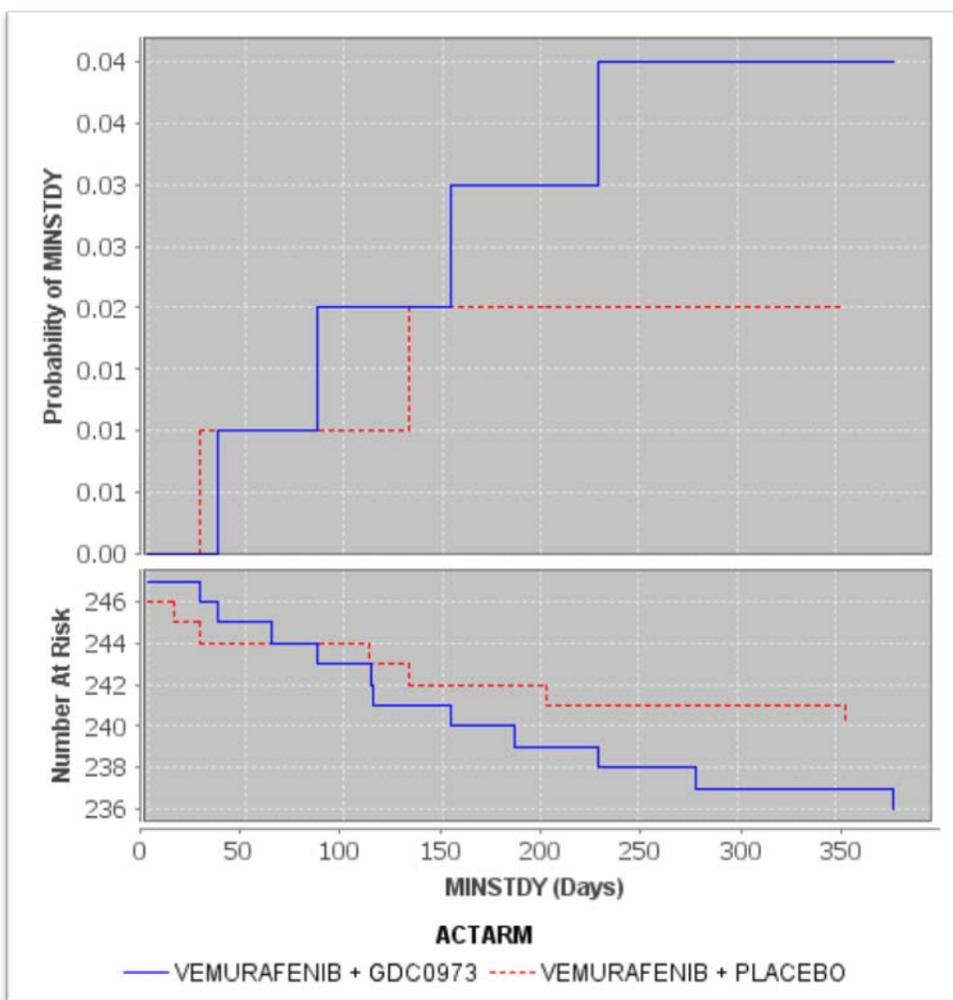
Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adae.xpt

Reviewer's comment: The reduction in incidence and the delayed occurrence of cusCC/KA observed with the addition of cobimetinib to vemurafenib therapy are similar to that seen with the addition the MEK-inhibitor, trametinib to BRAF-inhibitor therapy with dabrafenib. This decrease has been attributed to blockade of the paradoxical increase in signaling downstream of BRAF.

Basal Cell Carcinoma:

In contrast to cusCC, basal cell carcinomas were reported more commonly among patients in the Vem/Cobi treatment group than among patients in the Vem/Placebo treatment group. The median time of onset of basal cell carcinoma among the 6 (2%) patients treated with Vem/Placebo was 123 days (range: 14 to 355 days); the median time to onset of basal cell carcinoma among the 11 (4%) patients treated with Vem/Cobi was 115 days (range: 27 to 379 days). The cumulative per-patient incidence of basal cell carcinoma by study day of onset and treatment group is shown below.

Figure 26: GO28141 – Cumulative Per-Patient Incidence of Basal Cell Carcinoma by Study Day of Onset and Treatment Group (Safety Population; Data Cutoff Date: 19 SEP 2014)

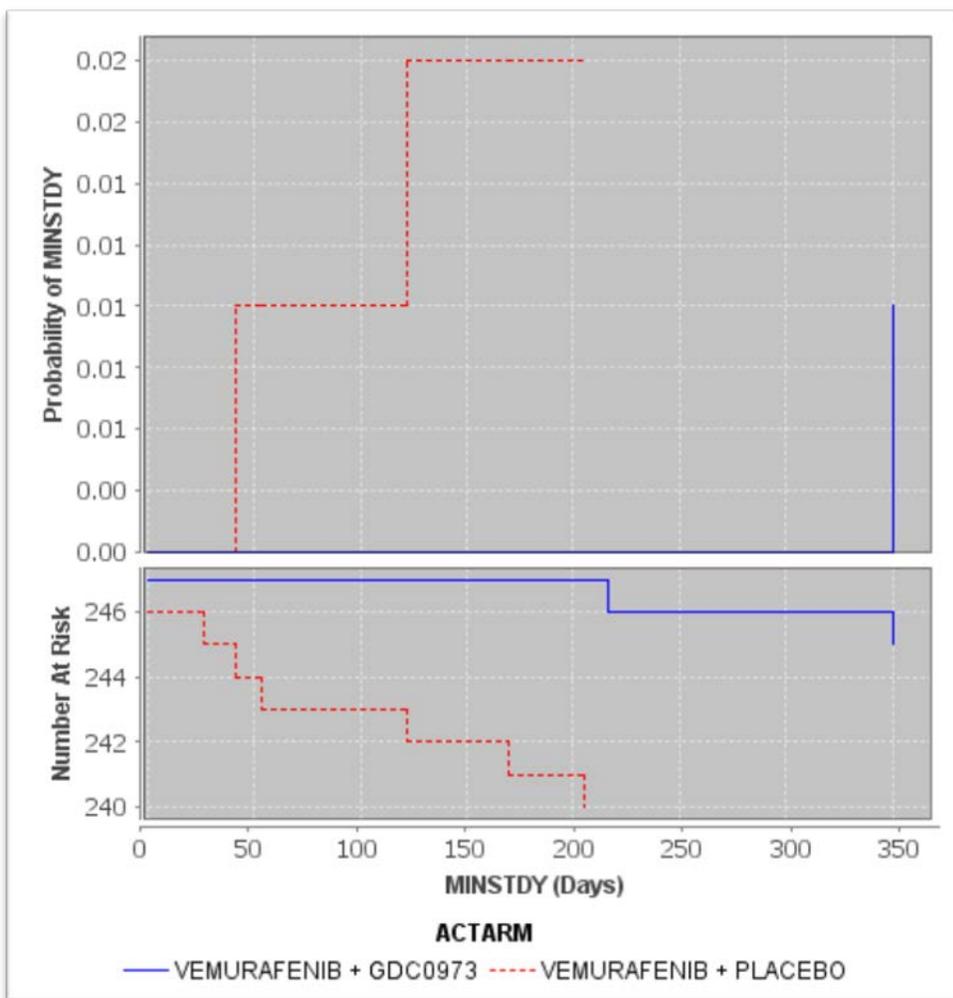


Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adae.xpt

Second Primary Melanoma:

Patients with new primary melanoma were identified as those having events in the MedDRA higher level group term (HLGT) Skin Neoplasms Malignant and Unspecified. Among the patients in this category, all patients with melanoma-related MedDRA primary terms (PT) were selected. These included the following PT: malignant melanoma (n=4), malignant melanoma in situ (n=3) and metastatic malignant melanoma (n=1). While the number of events was small in both groups, melanoma related PTs appeared to be less commonly reported among patients treated in the Vem/Cobi group and appeared to be reported later than among patients in the Vem/Placebo treatment group. The median time of onset among the 6 (2%) patients treated with Vem/Placebo was 88 days (range: 27 to 205 days). Two (1%) patients treated with Vem/Cobi were diagnosed with second primary melanoma, one at 216 days and one at 350 days. The cumulative per-patient incidence of by study day of onset and treatment group is shown below.

Figure 27: GO28141 – Cumulative Per-Patient Incidence of Second Malignant Melanoma and Precursor Lesions by Study Day of Onset and Treatment Group (Safety Population; Data Cutoff Date: 19 SEP 2014)



Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adae.xpt

Second non-cutaneous primary malignancies:

Patients with second primary non-cutaneous malignancies were identified as those patients with an adverse event MedDRA PT which mapped to either the SMQ Malignant tumors or the SMQ Tumors of unspecified malignancy, excluding those PTs in HLGT

Skin neoplasms malignant and unspecified. Ten tumors were identified in ten patients treated with Vem/Placebo and three tumors were identified in two patients treated with Vem/Cobi. The line listing of second primary malignancies diagnosed in patients treated on GO28141 by study arm is shown below.

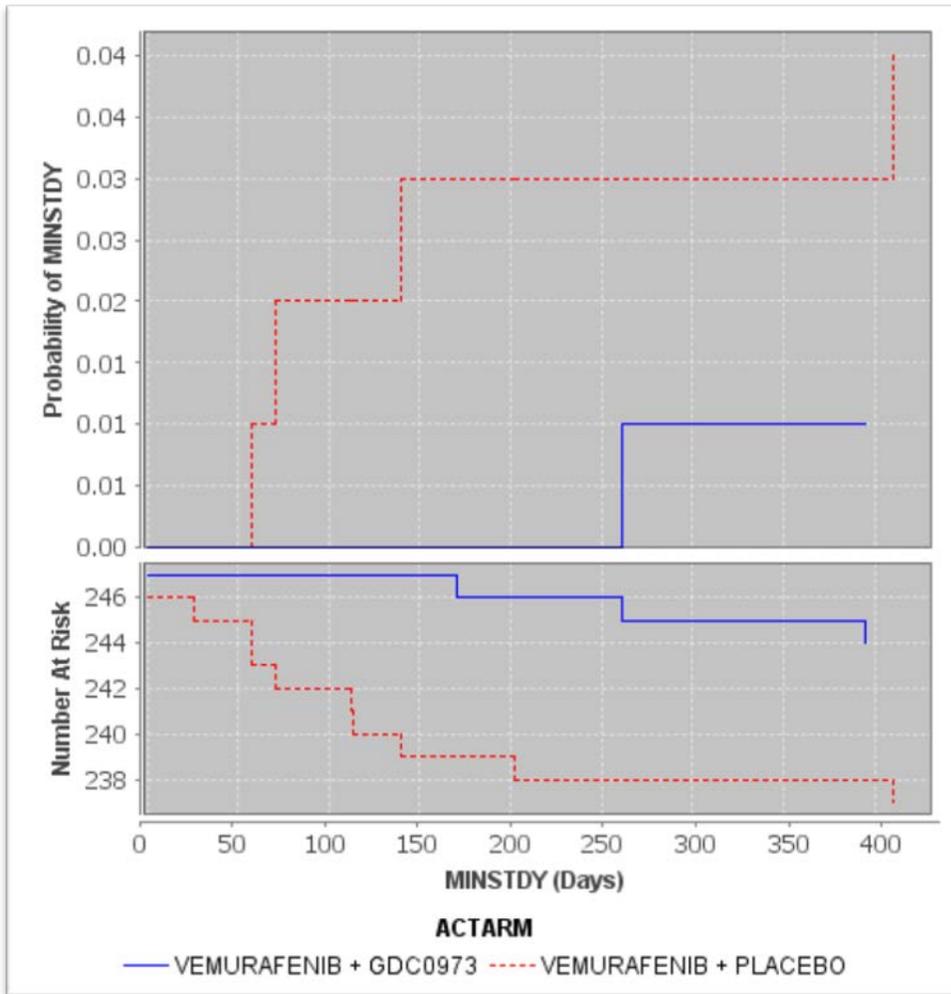
Table 47: GO28141 – Line Listing of Second Primary Non-Cutaneous Tumors by Treatment Group (Safety Population, Data Cutoff Date: 19 SEP 2014)

GO28141-254364-2170	VEMURAFENIB + GDC0973	COLON ADENOMA
GO28141-254364-2170	VEMURAFENIB + GDC0973	TRANSITIONAL CELL UROTHELIAL CARCINOMA
GO28141-257401-2302	VEMURAFENIB + GDC0973	UTERINE LEIOMYOMA
9GO28141-254358-2468	VEMURAFENIB + PLACEBO	ADENOCARCINOMA OF COLON
GO28141-252752-2040	VEMURAFENIB + PLACEBO	DUODENAL ADENOMA
GO28141-252752-2078	VEMURAFENIB + PLACEBO	DUODENAL ADENOMA
GO28141-252750-2143	VEMURAFENIB + PLACEBO	GENITOURINARY TRACT NEOPLASM
GO28141-254364-2036	VEMURAFENIB + PLACEBO	LEIOMYOMA, TONGUE
GO28141-253512-2306	VEMURAFENIB + PLACEBO	LIPOMA
GO28141-252735-2073	VEMURAFENIB + PLACEBO	MUCINOUS BREAST CARCINOMA, INVASIVE
GO28141-257401-2444	VEMURAFENIB + PLACEBO	ORAL PAPILLOMA, SUBLINGUAL
GO28141-256859-2382	VEMURAFENIB + PLACEBO	UTERINE LEIOMYOMA
GO28141-257401-2174	VEMURAFENIB + PLACEBO	UTERINE LEIOMYOMA

Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adae.xpt, GO28141 Safety Update, Clinical Narratives

The median time of onset of second non-cutaneous malignancy among the 10 tumors diagnosed in 10 patients treated with Vem/Placebo was 112 days (range: 26 to 410 days). Two patients in the Vem/Cobi arm were diagnosed with three second non-cutaneous malignancies between 170 and 395 days. Second primary non-cutaneous tumors appeared to be diagnosed less frequently and later in the Vem/Cobi treatment group than in the Vem/Placebo treatment group.

Figure 28: GO28141 - Cumulative Incidence of Second Non-Cutaneous Tumors by Study Day of Onset and Treatment Group (Safety Population; Data Cutoff Date: 19 SEP 2014)



Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adae.xpt

Reviewer's comment: While screening for SCC of the head and neck at baseline was fairly complete, many patients were missing the protocol specified end of study screening for anal and gynecologic cancers. The reported number of these tumors may be underestimates based on incomplete screening. While numbers are sparse, it appears that the number of second primary tumors is decreased and the onset may be delayed with the addition of cobimetinib to vemurafenib.

Rash:

For purposes of this analysis rash (acneiform and non-acneiform rash) included the following MedDRA PTs:

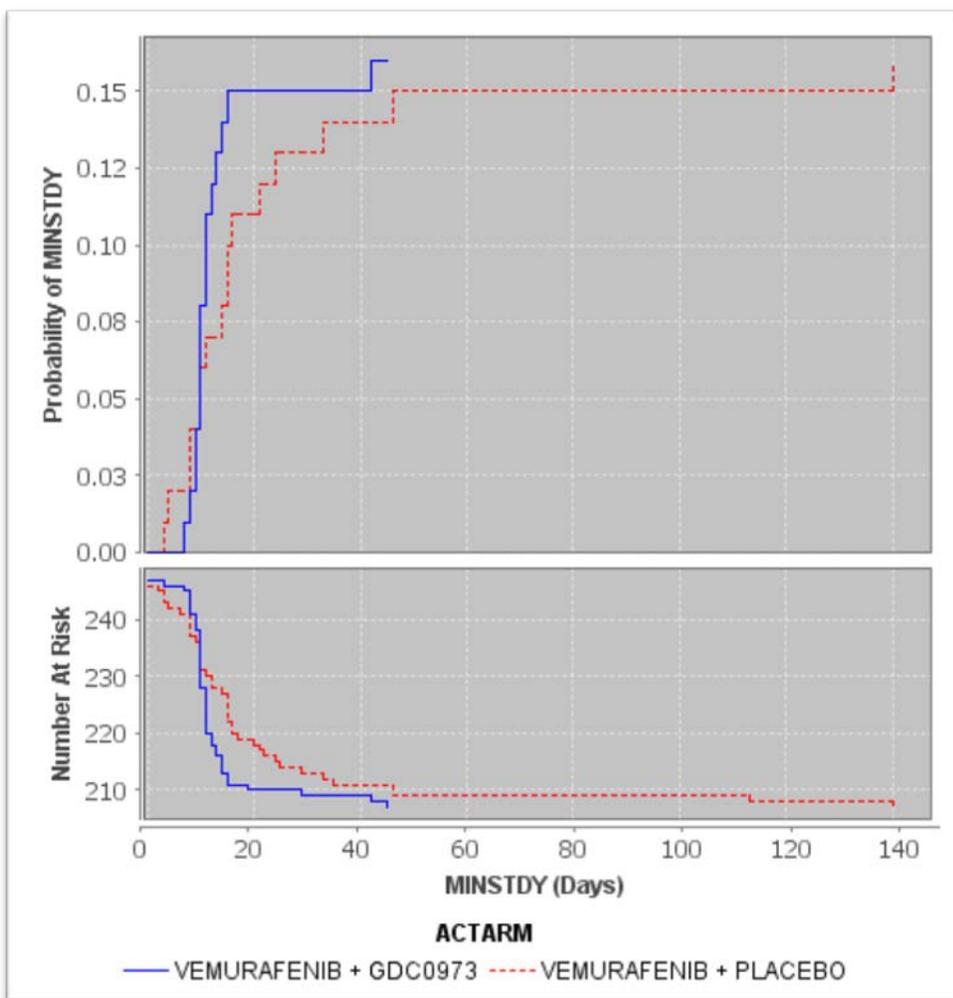
Table 48: GO28141 – MedDRA Primary Terms (PTs) Included in the Analysis of Rash (Acneiform and Non-Acneiform)

<ul style="list-style-type: none"> •Acne •Acne conglobata •Acne cosmetica •Acne cystic •Acne fulminans •Acne infantile •Acne occupational •Acne pustular •Acne varioliformis •Application site acne •Chloracne •Dermatitis acneiform •Iodo acne •Mechanical acne 	<ul style="list-style-type: none"> •Oil acne •Eyelid folliculitis •Folliculitis •Furuncle •Rash follicular •Rash pustular •Dermatitis •Dermatitis allergic •Dermatitis bullous •Dermatitis exfoliative •Drug eruption •Erythema •Exfoliative rash 	<ul style="list-style-type: none"> •Generalized erythema •Rash •Rash erythematous •Rash generalized •Rash macular •Rash maculo-papular •Rash maculovesicular •Rash morbilliform •Rash papular •Rash papulosquamous •Rash pruritic •Rash vesicular •Toxic skin eruption
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Source: Clinical Study Report – Protocol GO28141, Appendix

The rate and time to first occurrence of rash (Grade \geq 3) was similar in the two treatment groups. The median time of onset of rash among the 39 (16%) patients treated with Vem/Placebo was 11 days (range: 2 to 140 days); the median time to onset of rash among the 40 (16%) patients treated with Vem/Cobi was 15 days (range: 3 to 145 days). The cumulative per-patient incidence of rash (Grade \geq 3) by study day of onset and treatment group is shown below.

Figure 29: GO28141 – Cumulative Per-Patient Incidence of Rash (\geq Grade 3) by Study Day of Onset and Treatment Group (Safety Population; Data Cutoff Date: 19 SEP 2014)



Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adae.xpt

The most common types of rash by MedDRA primary term are listed below.

Table 49: GO28141 – Most Common (≥ 5%, All Grades) Skin Rashes by MedDRA Primary Term Occurring in the Vem/Cobi Treatment Group (Safety Population; Data Cutoff Date: 19 SEP 2014)

PT	Vem/Placebo N=246		Vem/Cobi N=247	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
RASH (UNSPECIFIED)	38	6	40	5
PRURITUS	19	0	19	1
RASH MACULO-PAPULAR	15	5	15	7
DERMATITIS ACNEIFORM	9	1	14	2
HYPERKERATOSIS	30	2	11	0
ERYTHEMA	13	0	10	0
PALMAR-PLANTAR ERYTHRODYSAESTHESIA SYNDROME	4	0	6	0

Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adae.xpt

Ten (4%) Vem/Cobi treated patients required hospitalization for a skin adverse event. In two patients, the hospitalization was thought to be related to a skin infection; in the remaining 8 patients, drug reaction was suspect. One of these cases was diagnosed as DRESS and one case was thought to be early Steven Johnson Syndrome.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Common Adverse Events Occurring in Patients Irrespective of Between Arm Difference

Common adverse events (AE) reported in 10% or more patients treated on the GO28141 trial irrespective of between-group differences are shown in Table 50 below. The rates of occurrence of these events in the NO25395 are provided for comparison.

Table 50: GO28141 – Common Adverse Drug Reactions¹ Occurring in ≥ 10% (All Grades) or ≥ 5% (Grades 3 or 4) of Patients Treated With COTELLIC in Combination with Vemurafenib (Safety Population; Data Cut-off Date: 19 SEP 2014)

SOC/PT	GO28141				NO25395	
	Vem/Placebo (n=246)		Vem/Cobi (n=247)		Vem/Cobi (n=39)	
	All Grades (%)	Grades 3-4 (%)	All Grades ^a (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
GASTROINTESTINAL DISORDERS						
DIARRHOEA	31	1	60	6	77	8
NAUSEA	25	1	41	1	51	3
VOMITING	13	1	24	1	36	-
ABDOMINAL PAIN ^b	14	1	15	-	26	-
STOMATITIS ^c	8	-	14	1	10	-
CONSTIPATION	11	-	10	-	10	-
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
RASH ^d	53	13	55	14	77	8
PHOTOSENSITIVITY REACTION ^e	35	-	46	4	75	3
PRURITUS	19	<1	19	1	33	-
ALOPECIA	30	<1	15	<1	15	-
DRY SKIN	16	-	14	1	28	-
ACNE, DERMATITIS ACNEIFORM	11	1	16	2	33	5
HYPERKERATOSIS	30	2	11	-	-	-
ERYTHEMA	13	<1	10	-	15	-
NEOPLASMS BENIGN, MALIGNANT AND PRENEOPLASTIC COND						
BASAL CELL CARCINOMA	2	2	4	4	15	5
ACTINIC KERATOSIS, SQUAMOUS CELL CARCINOMA OF SKIN	18	13	6	3	31	8
GENERAL DISORDERS AND ADMINISTRATION SITE COND						
FATIGUE	33	3	34	4	62	8
PYREXIA	23	-	28	2	28	-
EDEMA ^f	17	1	19	-	44	3
ASTHENIA	16	1	17	2	-	-
CHILLS	5	-	10	-	21	-
METABOLISM AND NUTRITION DISORDERS						
DECREASED APPETITE	20	<1	19	-	21	-
DEHYDRATION	1	-	4	2	-	-
NERVOUS SYSTEM DISORDERS						
HEADACHE	16	2	17	<1	18	3
DYSGEUSIA	11	1	15	-	15	-
VASCULAR DISORDERS						
HYPERTENSION	8	2	15	4	15	8

EYE DISORDERS						
CHORIORETINOPATHY	<1	-	13	<1	-	-
VISION BLURRED, IMPAIRED ^g	4	-	15	<1	28	-
RETINAL DETACHMENT	<1	-	9	2	-	-
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS						
ARTHRALGIA	40	5	36	2	41	10
MYALGIA	12	2	11	<1	18	-
PAIN IN EXTREMITY	14	2	10	1	10	-

Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adae.xpt

¹Excludes laboratory PTs.

^aNational Cancer Institute Common Terminology Criteria for Adverse Events, version 4.

^bIncludes the following terms: abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort.

^cIncludes the following terms: stomatitis, aphthous stomatitis, mouth ulceration, and mucosal inflammation.

^dIncludes the following terms: rash, rash generalized, rash macular, rash maculo-papular and rash morbilliform

^eIncludes the following terms: solar dermatitis, sunburn, photosensitivity reaction

^fIncludes the following terms: lymphedema, edema, and peripheral edema.

^gIncludes the following terms: vision blurred, visual acuity reduced, visual impairment

Adverse Events Occurring In Excess in Patients Treated With Cobimetinib in Combination With Vemurafenib

Adverse events occurring in excess among patients treated on the Vem/Cobi group compared to the Vem/Placebo group with a between group difference of all toxicity grades of $\geq 5\%$ or a between group difference for toxicities graded 3-4 of 2% is shown below in Table. Events reported in excess among patients treated with Vem/Cobi compared to patients treated with Vem/Placebo included ocular toxicities (chorioretinopathy, retinal detachment and blurred vision), gastrointestinal disorders (diarrhea, nausea and vomiting), elevated liver function tests, elevated CPK, rash and photosensitivity disorders. Additionally, anemia, decreased ejection fraction, hypertension and basal cell carcinoma were reported in excess.

Table 51: GO28141 – Adverse Reactions by MedDRA SOC/PT Occurring In Excess ($\geq 5\%$, All Grades or $\geq 2\%$ Grades 3-4) in Patients Treated With Cobimetinib With Vemurafenib (Safety Population; Data Cut-off Date: 19 SEP 2014)

SOC/PT	Vem/Cobi (n=247)		Vem/Placebo (n=246)	
	All Grades ^a (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
GASTROINTESTINAL DISORDERS				
DIARRHOEA	60	7	31	1
NAUSEA	41	1	25	1
VOMITING	24	1	13	1
STOMATITIS ^b	11	1	6	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
PHOTOSENSITIVITY REACTION ^c	46	4	35	0
DERMATITIS ACNEIFORM	14	2	9	1
INVESTIGATIONS				
BLOOD CREATINE PHOSPHOKINASE INCREASED	32	11	3	0
ALANINE AMINOTRANSFERASE INCREASED	25	11	18	6
ASPARTATE AMINOTRANSFERASE INCREASED	24	9	13	2
GAMMA-GLUTAMYLTRANSFERASE INCREASED	19	13	18	10
BLOOD ALKALINE PHOSPHATASE INCREASED	15	4	9	2
BLOOD CREATININE INCREASED	14	1	8	<1
EJECTION FRACTION DECREASED	9	2	4	1
BLOOD CHOLESTEROL INCREASED	6	2	3	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
PYREXIA	28	2	23	0
CHILLS	10	0	5	0
EYE DISORDERS				
CHORIORETINOPATHY	13	<1	<1	0
VISION BLURRED ^d	10	0	2	0
RETINAL DETACHMENT	9	2	<1	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
ANAEMIA	13	2	8	2
METABOLISM AND NUTRITION DISORDERS				
HYPONATRAEMIA	5	2	1	<1
NEOPLASMS BENIGN, MALIGNANT, UNSP				
BASAL CELL CARCINOMA	5	5	2	2
METABOLISM AND NUTRITION DISORDERS				
DEHYDRATION	4	2	1	0

Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adae.xpt

^aNational Cancer Institute Common Terminology Criteria for Adverse Events, version 4.

^bIncludes the following terms: stomatitis, aphthous stomatitis, mouth ulceration, and mucosal inflammation.

^cIncludes the following terms: solar dermatitis, sunburn, photosensitivity reaction

^dIncludes the following terms: vision blurred, visual acuity reduced, visual impairment

Adverse Events of Special Interest

The adverse events of special interest including rash, second cutaneous and non-cutaneous malignancies, and ocular toxicities are further described in Section 7.3.5 above. Laboratory abnormalities are further discussed in Section 7.4.2 below and QTc prolongation and decreased left ventricular ejection fraction are further described in Sections 7.4.4 and 7.4.5, respectively.

Exploration For Additional Safety Signals

Further exploration to isolate potential safety signals related to the addition of cobimetinib was undertaken by assessing the relative incidence of adverse events in the two treatment arms through the MedDRA hierarchy using the Exploratory MedDRA-Based Adverse Event Diagnostics (MAED) analysis tool (See Section 9.4, Table 69 through 72). As a result of this exercise, two additional safety signals, hemorrhage and hyperglycemia were further explored.

Hemorrhage:

Two patients in the Vem/Cobi treatment group and no patients in the Vem/Placebo treatment group were noted to have cerebral hemorrhage. While hemorrhage did not appear as a safety signal based on review of the MedDRA primary terms, exploration of the MedDRA SMQ (narrow) for Hemorrhages revealed 18 (7%) patients with 22 events in the Vem/Placebo treatment group and 32 (13%) patients with 41 events in the Vem/Cobi treatment group with events falling in this category. The distribution of patients reported to have events classified in the MedDRA SMQ (narrow) for Hemorrhages is shown below in Table.

Table 52: GO28141- Patients* Included in the MedDRA Hemorrhage SMQ (Narrow) by MedDRA SOC and PT (Safety Population; Data Cut-off Date: 19 SEP 2014)

SOC/PT	Vem/Placebo (n=246)				Vem/Cobi (n=247)			
	G1-2		G3		G1-2		G3	
	N	%	N	%	N	%	N	%
EYE DISORDERS								
CONJUNCTIVAL HAEMORRHAGE	0	-	0	-	1	0.4%	0	-
EYE HAEMORRHAGE	1	0.4%	0	-	0	-	0	-
RETINAL HAEMORRHAGE	2	0.8%	0	-	0	-	0	-
GASTROINTESTINAL DISORDERS								
GASTROINTESTINAL HAEMORRHAGE	0	-	0	-	1	0.4%	0	-
GINGIVAL BLEEDING	1	0.4%	0	-	0	-	0	-
HAEMATEMESIS	1	0.4%	0	-	0	-	0	-
HAEMATOCHYZIA	0	-	0	-	1	0.4%	0	-
HAEMORRHOIDAL HAEMORRHAGE	1	0.4%	0	-	1	0.4%	0	-
MELAENA	0	-	1	0.4%	2	0.8%	0	-
RECTAL HAEMORRHAGE	0	-	0	-	4	1.6%	0	-
INJURY, POISONING AND PROCEDURAL COMP								
CONTUSION	2	0.8%	0	-	1	0.4%	0	-
TRAUMATIC HAEMATOMA	0	-	0	-	2	0.8%	1	0.4%
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED								
TUMOUR HAEMORRHAGE	1	0.4%	1	0.4%	1	0.4%	0	-
NERVOUS SYSTEM DISORDERS								
CEREBRAL HAEMORRHAGE	0	-	0	-	1	0.4%	1	0.4%
SUBARACHNOID HAEMORRHAGE	0	-	0	-	1	0.4%	0	-
RENAL AND URINARY DISORDERS								
HAEMATURIA	2	0.8%	0	-	6	2.4%	0	-
REPRODUCTIVE SYSTEM AND BREAST DISORDERS								
HAEMORRHAGIC OVARIAN CYST	1	0.4%	0	-	0	0.0%	0	-
MENOMETRORRHAGIA	0	-	0	-	1	0.4%	0	-
MENORRHAGIA	0	-	0	-	1	0.4%	0	-
METRORRHAGIA	0	-	0	-	1	0.4%	0	-
UTERINE HAEMORRHAGE	0	-	0	-	1	0.4%	0	-
VAGINAL HAEMORRHAGE	0	-	0	-	1	0.4%	0	-
RESPIRATORY, THORACIC AND MEDIASTINAL DIS								
EPISTAXIS	3	1.2%	0	-	2	0.8%	0	-
HAEMOPTYSIS	1	0.4%	0	-	0	-	0	-
PULMONARY HAEMORRHAGE	1	0.4%	0	-	0	-	0	-
SKIN AND SUBCUTANEOUS TISSUE DISORDERS								

Clinical Review
Ruthann M. Giusti
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Cobimetinib in combination with Vemurafenib

ECCHYMOSIS	0	-	0	-	0	-	1	0.4%
NAIL BED BLEEDING	1	0.4%	0	-	0	-	0	-
PURPURA	0	-	0	-	1	0.4%	0	-
VASCULAR DISORDERS								
HAEMATOMA	1	0.4%	0	-	1	0.4%	0	-
HAEMORRHAGE	0	-	0	-	1	0.4%	0	-
SUBGALEAL HAEMATOMA	0	-	0	-	1	0.4%	0	-

Source: NDA206192/0036(37): GO28141:adae.xpt

*Each patient reported once for each reported PT and classified according to the maximum CTCAE grade

Reviewer's comment: Hemorrhage is not currently listed as an adverse reaction in the vemurafenib (Zelboraf) label. However, hemorrhage was noted and is included in the Warnings and Precautions section of the trametinib (Mekinist) label. Hemorrhage may represent a class effect for the MEK inhibitors. No CTCAE Grade 4 or 5 events were noted in either treatment group, given the relatively small size of the safety data base, routine post-marketing surveillance is warranted. The reviewer does not find sufficient evidence to warrant a Warnings and Precaution at the present time.

Hyperglycemia:

Hyperglycemia/new onset diabetes mellitus was identified as a potential safety signal based on an excess of cases among patients treated on the Vem/Cobi arm relative to cases identified on the Vem/Placebo arm at the level of the MedDRA Hyperglycemia SMQ (Narrow). Patients identified within this SMQ are listed by primary MedDRA below.

Table 53: GO28141 – Number of Patients Included in the MedDRA Hyperglycemia SMQ (Narrow) by MedDRA SOC and PT (Safety Population; Data Cut-off Date: 19 SEP 2014)

SOCPT	Vem/Placebo (n=246)	Vem/Cobi (n=247)			
	G1	G1	G2	G3	G4
INVESTIGATIONS					
BLOOD GLUCOSE INCREASED	0	2	0	0	0
METABOLISM AND NUTRITION DIS					
DIABETES MELLITUS	0	0	1	1	0
HYPERGLYCAEMIA	3	3	2	1	1*

*One patient was reported to have both Grade 4 hyperglycemia and Grade 2 Diabetes Mellitus

Source: NDA206192/0036(37): GO28141:adae.xpt

Three Vem/Placebo treated patients and ten Vem/Cobi treated patients were reported in the Hyperglycemia SMQ (Narrow). One Vem/Cobi treated patient (GO28141-252546-2270) was reported to have Grade 4 hyperglycemia and Grade 2 diabetes mellitus. This patient did not meet the criteria for submission for a clinical narrative and none was submitted. However, information abstracted from the case report form is summarized below. Two Vem/Cobi treated patients (GO28141-253108-2332 and GO28141-255383-2310) were reported to have Grade 3 adverse events (hyperglycemia and diabetes mellitus, respectively) and were treated with insulin. Assessment of these two cases is complicated by concomitant medications. None of these cases was assessed by the Applicant as drug-related. Case narratives/summary for these three patients are included below.

GO28141-252546-2270 (summarized from the case report forms):

The patient was a 55 year old male with a history of hypertension, coronary artery calcifications, diverticulosis and Grade 2 elevated glucose at baseline. Concomitant medications included aspirin, hydrochlorothiazide, bystolic, ibuprofen, hydrocodone, multivitamins and vitamin C and D supplements. The patient was diagnosed on Feb 13, 2013 to have a stage IIIc melanoma of the right posterior scalp. Surgical treatment included a palliative wide local excision and right posterior lateral neck dissection. The patient had had no prior systemic or radiation therapy for melanoma. The patient had a baseline ECOG performance status of 0. He received Vem/Cobi starting on 18 Sept 2013. The patient was reported to have a blood glucose within normal limits at baseline. Grade 4 hyperglycemia was reported on study day 68,

GO28141-253108-2332 (abstracted from the clinical narrative, Safety Update Report, page 294):

At screening ((b)(6)), the patient's height was 158 cm, weight was 109 kg, and blood glucose was 175 mg/dL (normal range: 70-139 mg/dL).

On (b)(6) (Study Day 179), the patient presented to emergency department with abdominal pain, groin pain, and worsening genital area pain accompanied by swelling and redness and was suspected with cellulitis. A CT was performed which confirmed Grade 3 **vulval cellulitis** of left labia majora (vulval cellulitis left labia majora; serious). On the same day (b)(6), the patient was noted to have Grade 3 **hyperglycemia** (serious) with blood glucose 676 (units not reported). She received 15 units of insulin. Due to the event hyperglycemia the vemurafenib was further interrupted. Reportedly, the patient was afebrile with WBC count 30,000 (units and normal range not reported). On (b)(6) *Study Day 180*, *treatment with vemurafenib and cobimetinib was permanently discontinued due to vulval infection*. On (b)(6) (Study Day 183), pelvic CT scan showed worsening of subcutaneous edema. On (b)(6) (Study Day 185), wound culture showed *Clostridium tetani*, *Escherichia coli* and enterococcus. She received treatment with piperacillin sodium/tazobactam sodium and hydromorphone hydrochloride for cellulitis. *The same day, hyperglycemia was considered resolved*. On (b)(6) (Study Day 189), the event of vulval cellulitis was considered resolved. The last dose of cobimetinib (40 mg) was administered

on (b) (6) (Study Day 162) and vemurafenib (480 mg) was administered on (b) (6) (Study Day 179). The investigator considered hyperglycemia to be unrelated to vemurafenib and cobimetinib. Concomitant medication (prednisone) was a possible etiological factor for the event of hyperglycemia.

GO28141-255383-2310 (abstracted from the clinical narrative, Safety Update Report, page 284):

At screening ((b) (6)), patient's height was 157 cm, weight 87 kg and blood glucose was 5.9 mmol/L (normal range: 4.2-6.3 mmol/L).

On (b) (6) (Study Day 59), the patient experienced Grade 2 fatigue (non-serious, related to both drugs) and Grade 1 tremor (non-serious, unrelated to both drugs). On (b) (6) (Study Day 75), the patient had pre-existing Grade 2 anxiety (non-serious, unrelated to both drugs). On (b) (6) (Study Day 136), the patient was noted to have Grade 3 **diabetes mellitus** (serious, blood glucose not reported), resulting in hospitalization. He was started on treatment with glucose, insulin, protamine zinc/insulin aspart and electrolyte solution with sodium acetate. On (b) (6) (Study Day 140), his p-glucose was 8.7 mmol/L. On (b) (6) (Study Day 150), treatment with vemurafenib was interrupted due to LFT elevated and was later permanently discontinued due to disease progression. On (b) (6) (Study Day 162), he was discharged from the hospital. The investigator considered diabetes mellitus to be unrelated to the vemurafenib and cobimetinib. Betamethasone sodium phosphate and unspecified treatment drugs was a possible etiological factor for the event.

Reviewer's comment: Both Hemorrhage and hyperglycemia are listed in the Warnings and Precautions section of the MEKINIST label and may represent class effects and a Warning should be considered for Hemorrhagic events in the COTELLIC label. Hemorrhagic events occurring among patients treated with Vem/Cobi were generally low grade. Hyperglycemia is labeled in the vemurafenib label. Routine monitoring for hyperglycemia was not conducted in the GO28141 and the number of events captured in the Hyperglycemia SMQ (Narrow) is small. At present while it is unclear whether the risk of hyperglycemia is increased when cobimetinib is used in combination with vemurafenib. This event should be monitored in the post-marketing setting.

Four patients, all treated with Vem/Cobi were classed in the Pregnancy and neonatal topics, Congenital, Familial and Genetic Disorders SMQ (Narrow). However, on inspection, all cases had primary terms more consistent with skin, ocular or pre-neoplastic conditions [(ichthyosis (n=2), corneal dystrophy (n=1), Bowen's Disease (n=1)].

7.4.2 Laboratory Findings

Laboratory screening for hematologic abnormalities was performed at baseline and prior to each cycle of treatment as outlined in Table. Hematologic assessments were done at screening and on D1 of each cycle. Laboratory screening for liver function and chemistry abnormalities was performed at baseline, on D1 and D15 through Cycle 3 and prior to each cycle of treatment thereafter. Routine testing for serum glucose was not performed.

Baseline screening for routine hematology (hemoglobin, WBC, platelet count), chemistry (electrolytes, creatinine, alkaline phosphatase, AST, ALT, and total bilirubin) was completed in excess of 98% of all patients. Baseline screening for magnesium level and creatinine phosphokinase was less complete (94% and 89%, respectively). For purposes of the analysis of laboratory findings below, the denominator was assumed to be the denominator of the safety population. If a baseline laboratory value was missing, it was assigned a normal at baseline (NCICTCAE Grade =0). Of note, numbers of patients with laboratory adverse events reported in Table 54 are based on the CTCAE grade as derived from actual lab values reported in the analysis laboratory data file adlb.xpt and may differ from the numbers of patients reported in Table 50 which is derived from events reported on the case report form and captured in the adverse event analysis file adae.xpt.

The number of patients with laboratory abnormalities worsening from baseline is shown below in Table 54.

Table 54: GO28141 – Per Patient Incidence of Laboratory Abnormalities Occurring in \geq 10% (All Grades) or \geq 2% (Grades 3-4) of Patients Treated with COTELLIC in Combination with Vemurafenib and Worsening from Baseline (Safety Population; Data Cut-off Date: 19 SEP 2014)

Laboratory Value	Vem/Placebo n=246		Vem/Cobi n=247	
	All Grades	Grades 3-4	All Grades	Grades 3-4
	%	%	%	%
Hematology				
Decreased WBC	14	1	25	1
Decreased Hemoglobin	38	3	57	2
Decreased Lymphocytes	34	5	46	7
Decreased Platelets	7	0	15	0
Liver Function Test				
Increased ALT	47	6	60	11
Increased alkaline phosphatase	40	3	62	7
Increased AST	38	2	63	7
Increased GGT	44	12	46	18
Increased TBili	41	1	32	2
Chemistry				
Decreased Albumin	13	0	34	1
Decreased Calcium	8	1	21	0
Increased Creatinine	96	1	96	3
Decreased Phosphate	32	5	59	10
Decrease Potassium	15	3	23	4
Increased Potassium	13	0	21	2
Decreased Sodium	28	2	36	5
Increased Sodium	2	0	7	0
Decreased Magnesium	7	<1	9	0
Other				
Increased Creatine Phosphokinase	9	<1	59	10

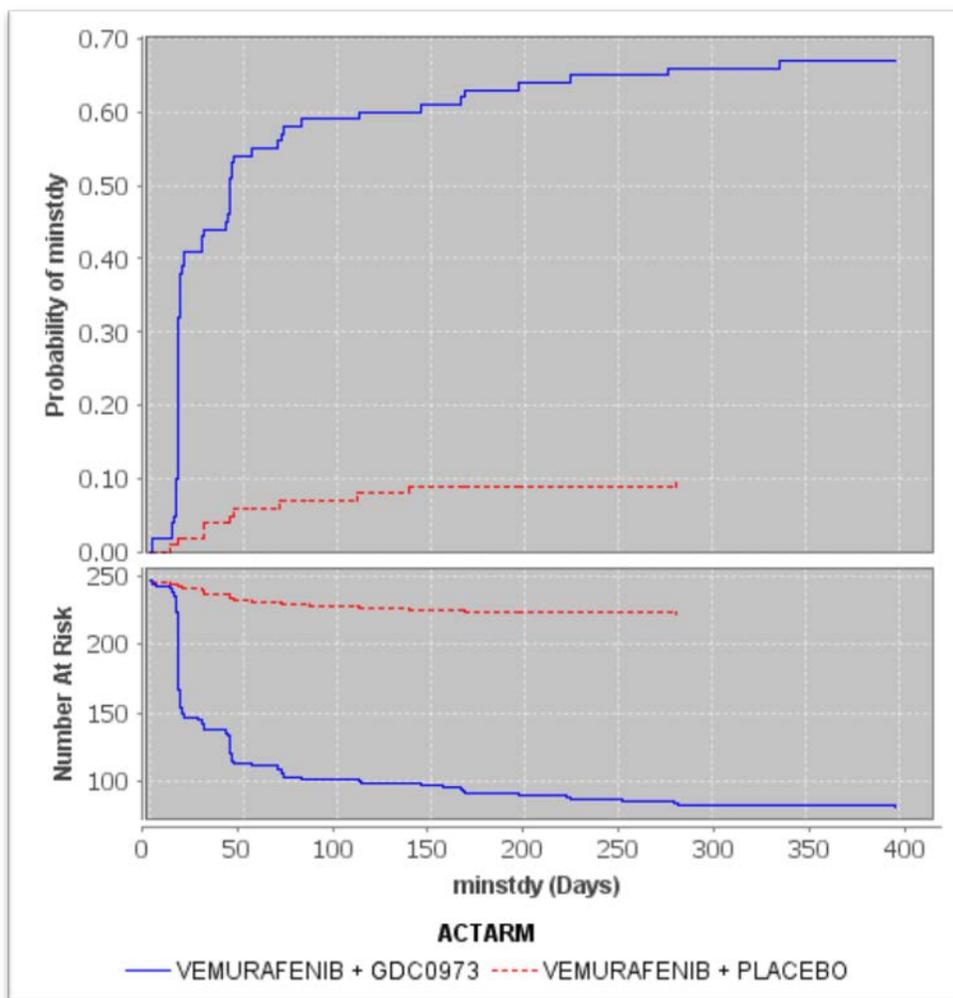
Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adlb.xpt and Applicant response to IR

Creatinine Phosphokinase (CPK) Elevation/Musculoskeletal Adverse Reactions:

The incidence of CPK elevation worsened over baseline was much higher among patients treated with Vem/Cobi than among patients treated with Vem/Placebo. Grade 3-4 CPK elevation worsened over baseline was reported in <1% of patients treated with Vem/Placebo and in 10% of patients treated with Vem/Cobi. Twelve patients, all treated with Vem/Cobi had a CPK elevation of Grade 4.

The median time of onset of CPK elevations in the Vem/Placebo treatment group was 43 days (range: 1 to 281 days); the median time to onset of CPK elevation in the Vem/Cobi treatment group was 16 days (range: 1 to 281 days). The cumulative per-patient incidence of CPK elevation by study day of onset and treatment group is shown below.

Figure 30: GO28141 – Cumulative Per-Patient Incidence of Patients Identified as Having Elevated CPK (\geq Grade1) and Worsened Over Baseline by Day on Study and Treatment Group (Safety Population; Data Cut-off Date: 19 SEP 2014)



Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adlb.xpt, adae.xpt

Rhabdomyolysis (defined as serum CK increase of more than 10 times the baseline value with a concurrent 1.5 –fold or greater increase in serum creatinine above baseline value) occurred in one (<1%) patient treated with Vem/Placebo and in eight (3%) patients treated with Vem/Cobi. Two additional patients (one in each treatment arm) were reported to have rhabdomyolysis but did not meet this definition.

Despite laboratory evidence of rhabdomyolysis, fewer patients treated with Vem/Cobi reported musculoskeletal adverse events (All Grades: 51% vs. 61% ; Grade 3 or 4: 10% vs. 6%).

Musculoskeletal adverse events led to a dosing modification in 23 (9%) of patients treated with Vem/Placebo and in 12 (5%) of patients treated with Vem/Cobi. The median time to dose adjustment was 16 days (range 3 to 220 days) in patients treated with Vem/Placebo and 51 days (range: 11 to 33 days) in the 12 patients treated with Vem/Cobi. Musculoskeletal events were reported to be serious in 6 (2%) of patients in each treatment group and resulted in hospitalization in 5 (2%) of patients in each treatment group.

The most commonly reported primary terms for musculoskeletal adverse events are shown in the table below.

Table 55: GO28141- MedDRA Primary Terms Within the MedDRA Musculoskeletal and Connective Tissue System Organ Class (SOC) Reported in $\geq 1\%$ of Patients Treated with Vemurafenib and Cobimetinib (Safety Population; Data Cut-off Date: 19 SEP 2014)

PT	Vem/Placebo n=246		Vem/Cobi n=247	
	All Grades	Grades 3-4	Grades 3-4	All Grades
	%	%	%	%
ARTHRALGIA	40	5	36	2
MYALGIA	12	2	11	0
PAIN IN EXTREMITY	14	2	10	1
BACK PAIN	5	0	6	0
MUSCULOSKELETAL PAIN	6	0	5	1
MUSCULAR WEAKNESS	1	0	3	0
MUSCLE SPASMS	2	0	2	0
GROIN PAIN	0	0	2	0
FLANK PAIN	0	0	1	0
MUSCULOSKELETAL STIFFNESS	0	0	1	0
NECK PAIN	1	0	1	0
PAIN IN JAW	1	0	1	0
SPINAL PAIN	0	0	1	0
ARTHRITIS	2	1	1	0
DUPUYTREN'S CONTRACTURE	0	0	1	0
JOINT STIFFNESS	1	0	1	0
JOINT SWELLING	2	0	1	0
MUSCULOSKELETAL CHEST PAIN	2	0	1	0
PLANTAR FASCIITIS	1	0	1	0
BONE PAIN	2	0	0	0

Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adae.xpt

Liver Function Abnormalities

Hepatotoxicity is labeled under Warnings and Precautions in the current USPI for vemurafenib. Liver function test abnormalities were common in patients treated with Vem/Placebo. However, the incidence and severity of LFT elevations increased with the addition of cobimetinib (see Table 56 through 59 below).

Table 56: GO28141 – Maximum AST Elevation Worsened from Baseline by Treatment Arm (Safety Population; Data Cut-off Date: 19 SEP 2014)

	Vem/Placebo (n=246)	Vem/Cobi (n=247)
AST Worsened From Baseline to:	n (%)	n (%)
AST > 2xULN <=3xULN	13 (5)	20 (7)
AST > 3xULN <=5xULN	10 (4)	21 (9)
AST > 5xULN <=10xULN	2 (1)	12 (5)
AST >10xULN <=15xULN	1 (<1)	3 (1)
AST >15xULN <=20xULN	0 (0)	1 (<1)
AST >20xULN	1 (<1)	0 (0)
Total: AST>2xULN	27(11)	57 (23)
AST >5xULN	4(2)	16(6)
AST >10xULN	2 (1)	4 (2)

Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adlb.xpt

Table 57: GO28141 – Maximum ALT Elevation Worsened from Baseline by Treatment Arm (Safety Population; Data Cut-off Date: 19 SEP 2014)

	Vem/Placebo (n=246)	Vem/Cobi (n=247)
ALT Worsened From Baseline to:	n (%)	n (%)
ALT > 2xULN <=3xULN	26 (11)	23 (9)
ALT > 3xULN <=5xULN	14 (6)	18 (8)
ALT > 5xULN <=10xULN	8 (3)	17 (7)
ALT >10xULN <=15xULN	0 (0)	3 (1)
ALT >15xULN <=20xULN	3 (1)	3 (1)
ALT >20xULN	0 (0)	1 (<1)
Total: ALT >2xULN	51(21)	65 (26)
ALT >5xULN	11(4)	24(10)
ALT>10xULN	3 (1)	7 (3)

Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adlb.xpt

Elevations in excess of 5xULN and 10xULN were noted in the Vem/Cobi treatment arm compared to the Vem/Placebo arm for both ALT and AST. Elevations in total bilirubin of greater than 2xULN occurred more commonly among patients treated with Vem/Placebo than among patients treated with Vem/Cobi (Table 58).

Table 58: GO28141 – Maximum Bilirubin Elevation Worsened from Baseline by Treatment Arm (Safety Population; Data Cut-off Date: 19 SEP 2014)

	Vem/Placebo (n=246)	Vem/Cobi (n=247)
BILI Worsened From Baseline to:	n (%)	n (%)
BILI > 2xULN <=3xULN	14 (6)	6 (2)
BILI > 3xULN <=5xULN	1 (<1)	0 (0)
BILI > 5xULN <=10xULN	1 (<1)	2 (<1)
Total BILI > 2xULN	16 (7)	8 (3)

Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adlb.xpt

The incidence of ALP elevations was higher among patients treated with Vem/Cobi than with Vem/Placebo; however a large percentage of patients with elevations fell into the category of ALP elevations \leq 3xULN which suggests non-specific hepatic injury and is less likely predictive of obstruction.

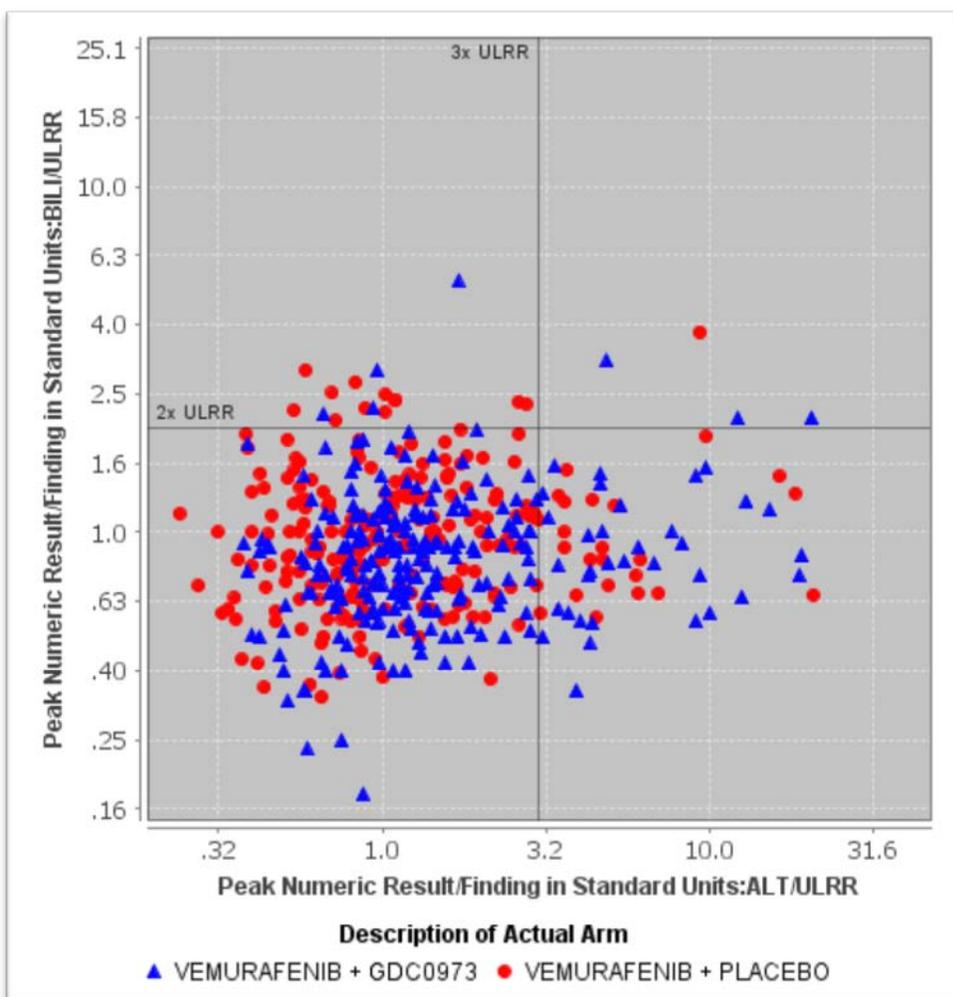
Table 59: GO28141 – Maximum ALP Elevation Worsened from Baseline by Treatment Arm (Safety Population; Data Cut-off Date: 19 SEP 2014)

	Vem/Placebo (n=246)	Vem/Cobi (n=247)
ALP Worsened From Baseline to:	n (%)	n (%)
ALP > ULN <=2xULN	72 (29)	97 (39)
ALP > 2xULN <=3xULN	10 (4)	13 (5)
ALP > 3xULN <=5xULN	6 (2)	15 (6)
ALP > 5xULN <=10xULN	7 (3)	12 (5)
ALP >10xULN <=15xULN	0 (0)	2 (1)
ALP >20xULN	0 (0)	1 (<1)
Total: ALP>ULN	95 (39)	140 (57)
ALP \leq 3xULN	82 (33)	110 (45)

Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adlb.xpt

One patient in the Vem/Placebo arm and three patients in the Vem/Cobi arm were identified as having met the following enzyme criteria: ALT > 3xULN; BILI >2xULN; ALP <2xULN and were identified as potential Hy's Law cases. The scatter gram for patients meeting the above criteria is shown below.

Figure 31: GO28141 – Peak Liver Function Lab Values by Study Group (Safety Population: Data Cutoff Date: 19 SEP 2014)



Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adlb.xpt

A broader definition of Hy's Law including patients with (ALT OR AST > 3xULN; BILI >2xULN; ALP <2xULN) yielded eight patients, three patients in the Vem/Placebo arm and five patients in the Vem/Cobi arm.

Table 60: GO28141- Potential Hy's Law Cases (defined as ALT or AST > 3xULN, BILI >2xULN and ALP <2xULN) (Safety Population: Data Cutoff Date: 19 SEP 2014)

	Vem/Placebo (n=246)	Vem/Cobi (n=247)
Hy's Law (ALT/AST > 3xULN; BILI >2xULN; ALP <2xULN)	3 (1)	5 (2)

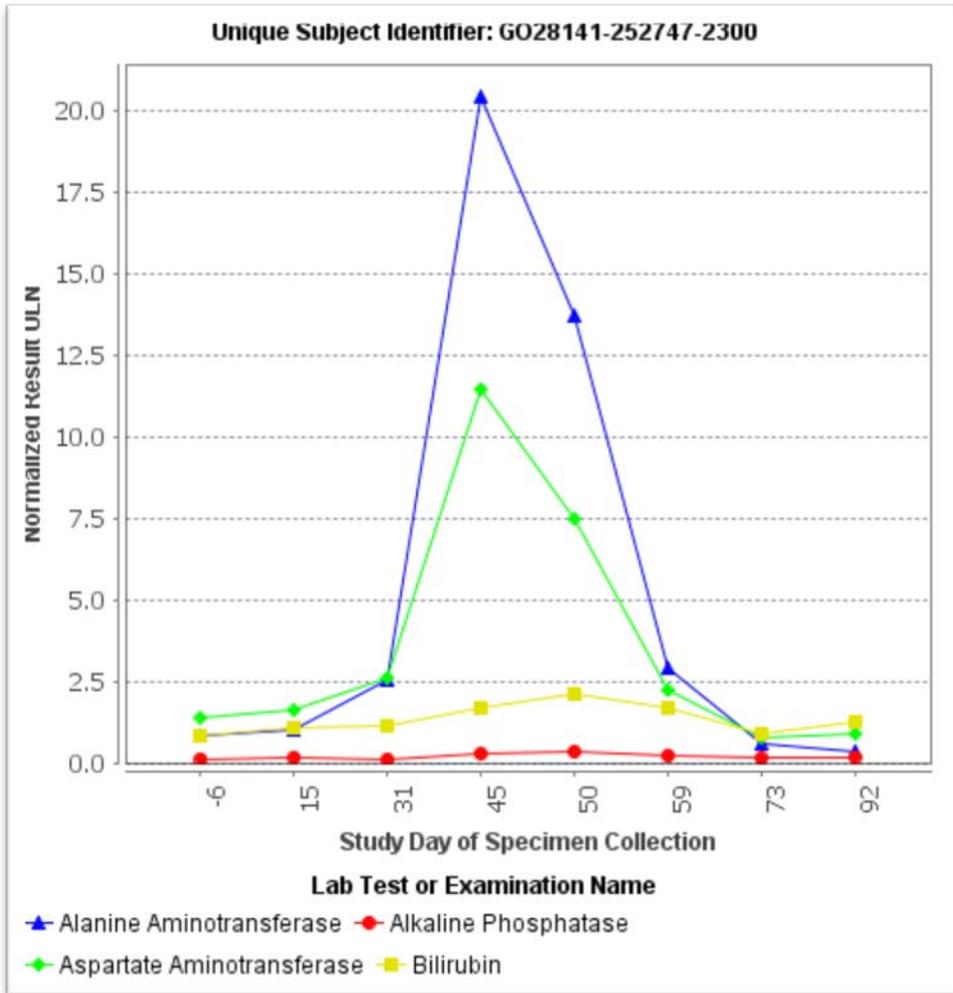
Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adlb.xpt

The five patients on the Vem/Cobi treatment group who met the above definition for Hy's Law are listed below:

GO28141-252747-2239*
GO28141-252747-2300
GO28141-254375-2289
GO28141-255383-2440*
GO28141-258059-2208*

The pattern of LFT elevation and the clinical narrative for these five patients were reviewed. Three of the above patients were felt to have patterns which were not suggestive of acute hepatic injury or narratives which suggested alternative explanations for the LFT elevations. The remaining two patients are discussed below.

GO28141-252747-2300:



Source: NDA206192/0036(37); 3/10/2015, p. 466

Site number.	252747
Patient number	2300
Age/Race/Gender	68-year-old White Female
Treatment arm	Cobimetinib plus vemurafenib
Grade and Event (Preferred Term [verbatim term]):	Grade 4 Alanine aminotransferase increased (alanine aminotransferase elevation) Grade 3 Aspartate aminotransferase increased (aspartate aminotransferase elevated) Grade 3 Gamma-glutamyltransferase increased (GGT elevation) Grade 1 Chorioretinopathy (central serous retinopathy)
Event categories	Grade \geq 3 elevated liver function tests, AE leading to treatment discontinuation, Any grade retinal detachment or serous retinopathy

This 68-year-old white female patient was randomized to study GO28141 on 04-Oct-2013 at a site in Czech Republic. The patient was diagnosed with nodular melanoma on the lower extremity on 07-Feb-2013. At screening, the patient's disease stage was IIIc with an ECOG performance status of 0. Previous diagnostic procedures and treatments for melanoma included right lower extremity excisional biopsy (x 2). No past medical and surgical history was reported for this patient. Concurrent conditions include hypercholesterolemia (since 2009) and hypertension (since 2011). Concomitant medication included telmisartan (since 01-Mar-2013). Treatment with vemurafenib 960 mg twice daily and cobimetinib 60 mg daily 21/7 schedule started on 07-Oct-2013 (Study Day 1).

Adverse Event 1: Alanine aminotransferase increased (elevated ALT)

Adverse Event 2: Aspartate aminotransferase increased (elevated AST)

Adverse Event 3: Gamma-glutamyltransferase increased (elevated GGT)

At screening (01-Oct-2013), laboratory work-up revealed aspartate aminotransferase (AST) 1.02 μ kat/L (normal range: 0.1-0.72 μ kat/L), alanine aminotransferase (ALT) 0.68 μ kat/L (normal range: 0.1-0.78 μ kat/L), gamma-glutamyl transferase (GGT) 7.32 μ kat/L (normal range: 0.14-0.84 μ kat/L) and total bilirubin 14.6 μ mol/L (normal range: 2-17 μ mol/L). On 21-Oct-2013 (Study Day 15), the patient was noted to have Grade 1 elevated alanine aminotransferase and elevated aspartate aminotransferase (ALT 0.81 μ kat/L; AST 1.17 μ kat/L; non-serious), Grade 3 elevated GGT (GGT 3.53 μ kat/L; non-serious) and Grade 2 elevated blood bilirubin (bilirubin 19 μ mol/L; non-serious; related to both drugs).

Due to the event of chorioretinopathy, vemurafenib was temporarily interrupted and the dose of cobimetinib was reduced to 40 mg. On 06-Nov-2013 (Study Day 31), treatment with vemurafenib (960 mg) was resumed and the treatment with cobimetinib was resumed at a reduced dose of 40 mg. On 20-Nov-2013 (Study Day 45), the patient was noted to have Grade 4 elevated alanine aminotransferase (ALT 15.93 μ kat/L) and Grade 3 elevated aspartate aminotransferase (AST 8.28 μ kat/L). The patient was asymptomatic. Relevant laboratory values are provided in the table below. On 18-Dec-2013 (Study Day 73), a laboratory work-up showed AST 0.59 μ kat/L, ALT 0.46 μ kat/L, GGT 3.62 μ kat/L and total bilirubin 16.1 μ mol/L and the events of elevated alanine aminotransferase, aspartate aminotransferase and blood

bilirubin were resolved. On 12-May-2014 (Study Day 218), the event of elevated GGT was considered resolved.

Relevant laboratory values:

Date (Study Day)	AST (normal range: 0.1-0.72 μkat/L)	ALT (normal range: 0.1-0.78 μkat/L)	GGT (normal range: 0.14-0.84 μkat/L)	Total bilirubin (normal range: 2-17 μmol/L)	ALP (normal range: 0-7.49 μkat/L)
01-Oct-2013 (screening)	1.02	0.68	7.32	14.6	1.23
21-Oct-2013 (Study Day 15)	1.17	0.81	3.53	19	1.45
06-Nov-2013 (Study Day 31)	1.91	2	3.11	19.9	1.14
20-Nov-2013 (Study Day 45)	8.28	15.93	7.82	28.9	2.39
25-Nov-2013 (Study Day 50)	5.41	10.70	10.35	36.6	2.88
04-Dec-2013 (Study Day 59)	1.61	2.28	6.35	29.6	1.94
18-Dec-2013 (Study Day 73)	0.59	0.46	3.62	16.1	1.29
06-Jan-2014 (Study Day 92)	0.66	0.31	2.43	22.3	1.56

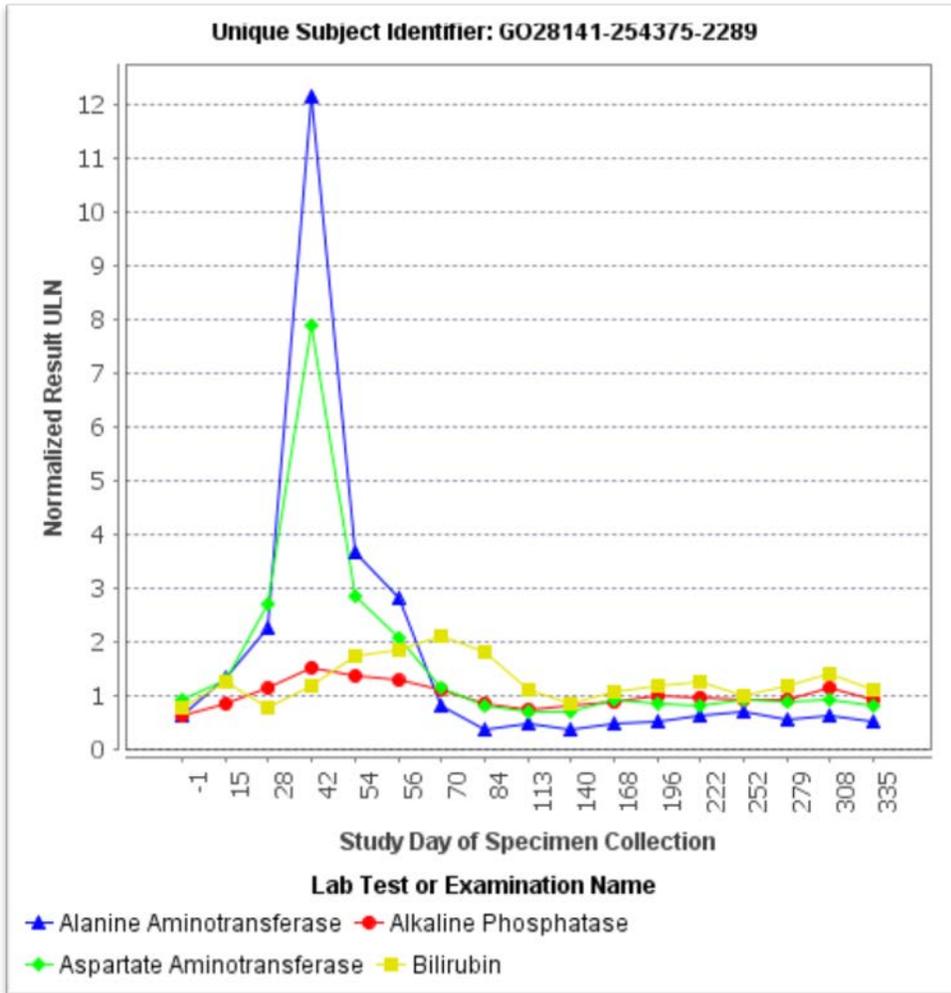
Treatment with vemurafenib and cobimetinib was not changed as result of the event of elevated GGT however; on 22-Nov-2013 (Study Day 47), treatment with vemurafenib and cobimetinib was permanently discontinued due to the events of elevated alanine aminotransferase and aspartate aminotransferase, with the last doses of vemurafenib (960 mg) and cobimetinib (40 mg) administered on the same day (22-Nov-2013). Subsequently she entered the follow-up phase of the study.

On 18-Dec-2013 (Study Day 73), an overall response assessment by CT scan showed disease progression with new lesions in the liver and skin (right lower leg). The investigator considered elevated alanine aminotransferase; elevated aspartate aminotransferase and elevated GGT to be related to vemurafenib and cobimetinib.

On 14-Jan-2014 (Study Day 100), the patient started 2nd line follow-up cancer therapy with vinblastine, dacarbazine and cycloplatin.

Reviewer's comment: Review of this case does not indicate alternative explanation for elevated LFTs (e.g., history of ethanol abuse, viral hepatitis, underlying liver disease and concomitant illness or medications likely to cause hepatotoxicity. Resolution of elevated LFTs suggests a positive de-challenge effect. Acute hepatotoxicity related to treatment with cobimetinib and/or vemurafenib cannot be ruled out.

GO28141-254375-2289:



Source: NDA206192/0036(37); 3/10/2015, p. 334

Site number.	254375
Patient number	2289
Age/Race/Gender	68-year-old White Female
Treatment arm	Cobimetinib plus vemurafenib
Grade and Event (Preferred Term [verbatim term]):	Grade 2 Retinal detachment (retinal detachment) Grade 2 Retinal detachment (retinal detachment) Grade 2 Abdominal pain (abdominal pain) Grade 3 Alanine aminotransferase (ALT) increased Grade 3 Aspartate aminotransferase (AST) increased
Event categories	Any grade retinal detachment or serous retinopathy, SAE, AE leading to treatment discontinuation, Grade \geq 3 elevations in liver function tests

This 68-year-old white female patient was randomized to study GO28141 on 27-Sep-2013 at a site in the Czech Republic. The patient was diagnosed with "melanoma with exulceration" on upper extremity in Dec-2010. At screening, the patient's disease stage was M1c with an ECOG performance status was of 1. Previous diagnostic procedures and treatment for melanoma included immunotherapy with interferon from 06-Nov-2012 to 14-Nov-2012, wide local excision of left upper extremity (× 2), re-excision in scar of left upper extremity (× 2) and residual tumor mass operation of left upper extremity. No past medical history was reported for this patient. Surgical history included plastic operation of umbilical hernia (1980), cholecystectomy (1982), appendectomy (1986) and total endoprosthesis of right knee (2000). Concurrent conditions included arterial hypertension, hypertonic changes of right retinal vessels (both since 2000), mitral insufficiency and tricuspid insufficiency (since unknown date). Concomitant medications included enalapril, salicylic acid, acebutolol, indapamide, allopurinol (since 2000), omeprazole (since 19-Sep-2013) and potassium chloride (since 2013). Treatment with vemurafenib 960 mg twice daily and cobimetinib 60 mg daily 21/7 schedule was started on 27-Sep-2013 (Study Day 1).

Adverse event 3: Abdominal pain

Adverse event 4: Alanine aminotransferase (ALT) increased

Adverse event 5: Aspartate aminotransferase (AST) increased

At screening (26-Sep-2013), GGT was 0.36 μ kat/L (normal range: 0.08-0.6 μ kat/L), AST 0.48 μ kat/L (normal range: 0-0.52 μ kat/L), ALT 0.36 μ kat/L (normal range: 0-0.55 μ kat/L) and total bilirubin 12 μ mol/L (normal range: 2-15 μ mol/L). On 11-Oct-2013 (Study Day 15), the patient experienced serious Grade 2 abdominal pain, and was noted to have Grade 3 elevated ALT and AST (ALT 0.74 μ kat/L and AST 0.68 μ kat/L) and Grade 2 elevated blood bilirubin (bilirubin 19 μ mol/L; non-serious; related to vemurafenib). On 14-Oct-2013 (Study Day 18), treatment with vemurafenib was interrupted due to the event of abdominal pain. On [REDACTED] ^{(b) (6)}, she was hospitalized. An abdominal ultrasound, X-ray and blood chemistry were without significant findings (details not provided). She received treatment with nimesulide and tramadol. No treatment was administered for elevated ALT and AST, and elevated blood bilirubin. Relevant laboratory values are represented in the table below. On [REDACTED] ^{(b) (6)}, study treatment with vemurafenib was resumed at a reduced dose of 480 mg. On [REDACTED] ^{(b) (6)}, the patient was discharged from the hospital on that day. Treatment with cobimetinib was not changed due to abdominal pain. Treatment with

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vemurafenib and cobimetinib was not changed due to ALT and AST increased. On 03-Nov-2013 (Study Day 38), treatment with cobimetinib was permanently discontinued due to retinal detachment. On 07-Nov-2013 (Study Day 42), the event of abdominal pain was resolved. On 05-Dec-2013 (Study Day 70), the event of elevated ALT was resolved. On 19-Dec-2013 (Study Day 84), the event of AST was resolved. On 13-Feb-2014 (Study Day 140), the event of elevated blood bilirubin was resolved.

Date (Study Day)	ALT (normal range: 0-0.55 μ kat/L)	AST (normal range: 0-0.52 μ kat/L)	GGT (normal range: 0.08-0.6 μ kat/L)	Bilirubin (normal range: 2-15 μ mol/L)
26-Sep-2013 (screening)	0.36	0.48	0.36	12
11-Oct-2013 (Study Day 15)	0.74	0.68	0.44	19
24-Oct-2013 (Study Day 28)	1.24	1.41	1.09	12
07-Nov-2013 (Study Day 42)	6.69	4.11	1.85	18
19-Nov-2013 (Study Day 54)	2.02	1.49	1.89	26
21-Nov-2013 (Study Day 56)	1.54	1.08	1.84	28
05-Dec-2013 (Study Day 70)	0.45	0.61	1.50	32
19-Dec-2013 (Study Day 84)	0.20	0.42	0.98	27
17-Jan-2014 (Study Day 113)	0.27	0.37	0.76	17

The investigator considered abdominal pain to be related to vemurafenib and unrelated to cobimetinib. The investigator considered events of elevated ALT and AST to be related to vemurafenib and unrelated to cobimetinib. On 27-Aug-2014 (Study Day 335), assessment of tumor response revealed disease progression. No new lesions were reported. Study treatment with vemurafenib was permanently discontinued due to disease progression with the last dose of vemurafenib (720 mg) administered on 26-Aug-2014 (Study Day 334). Subsequently, the patient entered follow-up phase of the study.

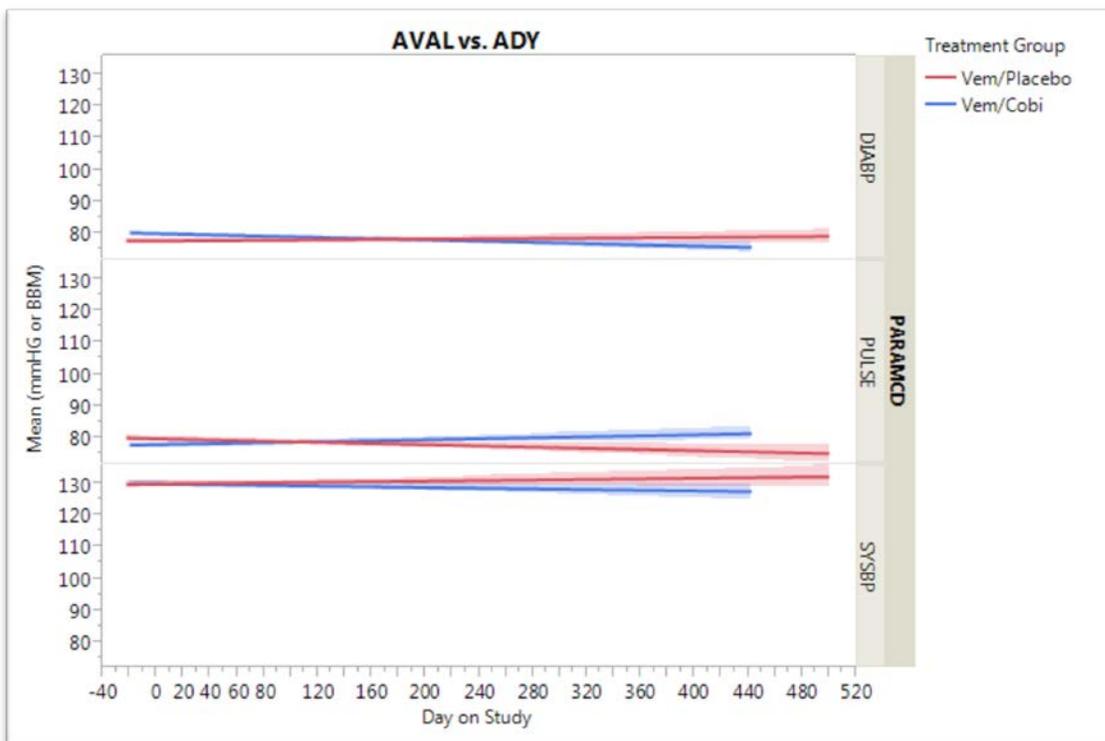
Reviewer's comment: This patient was taking multiple concurrent medications for an underlying cardiac condition including enalapril, salicylic acid, acebutolol, indapamide, allopurinol (since 2000), omeprazole (since 19-Sep-2013) and potassium chloride. Of these medications, allopurinol, enalapril, acebutolol and salicylic acid have been linked to rare cases of hepatotoxicity. Review of this case does not suggest a past history of ethanol abuse, viral hepatitis or underlying liver disease. The cause of the patient's abdominal pain was not identified. However, it is interesting to note the decrease in ALT/AST coincident with discontinuation of cobimetinib while vemurafenib was continued. While assessment of this case is complicated by multiple concomitant medications known rarely to cause hepatotoxicity, acute hepatotoxicity related to treatment with cobimetinib and/or vemurafenib cannot be ruled out. Nor can the potentiation of hepatotoxicity due to cobimetinib and/or vemurafenib due to drug-drug interaction.

Reviewer's comment: This reviewer assesses at least one case meeting the criteria of Hy's Law. A second case potentially meets Hy's Law criteria. The interpretation of this case is confounded by concomitant medications known rarely to cause hepatotoxicity. A positive dechallenge with the discontinuation of cobimetinib in this second case suggests the potential for drug-drug interaction at minimum. The identification of these cases along with the pattern of AST/ALT elevations noted in excess among patients treated in the Vem/Cobi treatment group suggests that hepatotoxicity may be increased with the addition of cobimetinib. The reviewer recommends that hepatotoxicity be included in the Warnings and Precaution section of the label. The potential for drug-drug interactions should be monitored in the post-marketing setting.

7.4.3 Vital Signs

A series of exploratory analyses were conducted to assess trends in changes in vital signs over time by treatment group. The tables below display the linear regression with confidence intervals. There was a suggestion of a decrease in respiratory rate, an increase in pulse rate, and a decrease in systolic and diastolic blood pressure in the Vem/Cobi group relative to the Vem/Placebo group over time. An increase in mean temperature and weight were noted in the Vem/Cobi group relative to the Vem/Placebo group over time.

Figure 32: GO28141 – Linear Regression Analysis of Systolic and Diastolic Blood Pressure and Pulse by Day on Study and Actual Treatment Group (Safety Population: Data Cutoff Date: 9 MAY 2014*)

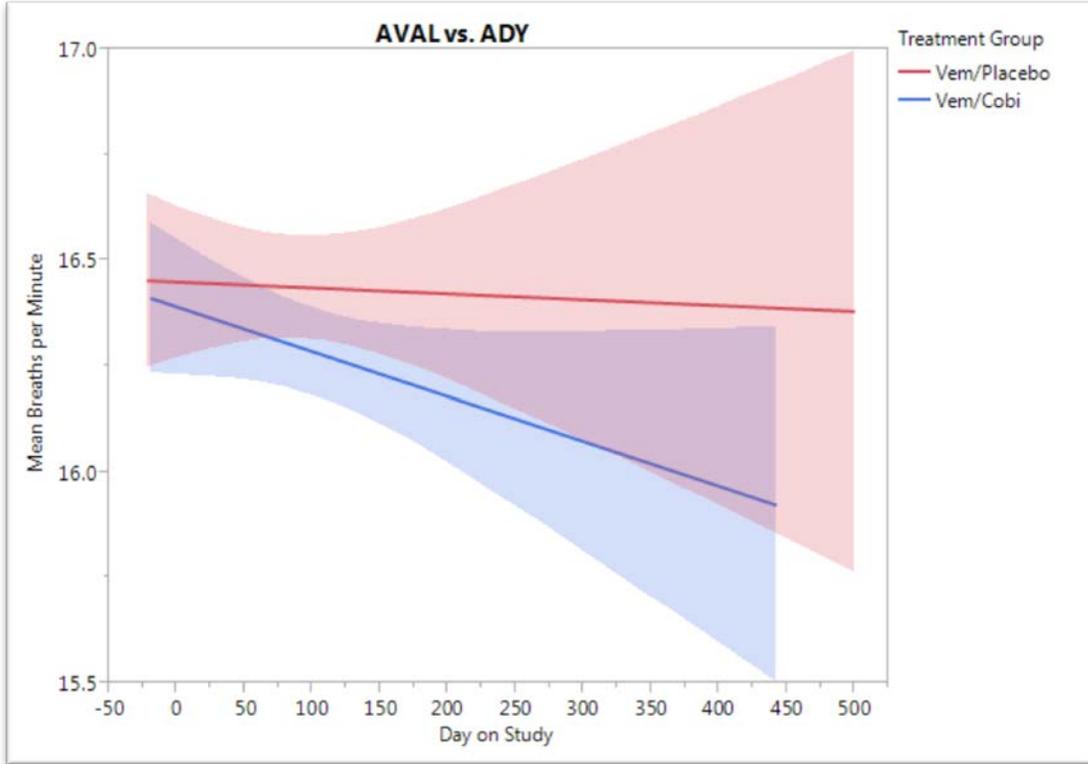


*Update in vital signs dataset not provided with 90D Safety Update. Data from the original submission used for this analysis.

Source: NDA206192/0001(2); 12/11/2014: 5.3.5.1: GO28141:adv.s.xpt

Reviewer's comment: It is interesting to note that while, overall, there was a trend towards decreased systolic and diastolic blood pressure and increased pulse rate among patients in the Vem/Cobi treatment group, which may be related to volume depletion given the high percentage of patients on the Vem/Cobi arm who experienced diarrhea, hypertension was reported as an adverse event more frequently in the Vem/Cobi arm as well (Table 50).

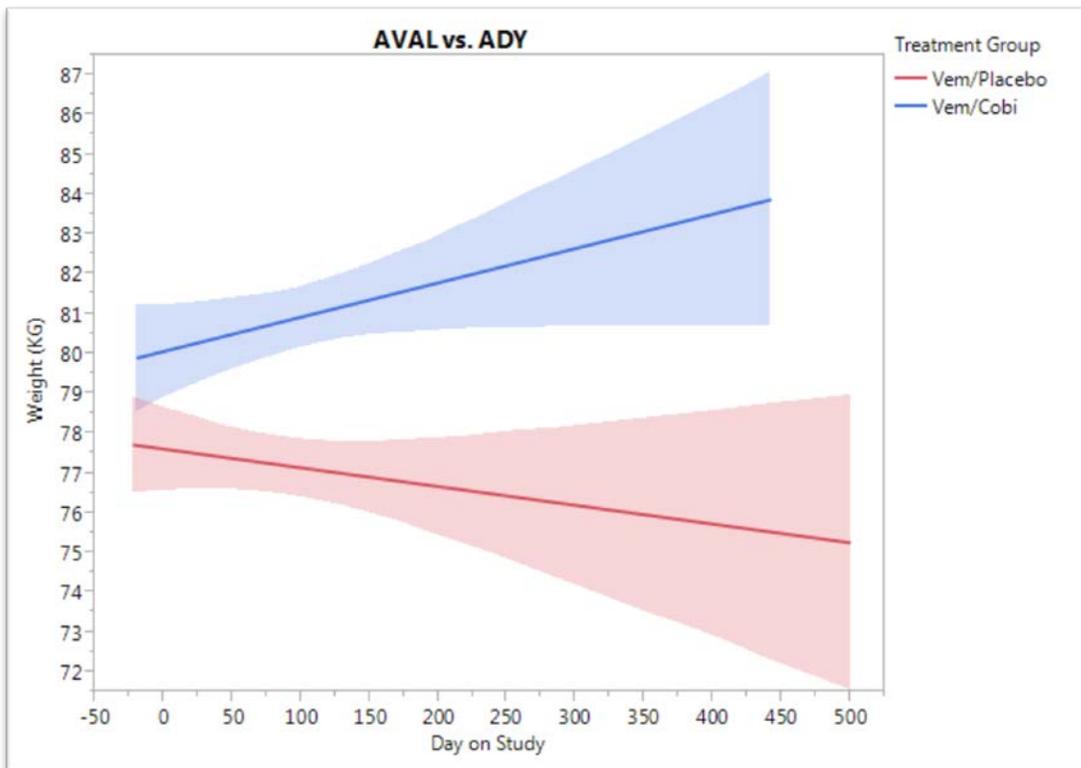
Figure 33: GO28141 – Linear Regression Analysis of Respiratory Rate by Day on Study and Actual Treatment Group (Safety Population: Data Cutoff Date: 9 MAY 2014*)



*Update in vital signs dataset not provided with 90D Safety Update. Data from the original submission used for this analysis.

Source: NDA206192/0001(2); 12/11/2014: 5.3.5.1: GO28141:adv.s.xpt

Figure 34: GO28141 – Linear Regression Analysis of Weight by Day on Study and Actual Treatment Group (Safety Population: Data Cutoff Date: 9 MAY 2014*)



*Update

in vital signs dataset not provided with 90D Safety Update. Data from the original submission used for this analysis.

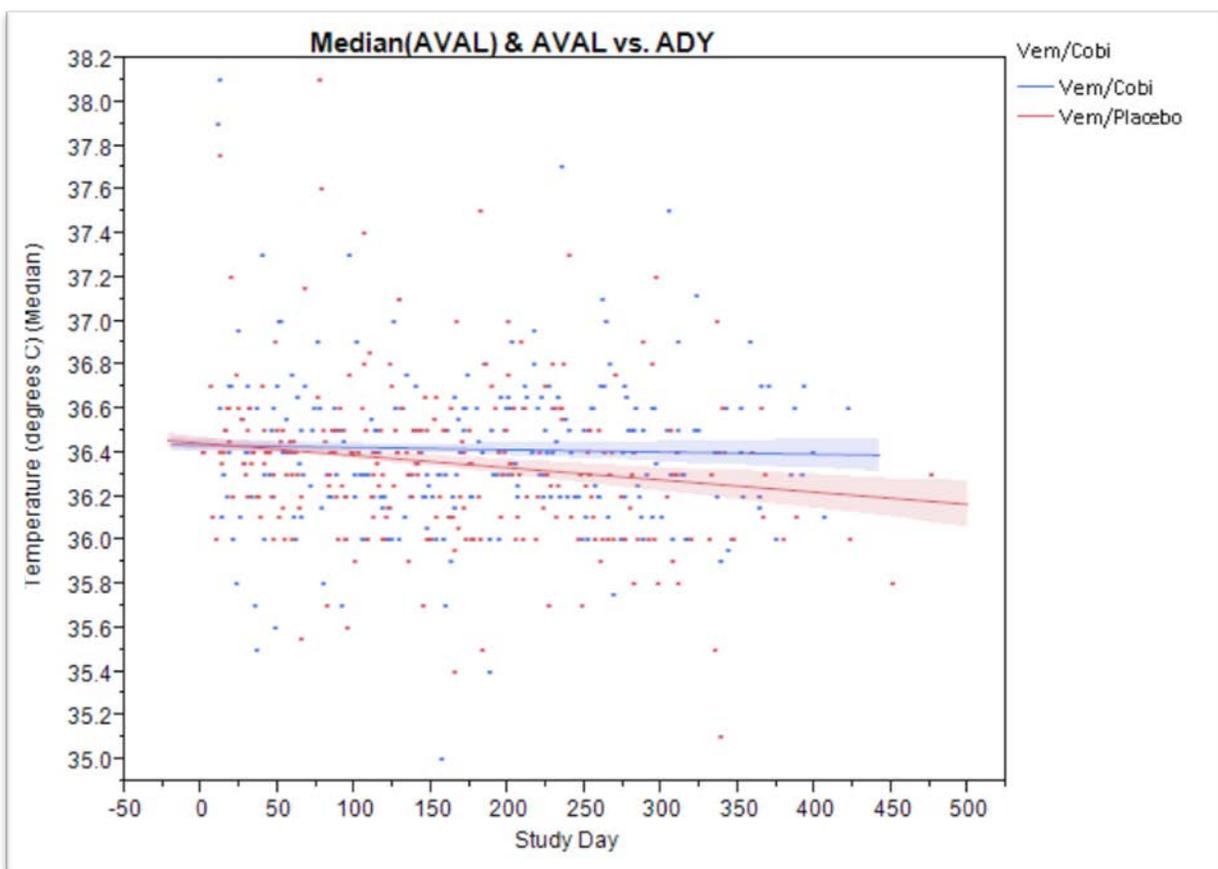
Source: NDA206192/0001(2); 12/11/2014: 5.3.5.1: GO28141:adv.s.xpt

Fever/Pyrexia:

Pyrexia as an adverse event (all Grades) was reported in 56 (23%) of patients treated with Vem/Placebo and in 69(28%) of patients treated with Vem/Cobi. Grade 3-4 pyrexia was reported in 0(0%) of patients treated with Vem/Placebo and in 4(2%) of patients treated with Vem/Cobi. Pyrexia was reported to be the cause of treatment discontinuation in 0(0%) of patients treated with Vem/Placebo and in 3(1%) of patients treated with Vem/Cobi and resulted in hospitalization in 2 (1%) of patients treated with Vem/Placebo and in 7(3%) of patients treated with Vem/Cobi. However, these fevers were not commonly associated with hypotension, rigors or chills. In two cases, fevers were associated with an underlying infection, in one case with a vasculitis, in one case with myalgias and in one case with a dermatitis.

Fever, defined as a temperature measurement of greater than or equal to a temperature of 37.5°C was reported in 25 (10%) of patients treated with Vem/Placebo and in 31 (13%) of patients treated with Vem/Cobi. The median value of temperature by day on study is shown below.

Figure 35: GO28141 – Linear Regression Analysis of Median Temperature by Day on Study and Actual Treatment Group (Safety Population: Data Cutoff Date: 9 MAY 2014*)



*Update in vital signs dataset not provided with 90D Safety Update. Data from the original submission used for this analysis.

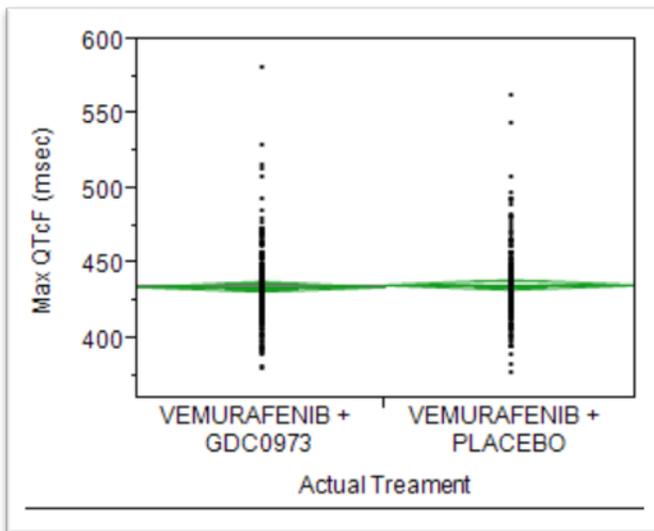
Source: NDA206192/0001(2); 12/11/2014: 5.3.5.1: GO28141:adv.s.xpt

Reviewer comment: While pyrexia and fever were common in both treatment arms, there appears to be an increased incidence of pyrexia on the Vem/Cobi arm. The median temperature appears to be somewhat higher on the Vem/Cobi arm as well, an effect that does not appear to diminish over time.

7.4.4 Electrocardiograms (ECGs)

ECG monitoring was done with triplicate studies at baseline using the Frederica adjustment (QTcF), on D15 Cycles 1, 2, and 3 and on D1 of subsequent cycles. There was no difference between treatment groups in the mean of the highest QTcF interval observed on treatment. This finding is consistent with the assessment of the Clinical Pharmacology QTIRC team (please see their review for details). However, 6 (2%) patients in the Vem/Placebo group compared to 12 (5%) patients in the Vem/Cobi group were identified as having a QTcF ≥ 500 msec or a change of ≥ 60 msec over baseline. There also appeared to be a trend towards an increase in the change in QTcF over baseline values in the Vem/Cobi treatment group.

Figure 36: GO28141 – Maximum QTc Interval (Frederica’s Correction Formula) by Actual Treatment Group (Safety Analysis Population: Data Cutoff Date: 19 SEP 2014)



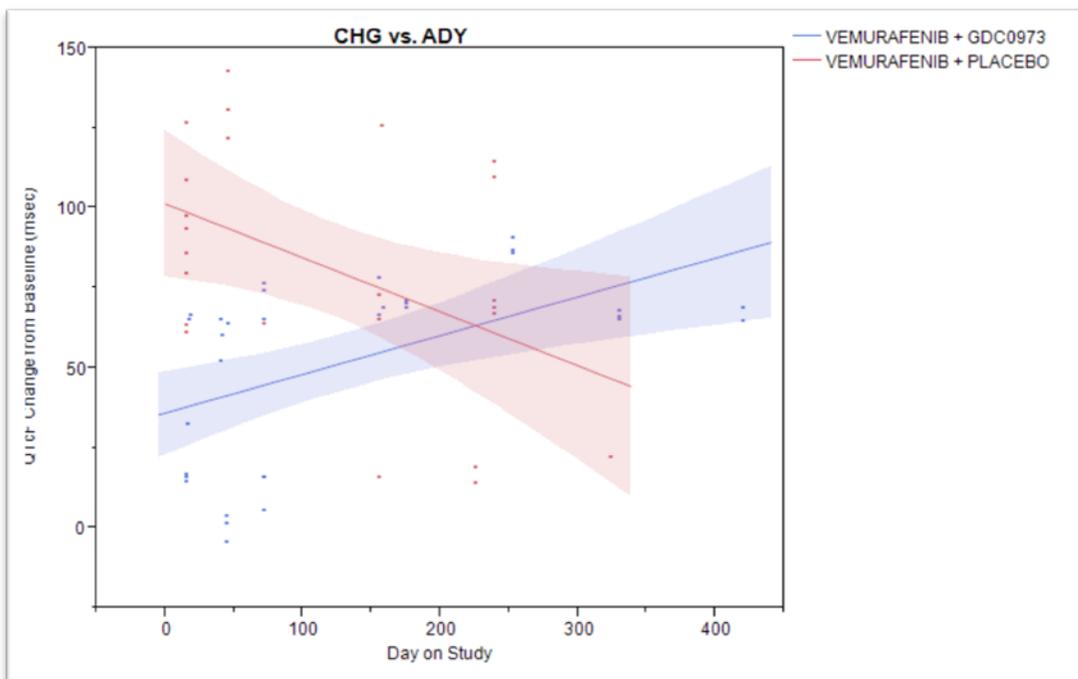
Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adv.xpt

Table 61: GO28141 - Maximum QTc Interval (Frederica's Correction Formula) by Actual Treatment Group (Safety Analysis Population: Data Cutoff Date: 19 SEP 2014)

Actual Treatment	N	Mean	Std Error	95% CI		T Ratio	p
				Lower	Upper		
Vem/Placebo	240	436.3	1.57	433.2	439.4	0.553	NS
Vem/Cobi	235	435.1	1.59	432.0	438.2		

Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adv.xpt

Figure 37: GO28141: Change in QTc Interval (Frederica's Correction) From Baseline by Day on Study and Actual Treatment Group (Safety Population: Date Cutoff Date: 19 SEP 2014)



Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adeg.xpt

Reviewer's comment: QTc prolongation is a labeled Warning in the Zelboraf (vemurafenib)

label. At this point in time there is insufficient information to assess whether the risk of QTc prolongation is increased when vemurafenib is used in combination with cobimetinib. The reviewer recommends ongoing monitoring in the post-market setting.

7.4.5 Special Safety Studies/Clinical Trials

To assess the risk of left ventricular dysfunction associated with the combination of vemurafenib and cobimetinib, Left ventricular function (LVEF) was assessed by ECHO or MUGA at baseline, on C2D1, C5D1 and every 2 cycles thereafter. The same method was used to assess LVEF for an individual patient over the course of the study. Per the clinical protocol, modifications were made to the dose of cobimetinib for a symptomatic decrease in LVEF or symptomatic heart failure. For an episode meeting these criteria, cobimetinib was held or was discontinued at the investigator’s discretion. Vemurafenib could be continued. If cardiac symptoms resolved completely within 28 days and LVEF returned to LLN, cobimetinib could be reintroduced with a reduction of 1 dosing level. The LVEF was to be monitored at two, four and six weeks after reintroduction of cobimetinib and then every six weeks for 12 weeks then per protocol. Following reintroduction of cobimetinib, if symptoms persisted or LVEF was below the LLN, cobimetinib was to be discontinued.

Events of LV dysfunction, if based on an assessment of LFEV were coded within the MedDRA Investigations Systems Organ Class (SOC). If based on a clinical assessment, such events could be classified under the MedDRA Cardiac Disorders SOC with a primary term of left ventricular dysfunction, cardiac failure, cardiomyopathy or congestive cardiomyopathy. Based on an analysis of data reported in the adverse events dataset (adae.xpt), nine (4%) patients in the Vem/Placebo treatment group and 21 (9%) patients in the Vem/Cobi treatment group experienced a decrease in left ventricular ejection fraction of CTCAE Grade ≥ 2 (defined as resting ejection fraction 50-40%; 10-19% drop from baseline).

Table 62: GO20141 – Per-Patient Incidence of LVEF Dysfunction by Reported MedDRA Primary Term (PT) and NCI-CTCAE Grade as Reported by the Applicant

PT	NCI-CTCAE Grade	Vem/Placebo		Vem/Cobi	
		n	%	n	%
Ejection fraction decreased	≥ 2	9	4	21	9
	2	6	2	17	7
	3	3	1	4	2

Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adae.xpt

Two additional patients, both treated with Vem/Placebo were reported to have a PT of LV dysfunction with a CTCAE Grade of ≥ 2 and were reported in the Cardiac Disorders SOC. No patients in either treatment group were reported to have a PT of congestive cardiomyopathy or cardiomyopathy.

The rate of LVEF decrease was also assessed using serial data from the advl.xpt dataset. Patients with less than a 10% decrement in ejection fraction from baseline were not included. CTCAE v. 4.02 were assigned as follows:

Grade 2: Resting ejection fraction 50-40% OR 10 – 19% drop from baseline

Grade 3: Resting ejection fraction 39-20% OR $\geq 20\%$ drop from baseline

Grade 4: Resting ejection fraction $<20\%$

The per-patient incidence by maximum CTCAE Grade based on the reported LVEF values is shown.

Table 63: GO28141 – Per-Patient Incidence of LVEF Dysfunction as Defined by Reported Left Ventricular Ejection Fraction (Safety Population: Data Cutoff Date: 19 SEP 2014)

Actual Treatment	Grade 2-4 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Vem/Placebo (n=246)	44 (18)	41 (17)	3 (1)	0 (0)
Vem/Cobi (n=247)	63 (26)	56 (23)	7 (3)	0 (0)

Source: GO28141:adv.xpt

The line listing of patients treated with Vem/Cobi who developed Grade 2 or 3 decrease in ejection fraction by maximum CTCAE Grade is shown below.

USUBJID	Grade
GO28141-252547-2213	2
GO28141-252559-2087	2
GO28141-252561-2124	2
GO28141-252736-2004	2
GO28141-252736-2009	2
GO28141-252747-2326	2
GO28141-252816-2054	2
GO28141-252816-2197	2
GO28141-252816-2234	2
GO28141-252818-2390	2
GO28141-252958-2258	2
GO28141-252958-2259	2
GO28141-252958-2471	2
GO28141-252969-2267	2
GO28141-253466-2132	2
GO28141-253512-2287	2
GO28141-253588-2025	2
GO28141-253784-2413	2
GO28141-254361-2479	2
GO28141-254366-2150	2
GO28141-254372-2265	2
GO28141-254392-2392	2
GO28141-254414-2252	2
GO28141-254414-2328	2
GO28141-254414-2341	2
GO28141-254415-2283	2
GO28141-254417-2079	2
GO28141-254417-2107	2
GO28141-254421-2139	2
GO28141-254423-2416	2
GO28141-254427-2175	2
GO28141-254905-2066	2
GO28141-254905-2329	2

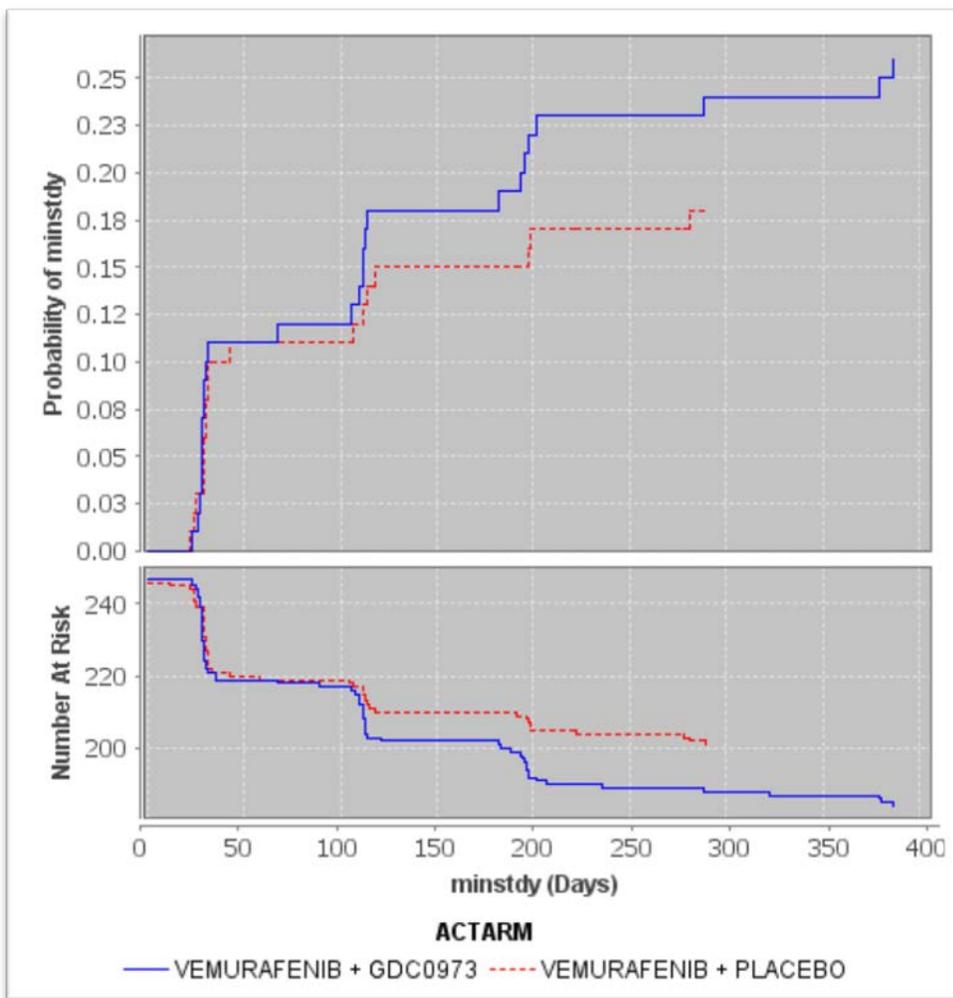
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GO28141-255078-2050	2
GO28141-255078-2072	2
GO28141-255078-2166	2
GO28141-255082-2454	2
GO28141-255085-2191	2
GO28141-255085-2313	2
GO28141-256298-2459	2
GO28141-256316-2164	2
GO28141-256316-2198	2
GO28141-256321-2257	2
GO28141-256326-2215	2
GO28141-256404-2324	2
GO28141-256831-2099	2
GO28141-256836-2293	2
GO28141-256896-2398	2
GO28141-257400-2354	2
GO28141-257401-2452	2
GO28141-257505-2277	2
GO28141-257517-2319	2
GO28141-257793-2011	2
GO28141-257793-2085	2
GO28141-257793-2260	2
GO28141-258059-2339	2
GO28141-252559-2123	3
GO28141-253468-2111	3
GO28141-253581-2312	3
GO28141-254358-2297	3
GO28141-254358-2383	3
GO28141-255080-2146	3
GO28141-257401-2302	3

Reviewer's comment: Assessment of LV dysfunction based on the recorded LVEF resulted in additional cases being identified. This discrepancy in case reporting based on the method of ascertainment has been previously discussed [29]. The reviewer recommends that data from the assessment of LVEF be included in labeling rather than the incidence reported in the adverse event file as this underestimates that actual incidence of LV dysfunction associated with cobimetinib.

The median time to onset of LV dysfunction was 108 days (range: 12 to 289 days) in patients treated with Vem/Placebo and 31 days (range 23 to 386 days) in patients treated with Vem/Cobi.

Figure 38: GO28141 – Cumulative Per-Patient Incidence of Left Ventricular Dysfunction ($\geq 10\%$ Decrease from Baseline or AE Coded to the MedDRA Cardiomyopathy SMQ*) by Study Day of Onset and Treatment Group (Safety Population; Data Cutoff Date: 19 SEP 2014)

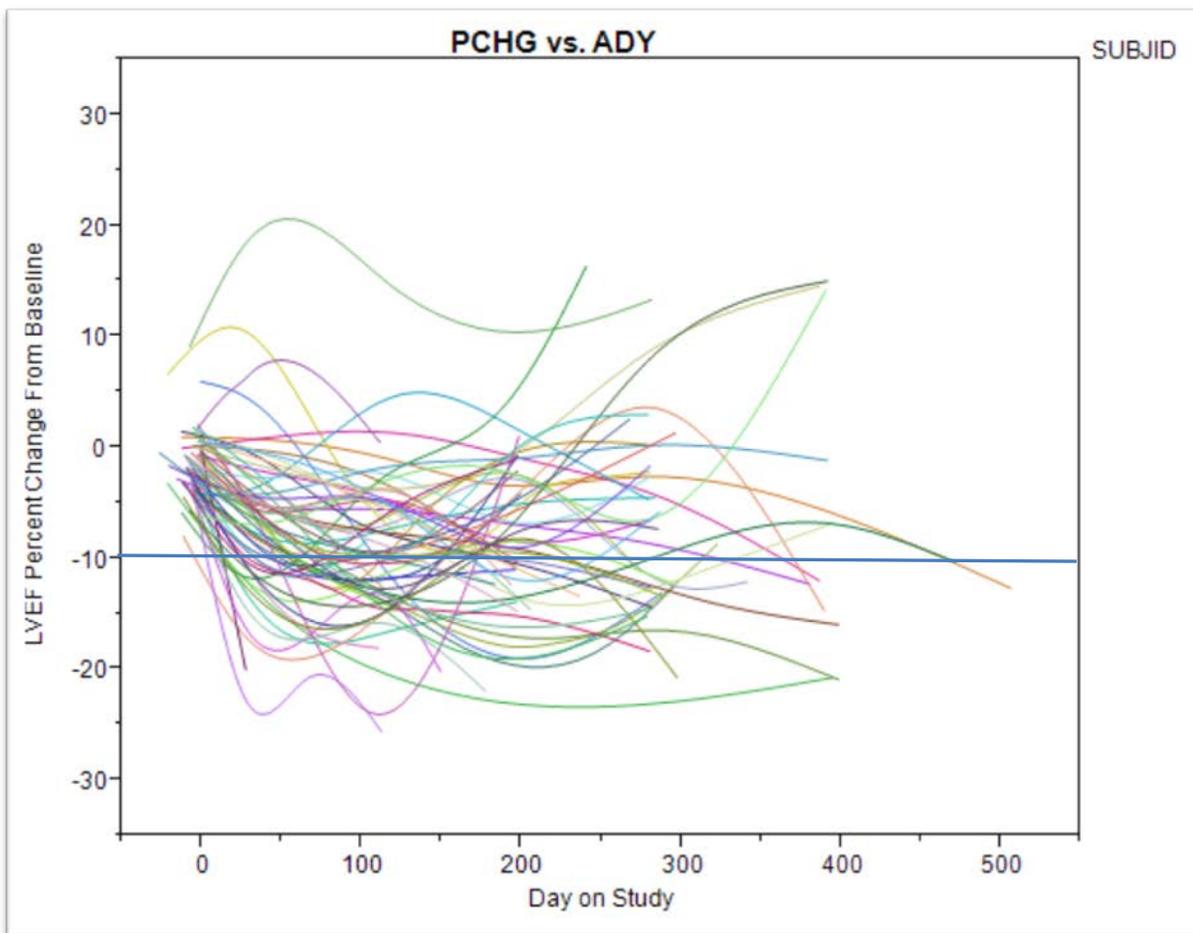


*AE Reported in the Narrow SMQ of Cardiomyopathy

Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adv.xpt

Figure 39 shows the percent change in LVEF from baseline levels by study day in the 63 patients treated with Vem/Cobi who were identified as having LV Dysfunction. In 33 (52%) of these patients, LVEF remained $\geq 10\%$ decreased from baseline at the time of the final LVEF assessment.

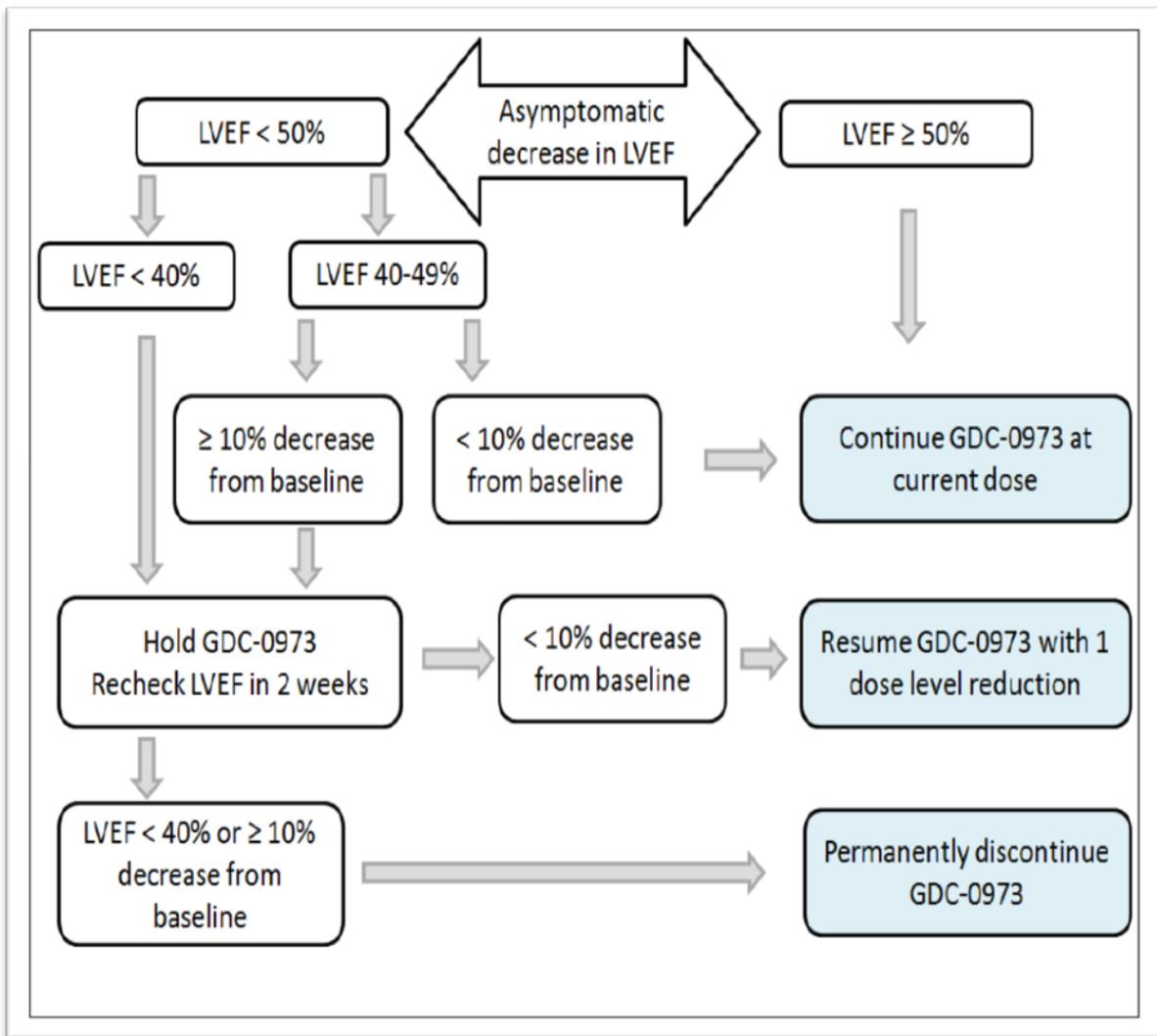
Figure 39: GO28141 – Percent Change in LVEF from Baseline levels in 63 Vem/Cobi-Treated Patients Who Developed LV Dysfunction by Study Date (Safety Population; Data Cutoff Date: 19 SEP 2014)



Source: GO28141: advl.xpt, adae.xpt

Patients who developed LV dysfunction were managed using the protocol defined schema (Figure 40).

Figure 40: GO28141 - Schema for Management of Asymptomatic Reduction in Ejection Fraction



Source: Protocol GO28141, Version 4, page 172; CSR p 7270

Ten patients were identified with one or more LVEF evaluation meeting the criteria for dose reduction. These patients are reviewed in

Table 64. Of these ten patients, six had underlying cardiac risk factors (hypertension, diabetes mellitus, hyperlipidemia, ischemic heart disease and mitral valve prolapse). In three patients, the decline in LVEF was in the setting of an acute myocardial infarction. In one of these cases, the event was fatal. Two of these patients were of advanced age with significant cardiac risk factors. The third patient, a 51 year old female with no prior cardiac history was confirmed to have coronary artery occlusion and was treated with stent placement. In this patient, LV dysfunction was attributed to the coronary event.

Of the remaining seven patients, cobimetinib was permanently discontinued due to the reduction in LVEF in one patient (a 30-year-old male with a 25% decrease in LVEF from baseline). Cobimetinib was interrupted and/or reduced in four patients and was continued in 2 patients.

A follow-up LVEF was available on 8 of the nine surviving patients. Among these eight patients, LVEF had not returned to $\leq 10\%$ of the baseline value in 3 patients ().

Table 64: GO28141 – Patients in the Vem/Cobi Treatment Group with Decreased Left Ventricular Ejection Fraction Resulting in Cobimetinib Dosing Modifications

Subject GO28141	Age / Sex	Cardiac History	LVEF ECHO/MUGA						Returned to ≤ 10% of Baseline LVEF	AEs temporally Associated with Worst Case LVEF decrease	Withhold (Day) / Rechallenged (Day) / Outcome
			LVEFLL N (%)	Screen LVEF (%)	Worst Case LVEF		Recovery LVEF				
					(%)	Day	(%)	Day			
255085-2313	37/F	Hypertension, Mitral valve Prolapse	55	59	47	108	52	124	No	Grade 1 Nausea, vomiting, anemia	Interrupted/D113 Reduced/D141
253468-2111	84/M	Ischemic Heart Disease	69	69	55	197	60	281	No	Grade 4 CPK Grade 3 MI Grade 1 photosensitivity reaction Basal Cell Carcinoma	Interrupted/D29 (for Grade 3 diarrhea) Reduced/D57
253466-2132	30/M	none	55	60	45	29	65	283	Yes	Pruritis (G2) Dermatitis(G1) Peripheral edema (G1)	Discontinued/D29
252816-2054	59/F	none	55	55	42	197	54	280	Yes	Asthenia (G2)	Interrupted/D202 Reduced/D203
252547-2213	65/F	Hypertension	59	56	44	110	59	113	Yes	Insomnia (G2) Acute renal failure (G1) UTI (G2)	Interrupted/D33
252818-2390	47/F	Hypertension	55	56	44	110	59	113	Yes	UTI(G2) Flank Pain (G1) Insomnia(G1)	-

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Subject GO28141	Age / Sex	Cardiac History	LVEF ECHO/MUGA						Returned to ≤ 10% of Baseline LVEF	AEs temporally Associated with Worst Case LVEF decrease	Withhold (Day) / Rechallenged (Day) / Outcome
			LVEFLL N (%)	Screen LVEF (%)	Worst Case LVEF		Recovery LVEF				
					(%)	Day	(%)	Day			
253588-2025	74/M	DM	50	50	40	27	-	-	-	Cardiac Arrest (G5) Fatigue (G2) PyrexiaG1	Discontinued/D27
254413-2283	51/F	none	50	52	41	25	51	190	Yes	Acute coronary Syndrome, anemia, (G3) Diarrhea, nausea (G2) Neuropenic panniculitis (G3)	Discontinued/D29
254417-2107	53/M	none	50	68	48	28	50	112	No	Hemiparesis (G5) Diarrhea, decreased appetite, rash (G2)	Reduced/D1
254427-2175	55/M	Hypercholesterolemia	50	60	49	197	-	-	-	Hypertension (G3) Alk Phos/CPK (G3)	Discontinued Vem/D113

Source: NDA206192/0036(37); 3/10/2015: 5.3.5.and case narratives. Verified and supplemented information from adae.xpt, adv.xpt
Abbreviations in Table: AE, adverse events; D, day; Echo, echocardiogram; F, female; LVEF, left ventricular ejection fraction; NA, not applicable; M, male; MUGA, multi-gated acquisition.

Reviewer's comment: Cobimetinib does appear to increase the risk of LV dysfunction over that seen with vemurafenib alone. The risk of worsened LV dysfunction may be worse among patients with a history of cardiovascular disease or with other cardiac risk factors. LVEF appears to return towards baseline following dose discontinuation/interruption in most patients for whom a follow-up assessment was available. Genentech has proposed a warning for the use of cobimetinib in combination with vemurafenib with this reviewer feels is appropriate.

7.4.6 Immunogenicity

There are no immunogenicity data in the Application.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Please see the FDA Clinical Pharmacology NDA review. Population pharmacokinetic (PK) and exposure-response (E-R) analyses using PK data identified diarrhea as related to drug exposure.

7.5.2 Time Dependency for Adverse Events

See Section 7.4.

7.5.3 Drug-Demographic Interactions

As expected within both treatment groups, serious adverse events and Grade ≥ 3 adverse events were more common in older individuals regardless of sex. The rate of serious adverse events and Grade ≥ 3 adverse event appeared similar between study groups for all age/sex groups. There were insufficient numbers of non-white patients to permit an analysis of drug-race interaction.

Table 65: GO28141 – Per-Patient Incidence of Serious Adverse Events and Adverse Events of \geq Grade 3 by Age and Sex Group (Safety Population; Data Cut-off Date 19 SEP 2014)

Event	Age/Sex	Vem/Placebo		Vem/Cobi	
		(n)	n (%)	(n)	n (%)
Serious adverse event					
	< 65/M	93	24(26)	112	31 (28)
	< 65/F	79	12 (15)	77	20 (26)
	\geq 65/M	40	17 (43)	39	20 (51)
	\geq 65/F	27	11 (41)	26	13 (50)
Grade ≥ 3 adverse event					
	< 65/M	93	53 (57)	112	73 (65)
	< 65/F	79	40 (51)	77	48 (62)
	\geq 65/M	40	29 (73)	39	31 (79)
	\geq 65/F	27	24 (89)	26	24 (92)

Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adae.xpt, adsl, xpt

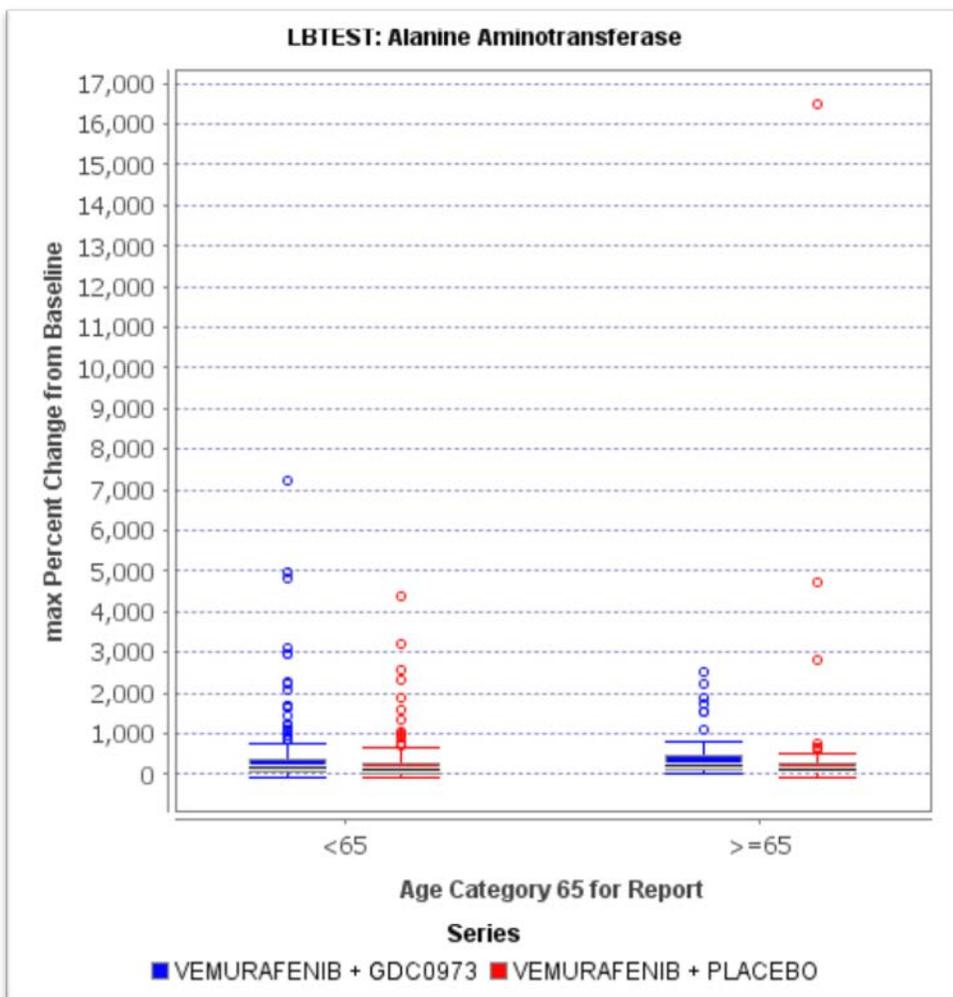


Table 66: GO28141 – Per-Patient Incidence of Serious Adverse Events and Adverse Events of \geq Grade 3 by BRAF V600 Mutation Subset (Safety Population; Data Cut-off Date 19 SEP 2014)

Event	Mutation	Vem/Placebo		Vem/Cobi	
Serious adverse event		(n)	n (%)	(n)	n (%)
	V600E	174	44 (25)	170	52 (31)
	V600K	30	9 (30)	25	8 (32)
Grade \geq 3 adverse event					
	V600E	174	96 (55)	170	114 (67)
	V600K	30	23 (77)	25	18 (72)

Source: NDA206192/0036(37); 3/10/2015: 5.3.5.1: GO28141:adae.xpt, adsl, xpt

7.5.4 *Drug-Disease Interactions*

Please refer to the FDA Clinical Pharmacology NDA review for details.

7.5.5 *Drug-Drug Interactions*

Please refer to the FDA Clinical Pharmacology NDA review for details.

7.6 Additional Safety Evaluations

7.6.1 *Human Carcinogenicity*

Please see FDA Non-Clinical NDA review for details.

Reviewer's comment: The incidence of primary cutaneous malignancies was less frequent on the Vem/Cobi group relative to the Vem/Placebo group, consistent with the clinical experience reported with dabrafenib/trametinib. However, the extent of the risk of cutaneous and non-cutaneous malignancies and the need for monitoring while on treatment cannot be established based on the limited safety database.

7.6.2 *Human Reproduction and Pregnancy Data*

There are no data available on the use of cobimetinib in pregnant or lactating women. Please see the FDA Pharmacology/Toxicology review for details.

7.6.3 *Pediatrics and Assessment of Effects on Growth*

Cobimetinib has not been studied in a pediatric population. The Applicant is requesting waiver of pediatric studies because cobimetinib qualifies for an exemption from PREA requirements (see Section 2.5).

7.6.4 *Overdose, Drug Abuse Potential, Withdrawal and Rebound*

In the non-clinical studies, high-affinity binding to the agonist site of the mu opioid receptor was reported. Decreased respiratory rates were observed in dog studies. These combined observation led to the concern of the potential for withdrawal effects in humans (See FDA Non-Clinical review for details). There was no clinical data to

suggest evidence of withdrawal or overdose potential. No cobimetinib overdoses were reported in the clinical trials.

Reviewer's comment: It is not likely that routine monitoring of patients following drug discontinuation would be sensitive enough to detect evidence of withdrawal effect. There may be a potential for cobimetinib to compete with opioid analgesics or for withdraw effect to result in increased risk of suicide or depression. The Applicant has been requested to provide additional information concerning the use of concomitant opioid use in patients on the GO28141 trial and for an analysis of suicide/depression reported to the cobimetinib database. It seems likely that these events could be effectively monitored with post marketing surveillance.

7.7 Additional Submissions / Safety Issues

There were no additional submission or safety issues.

8 Postmarket Experience

Cobimetinib is a new molecular entity with no prior approval history. There is no post market experience.

9 Appendices

9.1 Labeling Recommendations

Please refer to the draft package insert of Cotellic included in the action package.

9.2 GO28141 Schedule of Assessments and Procedures

Table 67: GO28141 – Schedule of Assessments and Procedures

Period	Screening	Study Treatment										End-of-study treatment	Follow-up after treatment discontinuation			
		Cycle 1		Cycle 2		Cycle 3		Cycle 4	Cycle 5	Cycle 6			Cycles 7 +	4 wks	12 wks	6 mths
Cycle		1	15	1	15	1	15	1	1	1	15	1				
Day		1	15	1	15	1	15	1	1	1	15	1				
Informed consent ¹	X															
Tumor tissue for BRAF ^{V600} mutation testing ¹	X															
Randomization ²		X														
Medical history and demographics	X															
Interval medical history		X	X	X	X	X		X	X	X		X	X			
Physical exam including HEENT, vital signs, height, weight ³	X	X	X	X	X	X		X ³	X	X		X ³	X	X		
Anal and gynecological exam ^{3A}	X												X			X
ECOG Performance Status	X	X	X	X	X	X		X	X	X		X				
EORTC QLQ-C30 ⁴		X	X	X	X			X		X		X ⁴	X	X		

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Period	Screening	Study Treatment										End-of-study treatment	Follow-up after treatment discontinuation		
		Cycle 1		Cycle 2		Cycle 3		Cycle 4	Cycle 5	Cycle 6			Cycles 7+	4 wks	12 wks
Day		1	15	1	15	1	15	1	1	1	15	1			
EQ-5D Questionnaire ⁴		X		X				X		X		X ⁴	X	X	
12-lead ECG ⁵	X		X		X		X				X ₅	X ⁵			
ECHO or MUGA ⁶	X			X					X			X ⁶	X ⁶		
Hematology ⁷	X	X		X		X		X	X	X		X			
Chemistry and LFTs ⁸	X	X	X	X	X	X	X	X	X	X		X			
Serum pregnancy tests ⁹	X														
Fasting blood glucose and lipid panel ¹⁰	X														
CT/MRI brain ¹¹	X														
Radiologic tumor assessment ¹²	X					X ¹²			X ¹²			X ¹²			
Mandatory whole blood sample for genotyping		X													
PK blood samples ¹³		X	X		X										
Vemurafenib		X	X	X	X	X	X	X	X	X	X	X			

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Period	Screening	Study Treatment											End-of-study treatment	Follow-up after treatment discontinuation			
		Cycle 1		Cycle 2		Cycle 3		Cycle 4	Cycle 5	Cycle 6		Cycles 7+		4 wks	12 wks	6 mths	
		1	15	1	15	1	15	1	1	1	15	1					
administration ¹⁴																	
Cobimetinib (GDC-0973) administration ¹⁴		X	X	X	X	X	X	X	X	X	X	X					
Drug accountability ¹⁵		X	X	X	X	X		X	X	X		X	X				
Concomitant medications ¹⁶	X ¹⁶	X	X	X	X	X		X	X	X		X	X				
Adverse events ¹⁷		X	X	X	X	X		X	X	X		X	X	X ¹⁷			
Survival assessment and subsequent anti-cancer therapy ¹⁸															X ¹⁸	→	
Dermatologic exam ¹⁹	X			X					X			X ¹⁹	X ¹⁹				X ¹⁹
Ophthalmologic exams ²⁰	X			X					X			X ²⁰	X ²⁰				
Tumor biopsy for biomarker analyses ²¹	X				X								X ^{21A}				
Blood samples for biomarker ²²		X				X			X				X				

Period	Screening	Study Treatment										End-of-study treatment	Follow-up after treatment discontinuation			
		Cycle 1		Cycle 2		Cycle 3		Cycle 4	Cycle 5	Cycle 6			Cycles 7+	4 wks	12 wks	6 mths
Day		1	15	1	15	1	15	1	1	1	15	1				
Cutaneous SCC tumor tissue or suspicious neoplasms ²³	X	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
CT/MRI of chest to monitor for SCC ²⁴						X ²⁴			X ²⁴							X ²⁴
Optional whole blood sample for RCR		X														

CT = computerized tomography scan; ECG = electrocardiogram; ECHO = echocardiogram; HEENT = head, ears, eyes, nose and throat; LFT = liver function test; MRI = magnetic resonance imaging scan; MUGA = Multiple Gated Acquisition; RCR = Roche Clinical Repository; SCC = squamous cell carcinoma

→ Assessment or procedure is performed throughout the study.

Schedule of Assessments – Footnotes

Notes: Assessments scheduled on the day of study drug administration should be performed prior to study drug dosing, unless otherwise specified.

Unless otherwise specified, assessments that are done every 2 weeks, should be performed within a ± 2 days window. Assessments performed monthly, should be performed within a window of ± 3 days.

A clinic visit should be scheduled any time there is a safety issue or any unscheduled assessments need to be performed.

1. Informed consent must be obtained before any study specific screening assessments are performed. Screening assessments are to be performed within 28 days prior to Cycle 1 Day 1 unless otherwise noted. Assessments performed as standard of care before signed informed consent form but within the screening window may be used for screening. Screening exams for ECG, hematology, and chemistry must be performed within 14 days of first dose. Melanoma tissue must be tested for BRAF^{V600} mutation using the cobas[®] 4800 BRAF V600 mutation may be performed at a Roche-designated Central Reference Laboratory or at a non-Roche-designated laboratory. If a non-Roche-designated laboratory is used for BRAF^{V600} mutation testing, documentation of the test procedures and results must be included as source documentation. Testing requires an FFPE tumor block or 5 unstained sections. BRAFV600 mutation testing must be performed prior to additional screening tests and requirements. Standard-of-care tests or examinations may be performed concurrently with the BRAFV600 mutation testing. The 28-day window (Day-28 to Day-1) for performing screening assessments opens at the time the first additional screening assessment is performed after the cobas[®] 4800 BRAF V600 mutation test result is available.
2. Randomization can be done up to 72 hours prior to Cycle 1 Day 1.
3. Physical exam will be performed during screening and subsequently at each study visit. After initial screening physical exam, a symptom-directed exam that contains an evaluation of the oral cavity, oropharynx, neck, lungs, heart, abdomen, and skin, will be performed. Patients will be asked about skin and vision changes at each symptom-directed physical exam. Assessments must be done before study drug dosing, where applicable. Note: If vital signs and physical examination are assessed within 7 days of the Cycle 1, Day 1 visit, they do not have to be repeated at Day 1. Weight, and vital signs, which include temperature, heart rate, respiratory rate, and systolic and diastolic blood pressures while the patient is in a seated position, will be collected at each study visit that a physical exam is performed. Blood pressure and heart rate measurements will be recorded after a 5-minute rest in a seated position. Height will be collected only at screening/baseline.
- 3A Visual inspection of the anus and digital examination of the anal canal will be performed at screening, discontinuation of study treatment, 6 months after treatment discontinuation and at other times as clinically indicated to monitor for SCC. Colonoscopy, sigmoidoscopy, or anoscopy is not required but may be performed if clinically indicated. All female patients will undergo pelvic examination including visual inspection of the uterine cervix and Pap smear at screening, end-of-study treatment visit, 6 months after treatment discontinuation, and at other times as clinically indicated to monitor for cervical carcinoma.
4. Quality of life will be assessed with the EORTC QLQ-C30 and EQ-5D questionnaires. Both questionnaires will be administered prior to starting study treatment on Cycle 1 Day 1 and at the end-of-study treatment visit. For study visits requiring PRO questionnaire collection, both questionnaires (if applicable) are to be administered prior to any of the other study-related assessments on the day of the study visit. The EORTC QLQ-C30 will be administered on Cycle 1 Day 15, Cycle 2 Day 1 and Cycle 2 Day 15 as well as every 2 cycles thereafter while on study (Day 1 of Cycles 4, 6, 8, etc.) and at the end-of-study treatment visit and 4 weeks after the end-of-study treatment visit. The EQ-5D will be administered on Cycle 2 Day 1 and every 2 cycles thereafter while on study (Day 1 of Cycles 4, 6, 8, etc.), at the end-of-study treatment visit and 4 and 12 weeks after the end-of-study treatment visit.
5. Standard 12-lead surface ECG will be performed in triplicate for each assessment time-point:
 - Screening
 - Pre-dose on Cycle 1, Day 15 ± 3 days of study treatment
 - 2–4 hours post-dose on Cycle 1, Day 15 ± 3 days of study treatment

- Cycle 2, Day 15 ± 3 days of study treatment
- Cycle 3, Day 15 ± 3 days of study treatment
- Day 15 ± 3 days of every 3 treatment cycle (Cycle 6, 9, 12, etc.)

ECG monitoring should be performed more frequently if clinically indicated. For all ECGs, patients should be resting in a supine position for ≥ 10 minutes prior to ECG collection. For the ECGs scheduled for Day 15 ± 3 of every 3 treatment cycles (Cycle 6, 9, 12, etc.), a limited physical examination should be performed after the ECG.

6. All patients will undergo evaluation of left ventricular function, either by ECHO or MUGA at the following timepoints:

- Screening
- Cycle 2, Day 1 ± 1 week
- On Day 1 of Cycles 5, 8, and 11 (every 3 treatment cycles) ± 2 weeks
- On Day 1 of Cycles 15, 19, 23 (every 4 treatment cycles) ± 2 weeks
- On Day 1 of Cycles 29, 35, 41, 47 etc. (every 6 treatment cycles) ± 2 weeks
- End-of-study-treatment visit

Evaluation of left ventricular function does not need to be performed at end-of-study-treatment visit if it has been performed within the last 12 weeks. Any patient who develops clinical signs or symptoms suspicious of cardiac failure should undergo an LVEF assessment. Evaluation of left ventricular function must be performed by the same method for each patient.

7. Hematology includes hemoglobin, hematocrit, WBC with differential (neutrophils, lymphocyte, monocyte, eosinophil and basophil counts, and other cells), and platelet count. Screening hematology values must be obtained within 14 days of Cycle 1 Day 1. Note: If screening laboratory specimens are collected within 7 days of the Cycle 1, Day 1 visit, they do not have to be repeated at Day 1.
8. Chemistry includes BUN, creatinine, sodium, potassium, chloride, bicarbonate, phosphorus, magnesium, total calcium, albumin, LDH, and CPK. LFTs include ALT, AST, total bilirubin, alkaline phosphatase, and GGT. Screening chemistry values must be obtained within 14 days of Cycle 1 Day 1. Note: If screening laboratory specimens are collected within 7 days of the Cycle 1, Day 1 visit, they do not have to be repeated at Day 1.
9. For women of childbearing potential, a serum pregnancy test is required at screening within 14 days prior to Cycle 1 Day 1. Women who have had amenorrhea for > 12 months but < 2 years should have an FSH test at screening for eligibility purposes.
10. This is performed only during screening. Both blood glucose and lipid panel must be obtained after at least an 8-hour fast. Lipid panel should include total cholesterol, low-density lipoprotein and triglycerides.
11. All patients must have a screening brain CT or MRI to assess for brain metastasis, and subsequently only as clinically indicated.
12. Tumor assessments will include contrast-enhanced CT or MRI of the chest, abdomen, and pelvis as well as the site of the primary tumor (if applicable). Evaluation of tumor response conforming to RECIST v1.1 must be documented every 8 weeks ± 1 week (during the last week of every 2 treatment cycles) from the date of first study drug administration (Cycle 1 Day 1) until documented investigator-determined PD or the patient dies. Tumor assessments must be performed independent of changes to the study treatment administration schedule (e.g., dose delay). If a tumor assessment has to be performed early or late, subsequent assessments should be conducted according to the original schedule based on the date of first study drug administration (Cycle 1 Day 1).

13. PK sample for analysis of vemurafenib concentration will be collected in sodium heparin tubes and will require 2mL of venous blood at each timepoint. PK sample for analysis of cobimetinib (GDC-0973) concentration will be collected in K2-EDTA tubes and will require 3mL of venous blood at each timepoint. The time and date of all PK samples must be documented. Plasma samples for vemurafenib and cobimetinib (GDC-0973) concentration measurement will be collected at the following time-points:
- 1–4 hours after the first dose on Cycle 1, Day 1
 - Pre-dose on Cycle 1, Day 15 \pm 3 days
 - 2–4 hours post-dose on Cycle 1, Day 15 \pm 3 days
 - Pre-dose on Cycle 2, Day 15 \pm 3 days
14. For both investigational drugs, dosing will continue until disease progression, consent withdrawal, or unacceptable toxicity. Dispense a sufficient number of vemurafenib and cobimetinib (GDC-0973) to last until the next visit. Extra medications may be dispensed if there is a reasonable possibility that the patient's next visit may be delayed (e.g., because of inclement weather or distance of patient's home from study center).
15. Provide a medication diary. Instruct patient to record the time and date they take each study drug dose in the diary and to return all unused capsules at each study visit to assess compliance. Collect and review medication diary, collect unused medications, and assess compliance at each subsequent visit. At least 7 days off cobimetinib (GDC-0973) are required prior to starting a new treatment cycle.
16. Review and capture of all concomitant medications will be performed at each study visit. Concomitant medications are defined as any prescription medications, over-the-counter preparations and supplements used by a patient within 7 days prior to Cycle 1, Day 1 and continuing through the study completion visit.
17. All adverse events and serious adverse events will be collected. All adverse events or serious adverse events occurring after study discontinuation will be recorded until 28 days after the last dose of study treatment or until initiation of another subsequent anti-cancer therapy, whichever occurs first. Any second non-cutaneous primary malignancy (related or unrelated to study treatment) that develop during or up to 12 months after study treatment completion must be reported as a serious adverse event.
18. Survival assessment will be used to collect overall survival during long-term follow-up; patient should be followed up every 12 weeks until death, withdrawal of consent, or loss to follow-up. Subsequent anti-cancer therapy information will be collected at the same time as survival assessment.
19. Dermatology evaluation: Complete evaluation of the skin by a dermatologist, or qualified equivalent medical specialist, will be conducted at baseline (up to 28 days prior to Cycle 1, Day 1), Cycle 2, Day 1 (\pm 1 week), every 3 treatment cycles (12 weeks \pm 2 weeks) thereafter while receiving study treatment, and at the end-of-study-treatment visit. Dermatologic examination does not need to be performed at end-of-study-treatment visit if one has been performed within the last 12 weeks. A final dermatologic examination will be performed 6 months (\pm 2 weeks) after discontinuation of study treatment.
20. All patients will undergo ophthalmologic examination at the following timepoints:
- Screening
 - Cycle 2, Day 1 \pm 1 week
 - On Day 1 of Cycles 5, 8 and 11 (every 3 treatment cycles) \pm 2 weeks

- On Day 1 of Cycles 15, 19, 23 (every 4 treatment cycles)±2 weeks
- On Day 1 of Cycles 29, 35, 41, 47 etc. (every 6 treatment cycles)±2 weeks
- End-of-study-treatment visit

Ophthalmologic examination does not need to be performed at end-of-study-treatment visit if one has been performed within the last 12 weeks. Baseline ophthalmologic examination evaluates for evidence of retinal pathology that is considered a risk factor for neurosensory retinal detachment, RVO, or neovascular macular degeneration. Risk factors for RVO include elevated serum cholesterol, hypertriglyceridemia, hyperglycemia, hypertension and glaucoma. Ophthalmologic examination will include visual acuity testing, intraocular pressure measurements by tonometry, slit lamp ophthalmoscopy, indirect ophthalmoscopy, and spectral domain optical coherence tomography (spectral domain OCT, if not available, may be substituted with time domain OCT).

21. Biopsies of accessible melanoma lesions are mandatory upon patient's consent to participate in the trial. Either FFPE or fresh-frozen biopsies (or both) will be obtained at 3 timepoints:

- Baseline sample: during screening within 28 days of Cycle 1 Day 1
- On treatment cycle: on Cycle 2, Day 15 (±1 week)
- Disease progression sample: at time of progressive disease

Baseline sample biopsies should be completed at least 48 hours before the initiation of study drug therapy on Cycle 1 Day 1. Archival tissue may be submitted in place of newly obtained tumor tissue for the baseline sample biopsy. It is highly recommended that the biopsy at disease progression be collected within 3 days after last study treatment. Excisional biopsies, punch biopsies, 14-gauge core needle biopsies are acceptable. Fine needle aspiration (FNA) biopsies are not acceptable.

21A. Biopsy will only be performed if patient has accessible lesion and disease progression.

22. Blood samples for biomarker analysis will be obtained on Day 1 of Cycles 1, 3, and 5, and at the time of disease progression. Blood sample required at each timepoint: one 6-mL blood sample anticoagulated in EDTA.

23. If a patient develop any cutaneous lesion(s) suspicious for SCC or KA during the study, biopsy tissue and a paired normal skin biopsy must be obtained for central pathology review. Only one normal skin biopsy is required per patient, regardless of the number of SCC lesions identified and biopsied during the study. Any suspicious lesions (cutaneous or non-cutaneous) thought to be malignant must also be sent for central pathology review and may undergo molecular characterization.

- Any second non-cutaneous primary malignancy (related or unrelated to study treatment) that develop during or up to 12 months after study treatment completion must be reported as a serious adverse event and tumor tissue sent for central pathology review.

24. Patients will undergo CT/MRI of the chest to monitor for the occurrence of SCC while on study treatment and 6 months after the end-of-study treatment visit. The routinely scheduled chest CT/MRI scan performed as part of the tumor assessment may be used for lung SCC surveillance while on study treatment.

Source: GO28141 Protocol Version 4, GO28141 Clinical Study Report, page 7250-7257.

9.3 GO28141 – Treatment Modification Plan for Toxicity

Table 68: GO28141 – Management of Specific Toxicities and Dose Modification Guidelines

Adverse Event	Action
A) Rash Grade ≥ 3	<p>The appearance of rash must be characterized as acneiform or non-acneiform.</p> <p>No change in vemurafenib and cobimetinib (GDC-0973) dosing will be implemented for Grade ≤ 2 rash; patients should receive maximal supportive care per institutional guidelines.</p> <p><u>Acneiform rash</u></p> <p>Hold cobimetinib (GDC-0973) dosing until Grade ≤ 2. Vemurafenib dosing may continue when cobimetinib (GDC-0973) is interrupted.</p> <p>Reduce cobimetinib (GDC-0973) by 1 dose level. If after restarting at reduced dose, the patient experiences skin toxicity Grade ≥ 3, further reduce cobimetinib (GDC-0973) by another dose level. Permanently discontinue cobimetinib (GDC-0973) if restarting after second dose reduction, the patient experiences skin toxicity Grade ≥ 3.</p> <p>Permanently discontinue cobimetinib (GDC-0973) if rash Grade ≥ 3 persists for > 28 days despite adequate supportive care.</p> <p><u>Non-acneiform or maculo-papular rash</u></p> <p>Delay vemurafenib dosing until Grade ≤ 2. Cobimetinib (GDC-0973) dosing may continue when vemurafenib is interrupted.</p> <p>For Grade 3 rash, reduce vemurafenib by 1 dose level. If after restarting at reduced dose, the patient experiences skin toxicity Grade ≥ 3, further reduce vemurafenib by 1 dose level. Permanently discontinue vemurafenib if restarting after second dose reduction, the patient experiences recurrent skin toxicity Grade ≥ 3.</p> <p>For Grade 4 rash, reduce vemurafenib by 2 dose levels. Permanently discontinue vemurafenib if after restarting at reduced dose, the patient experiences skin toxicity Grade ≥ 3.</p>

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Adverse Event	Action						
<p>B) Photosensitivity Grade ≥ 3</p>	<p>a) Grade ≤ 2 photosensitivity should be managed with supportive care and treatment of both vemurafenib and cobimetinib (GDC-0973) may be continued.</p> <p>If Grade 2 photosensitivity does not resolve to Grade ≤ 1 after 7 days or if photosensitivity worsens to Grade ≥ 3 despite best supportive care, then both vemurafenib and cobimetinib (GDC-0973) treatment must be interrupted until the photosensitivity resolves to a Grade ≤ 1.</p> <p>b) If resolution to Grade ≤ 1 occurs within 28 days, treatment may be re-initiated with vemurafenib dose reduced by 1 level and without change in cobimetinib (GDC-0973) dose.</p> <p>If the photosensitivity does not resolve to Grade ≤ 1 by 28 days, then the therapy with vemurafenib and cobimetinib (GDC-0973) should be discontinued.</p> <p>c) If the photosensitivity recurs to Grade ≥ 3 with vemurafenib and cobimetinib (GDC-0973), re-initiation despite prophylactic measures and dose reduction of vemurafenib, then both agents should be held until the photosensitivity resolves to Grade ≤ 1 or less. The dose of vemurafenib should be reduced by another dose level.</p> <p>d) If photosensitivity recurs a second time to Grade ≥ 3 despite prophylactic measures and the aforementioned 2 dose reductions of vemurafenib, vemurafenib should be discontinued. The patient may continue on study treatment with cobimetinib (GDC-0973)/placebo alone.</p>						
<p>C) New skin lesion, suggestive of any cutaneous primary malignancy.</p> <p>Any cutaneous primary malignancy is considered a Grade 3 event in this study.</p>	<p>a) Follow SCC Risk Management Plan detailed in protocol</p> <p>b) Interrupt vemurafenib and cobimetinib (GDC-0973) for 48 hours before and after excisional biopsy. This period of interruption may be altered based upon experience in this study.</p> <p>c) If lesion is diagnosed as cuSCC, treatment may be re-instituted with vemurafenib and cobimetinib (GDC-0973) at pre-event dose levels after the lesion is excised. If the lesion is not excised, vemurafenib treatment must be discontinued.</p> <p>d) If the lesion is not an SCC, then treatment with vemurafenib and cobimetinib (GDC-0973) may be restarted at the most recent dose level.</p>						
<p>D) Visual symptoms \geq Grade 2</p>	<p>NCI CTCAE v4.0 Eye Disorders – Other, specify:</p> <table border="1" data-bbox="548 1331 1079 1539"> <thead> <tr> <th data-bbox="548 1331 630 1367">Grade</th> <th data-bbox="630 1331 1079 1367">Description</th> </tr> </thead> <tbody> <tr> <td data-bbox="548 1367 630 1457">1</td> <td data-bbox="630 1367 1079 1457">Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated</td> </tr> <tr> <td data-bbox="548 1457 630 1539">2</td> <td data-bbox="630 1457 1079 1539">Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL</td> </tr> </tbody> </table>	Grade	Description	1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	2	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL
Grade	Description						
1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated						
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental ADL						

Adverse Event	Action	
	3	Severe or medically significant but not immediately sight threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL
	4	Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye
	<p>Interrupt cobimetinib (GDC-0973) and vemurafenib.</p> <p>Consult ophthalmology and undergo complete ophthalmologic examination, which includes visual acuity testing, intraocular pressure measurements by tonometry, slit-lamp ophthalmoscopy, indirect ophthalmoscopy, and spectral domain optical coherence tomography</p> <p>If retinal vein occlusion (RVO) is diagnosed, vemurafenib and cobimetinib (GDC-0973) dosing should be permanently discontinued and RVO treated per institutional guidelines.</p> <p>If neurosensory retinal detachment is diagnosed, cobimetinib (GDC-0973) dosing should be interrupted until symptoms improve to Grade 1. <i>Then</i> cobimetinib (GDC-0973) should be dose reduced by 1 dose level <i>when restarting</i>. If visual symptoms of Grade ≥ 2 recur despite 2 dose level reductions of cobimetinib (GDC-0973), cobimetinib (GDC-0973) should be permanently discontinued.</p> <p><i>If uveitis/iritis is diagnosed, Grade ≤ 2 uveitis/iritis can be managed with ophthalmologic input using local non-invasive therapies and/or short courses of systemic therapy. Dose reduction of study drugs is NOT required if uveitis/iritis is Grade ≤ 2. For Grade ≥ 3 uveitis/iritis, vemurafenib should be reduced by 1 dose level.</i></p> <p>If RVO, neurosensory retinal detachment or uveitis/iritis are NOT identified:</p> <ul style="list-style-type: none"> • and visual symptoms have not resolved to Grade 1 or less (with the continued use of local / non-invasive supportive care) within 28 days, then discontinue both drugs permanently. • and visual symptoms have resolved to Grade 1 or less (with the continued use of local / non-invasive supportive care) within 28 days, resume use of vemurafenib and cobimetinib (GDC-0973) at current doses. • If visual symptoms of Grade ≥ 2 (despite the optimal use of 	

Adverse Event	Action
	<p>local / non-invasive supportive care) recur, vemurafenib and/or cobimetinib (GDC-0973) should be dose reduced by 1 level, depending on which agent is implicated. If visual symptoms of Grade ≥ 2 recurs despite 2 dose level reductions of both vemurafenib and cobimetinib, and maximal supportive care, vemurafenib and cobimetinib (GDC-0973) should be permanently discontinued.</p>
<p>E) Diarrhea Grade >3</p>	<p>a) No change in vemurafenib and cobimetinib (GDC-0973) dosing will be implemented for Grade ≤ 2 diarrhea; patients should receive maximal supportive care.</p> <p>b) If Grade ≥ 3 diarrhea occurs despite adequate supportive care, then both drugs should be held until the diarrhea has improved to Grade ≤ 1.</p> <ul style="list-style-type: none"> • If this occurs within 28 days, vemurafenib and cobimetinib (GDC-0973) may be restarted with cobimetinib (GDC-0973) reduced by 1 dose level, with continued supportive care or prophylaxis. • If bowel movement characteristics have NOT improved to Grade ≤ 1 or baseline with maximal supportive care by 28 days, then both drugs should be discontinued. <p>d) If Grade ≥ 3 diarrhea recurs despite supportive care and cobimetinib (GDC-0973) dose reduction, vemurafenib and cobimetinib (GDC-0973) should be held until the diarrhea resolves to Grade ≤ 1. If this occurs within 28 days, then therapy may be re-initiated with vemurafenib reduced by 1 dose level. The cobimetinib (GDC-0973) dose will be maintained at the previously reduced dose.</p> <p>e) If the diarrhea recurs at Grade ≥ 3 despite supportive care and dose reductions of 2 dose levels in both drugs (i.e., vemurafenib to 480 mg BID and cobimetinib (GDC-0973) to 20 mg QD), then both drugs should be permanently discontinued.</p>
<p>F) Grade ≥ 3 CPK elevations</p>	<p>a) Rule out cardiac cause (check ECG, serum cardiac troponin, and CK-MB fraction) and rule out rhabdomyolysis (clinical examination; serum creatinine, potassium, calcium, phosphorus, uric acid, and albumin; and urine myoglobin). Consider permanent discontinuation of cobimetinib (GDC-0973) if there is evidence of clinically significant cardiac injury or rhabdomyolysis.</p> <p>b) Assess patient for any history of strenuous physical activity, blunt trauma, or recent intramuscular injections.</p> <p>c) For Grade 3 CPK elevations that are asymptomatic and deemed not clinically significant, continue cobimetinib (GDC-0973) at current dose and schedule. Recheck CPK at least once a week. If CPK remains Grade 3 or decreases,</p>

Adverse Event	Action
	<p>continue cobimetinib (GDC-0973) at current dose and schedule.</p> <p>d) For Grade 4 CPK elevations that are asymptomatic and deemed not clinically significant, hold cobimetinib (GDC-0973) and recheck CPK within 3 days. When CPK is Grade ≤ 3, cobimetinib (GDC-0973) may be resumed with a dose reduction by 1 dose level on the same schedule (e.g., 60 mg to 40 mg). If Grade 4 CPK elevation recurs after 1 dose reduction, cobimetinib (GDC-0973) may be reduced by another dose level (e.g., 40 mg to 20 mg). Permanently discontinue cobimetinib (GDC-0973) if Grade 4 CPK elevation recurs after 2 dose reductions of cobimetinib (GDC-0973).</p>
G) LFT elevations	<p>a) If Grade ≤ 2, continue current dose of vemurafenib and cobimetinib (GDC-0973).</p> <p>b) If Grade 3, hold vemurafenib. Continue current dose of cobimetinib (GDC-0973). Upon resolution of LFT to Grade ≤ 1, resume vemurafenib at 1 lower dose level (e.g., 960 mg to 720 mg, or 720 mg to 480 mg).</p> <p>c) If Grade 4, see Section J below.</p> <p>d) No dose modification is required for isolated GGT elevation in the absence of elevation above baseline grade in AST, ALT, alkaline phosphatase, bilirubin or hepatic .</p>
H) QTcF interval prolongation on ECG Grade ≥ 3	<p>a) Rule out other risk factors for arrhythmia (e.g., myocardial ischemia); check for electrolyte disturbances (particularly potassium and magnesium levels) in all cases.</p> <p>b) Evaluate concomitant medications to determine if there is co-administration of drugs that prolongs QTc interval in all cases (e.g., 5-HT₃ receptor antagonist anti-emetics; see Appendix 9).</p> <p>c) Interrupt dosing of vemurafenib ECG monitoring should be performed until QTc interval decreases below 500 ms. Electrolytes abnormalities should be corrected in all cases. Continue dosing with cobimetinib (GDC-0973) at the current dose if otherwise tolerated.</p> <p>d) Plan to seek a cardiologist consultation or advice.</p> <p>e) If QTc interval does not improve within 28 days after interruption of vemurafenib dosing, permanently discontinue vemurafenib; continue dosing with cobimetinib (GDC-0973) at the current dose.</p> <p>f) If QTc improves within 28 days, restart dosing of vemurafenib at 1 reduced dose level.</p> <p>g) Repeat 12-lead ECG monitoring at 2 weeks and 4 weeks of restarting vemurafenib at the lower dose. Additional ECG monitoring will be performed at Day 15 of each subsequent Cycle for 3 cycles, and every 3 months thereafter.</p> <p>h) If second increase in QTc interval to >500 msec occurs at</p>

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Adverse Event	Action
	cobimetinib (GDC-0973) by 1 dose level. c) If the AE does not resolve to Grade \leq 1 by 28 days, discontinue study treatment. d) If the Grade 4 AE recurs (a second time), then both agents should be discontinued.

ADL = activities of daily living; AE = adverse event; BID = twice daily; CPK = creatine phosphokinase; cuSCC = cutaneous squamous cell carcinoma; EF = ejection fraction; GGT = γ glutamyltransferase; LFT = liver function test; LLN = lower limit of normal; LVEF = left ventricular ejection fraction; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; QD = once daily; QTc = corrected QT interval; RVO = retinal vein occlusion; SCC = squamous cell carcinoma

Source GO28141 CSR, p7214 - 2710

9.4 GO28141 – Exploratory MedDRA-Based Adverse Event Diagnostics (MAED) Analysis

The MedDRA-Based Adverse Event Diagnostic (MAED) Service is a server-based adverse event (AE) analysis tool which enables analysis of clinical trials using standard medical terms or codes from the Medical Dictionary for Regulatory Activities (MedDRA). Across all levels of the MedDRA hierarchy, as well as create Standardized MedDRA Queries (SMQs)—narrow, broad, and algorithm.

MAED compares adverse events in one or more treatment groups with a reference group such as placebo using the Likelihood Ratio Test (LRT) method to systematically generate safety signals. Analyses are not controlled for multiple comparisons and are considered exploratory. The p-values included are used to rank order the strength of potential signals for further analysis and do not imply significance.

Contained in this section are the results of the MAED analysis for the GO28141 trial. Relevant findings are further explored and discussed the in the body of the review.

Table 68 shows an exploratory analysis at the MedDRA Higher Level Term (HLT) level. Five HLTs represent potentially new safety flags and are discussed below.

Primary terms included in the apocrine and endocrine gland disorders HLT included the MedDRA lower level terms “night sweats”, “sweating, diaphoresis, hyperhidrosis, hidradentis and milia. These terms likely represent terms captured by the primary terms “pyrexia” and under rash and thus were not thought to represent a new safety signal. PTs captured under the vascular hypertensive disorders, NEC HLT were hypertension and prehypertension. These did not represent new safety signals. Nine of the ten patients captured under the Pneumothorax and pleural effusions NEC HTL had pleural effusions and one had a pneumothorax. These represented tumor-related events and were not felt to represent new safety signals. Patients within the Stomatitis and ulceration HLT had the following PTs: aphous stomatitis, mouth ulceration, oral mucosa erosion and stomatitis. These PTs represent different names for a common event and so should be grouped together and included for labeling purposes as this event meets the criteria for inclusion into Table. Six patients were reported to have had events in the Central nervous system hemorrhages and cerebrovascular accidents HLT. All of these patients received treatment with Vem/Cobi. Adverse event terms included cerebrovascular accident (n=3), cerebral vascular accident (n=2), subarachnoid hemorrhage (n=1), and ischemic stroke (n=1). The date of onset of these events ranged from 22 days to 376 days. In four events, the underlying cause was attributed to the disease under study. However, this distribution is unlikely to have occurred by chance alone ($X^2 = 0.0$; $p < .001$).

Reviewer’s comment: This exploratory analysis of the between arm differences suggests that

a composite event, stomatitis, including the terms aphthous stomatitis, mouth ulceration, oral mucosa erosion and stomatitis should be added to the label. Of note, major hemorrhagic events are included in the WARNINGS and PRECAUTIONS section of the Mekinist label, reported when Mekinist is used in combination with dabrafenib. A parallel warning should be considered in the Cobimetinib label.

Table 69: GO28141 – Exploratory MedDRA-Based Adverse Event Diagnostics (MAED) Analysis for MedDRA Higher Level Terms* (Safety Population; Data Cut-off Date: 19 SEP 2014)

<i>HLT*</i>	<i>Vem/ Placebo</i>	<i>Vem/ Cobi</i>	<i>Vem/Cobi vs. Vem/Placebo</i>		
	(%)	(%)	<i>RR</i>	<i>RR C.I. (lower bound)</i>	<i>RR C.I. (upper bound)</i>
Skeletal and cardiac muscle analyses	3.25	32.39	9.96	4.921	20.157
Diarrhea (excl infective)	30.89	59.92	1.939	1.568	2.4
Hyperkeratoses	38.21	13.77	0.36	0.254	0.511
Retinal structural change, deposit and degeneration	2.85	18.62	6.545	3.014	14.211
Choroid and vitreous structural change, deposit and degeneration	2.85	14.57	5.122	2.324	11.287
Alopecias	30.49	14.98	0.491	0.346	0.699
Visual disorders NEC	3.66	13.77	3.762	1.844	7.677
Nausea and vomiting symptoms	30.08	46.96	1.561	1.238	1.969
Skin neoplasms benign	25.61	12.55	0.49	0.331	0.725
Skin neoplasms malignant and unspecified (excl melanoma)	21.54	9.72	0.451	0.288	0.706
Photosensitivity and photodermatitis conditions**	22.36	37.25	1.666	1.255	2.212
Apocrine and endocrine gland disorders	7.32	1.62	0.221	0.076	0.645
Sodium imbalance	0.81	4.86	5.976	1.351	26.422
Vascular hypertensive disorders NEC	7.72	14.98	1.939	1.148	3.276
Panniculitides	2.44	7.29	2.988	1.206	7.4
Pneumothorax and pleural effusions NEC	3.25	0.4	0.124	0.016	0.988
Mass conditions NEC	4.07	0.81	0.199	0.044	0.9
Stomatitis and ulceration	5.69	11.74	2.063	1.118	3.808
Central nervous system hemorrhages and cerebrovascular accidents	0	2.43	12.948	0.733	228.594
Renal function analyses	8.13	14.57	1.793	1.069	3.007
Skin preneoplastic conditions NEC	9.35	4.45	0.476	0.237	0.956
Total fluid volume decreased	0.81	4.05	4.98	1.102	22.494
Cardiac function diagnostic procedures	4.07	8.91	2.191	1.06	4.53
Liver function analyses	30.08	38.87	1.292	1.01	1.653
Tissue enzyme analyses NEC	10.16	16.6	1.633	1.026	2.6

* Ranked in order of the p-value for the Likelihood Ratio Test (LRT). Terms with P-value for relative Risk ≤0.05.

**This HLT included photodermatitis/photosensitivity reactions.

Source: NDA206192/0036(37): GO28141:adae.xpt

An exploratory MAED analysis by MedDRA Higher Level Group Terms (HLGT) is shown below in Table 70. Three HLGTs, Electrolyte and fluid balance conditions, Angioedema and urticarial and Bone, calcium, magnesium and phosphorus metabolism disorders represent potentially new safety signals and are discussed below.

PTs included in the Electrolyte and fluid balance conditions HLGT include dehydration, hyperkalemia, hypokalemia, and hyponatremia. Dehydration is likely related to the increased incidence of diarrhea among patients treated with Vem/Cobi and does not represent a new safety signal. Laboratory abnormalities are further explored in Section 7.4.2 below. Events classed in the Bone, calcium, magnesium and phosphorus metabolism disorders HLGT represent laboratory abnormalities and are also discussed in Section 7.4.2 below. In the Angioedema and urticarial HLGT, three patients in each treatment group were reported to have had the PT “Swelling, face”, eight patients in the Vem/Cobi treatment group were reported to have had urticarial and one to have had angioedema. Three events, all urticarial were reported to have a CTCAE grade of 3; only one event was assessed as serious.

This patient (GO28141-252958-2184) was reported to have developed a macular rash over 30 % of this body and was treated with phenergan and prednisone. A Biopsy of two skin areas were taken and the rash was assessed to be consistent with urticarial and not erythema multiforme. Vemurafenib was discontinued. Cobimetinib was not discontinued. The other two events (GO28141-256298-2301 and GO28141-2558383-2172), were assessed as Grade 3 events, but non-serious. These events were attributed to vemurafenib and reported as resolved without discontinuation of cobimetinib therapy. The remaining patient (GO28141-252961-2396) was reported to have Grade 2 angioedema (Quickne’s Edema) with a prior event reported as a Grade 2 drug eruption. The event was attributed to vemurafenib, cobimetinib was continued and the event was reported as ongoing.

Reviewer’s comment: The signal of angioedema/urticarial was not a strong one. In only one case was the event considered to be serious. In all cases, the event was attributed to vemurafenib. It is possible that cobimetinib was contributory or independently associated with the event. In any case, this reviewer concludes that this potential flag should be monitored through post-market surveillance and that the level of risk does not justify inclusion as a warning at the present time.

Table 70: GO28141 – Exploratory MedDRA-Based Adverse Event Diagnostics (MAED) Analysis for MedDRA Higher Level Group Terms* (Safety Population; Data Cut-off Date: 19 SEP 2014)

<i>HLGT*</i>	<i>Vem/ Placebo</i>	<i>Vem/ Cobi</i>	<i>Vem/Cobi vs. Vem/Placebo</i>		
	(%)	(%)	<i>RR</i>	<i>RR C.I. (lower bound)</i>	<i>RR C.I. (upper bound)</i>
Ocular structural change, deposit and degeneration NEC	5.69	31.58	5.549	3.231	9.53
Enzyme investigations NEC	11.79	41.3	3.503	2.413	5.085
Cornification and dystrophic skin disorders	44.31	17.41	0.393	0.289	0.533
Gastrointestinal motility and defecation conditions	37.4	62.75	1.678	1.39	2.025
Vision disorders	4.88	16.6	3.403	1.833	6.317
Cutaneous neoplasms benign	25.61	12.55	0.49	0.331	0.725
Skin neoplasms malignant and unspecified	21.54	10.53	0.489	0.316	0.755
Gastrointestinal signs and symptoms	43.09	55.06	1.278	1.065	1.534
Vascular hypertensive disorders	7.72	15.38	1.992	1.182	3.356
Electrolyte and fluid balance conditions	5.28	11.74	2.222	1.183	4.171
Pleural disorders	3.25	0.4	0.124	0.016	0.988
Central nervous system vascular disorders	0	2.43	12.948	0.733	228.594
Angioedema and urticaria	1.22	4.86	3.984	1.138	13.943
Tissue disorders NEC	4.47	1.21	0.272	0.077	0.962
Renal and urinary tract investigations and urinalyses	8.54	14.98	1.755	1.058	2.909
Bone, calcium, magnesium and phosphorus metabolism disorders	2.44	6.48	2.656	1.057	6.674
Hepatobiliary investigations	30.08	38.87	1.292	1.01	1.653

*Ranked in order of the p-value for the Likelihood Ratio Test (LRT). Terms with P-value for relative Risk ≤0.05.
Source: NDA206192/0036(37): GO28141:adae.xpt

An exploratory MAED analysis using MedDRA System Organ Class (SOC) terms (Table 71) did not suggest any new safety signals.

Table 71: GO28141 – Exploratory MedDRA-Based Adverse Event Diagnostics (MAED) Analysis for MedDRA System Organ Class Terms* (Safety Population; Data Cut-off Date: 19 SEP 2014)

SOC*	Vem/ Placebo	Vem/ Cobi	Vem/Cobi vs. Vem/Placebo		
	(%)	(%)	RR	RR C.I. (lower bound)	RR C.I. (upper bound)
Investigations	48.37	71.26	1.473	1.266	1.714
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	43.5	24.29	0.558	0.43	0.726
Eye disorders	30.89	50.2	1.625	1.298	2.034
Gastrointestinal disorders	62.6	78.95	1.261	1.123	1.416
Musculoskeletal and connective tissue disorders	60.57	50.61	0.836	0.713	0.98
Congenital, familial and genetic disorders	4.47	1.21	0.272	0.077	0.962
Respiratory, thoracic and mediastinal disorders	30.89	22.27	0.721	0.535	0.972
Vascular disorders	16.26	24.29	1.494	1.043	2.139

*Ranked in order of the p-value for the Likelihood Ratio Test (LRT). Terms with P-value for relative Risk ≤0.05.
Source: NDA206192/0036(37): GO28141:adae.xpt

An exploratory analysis using the MedDRA-Based Adverse Event Diagnostics (MAED) tool was conducted for the Narrow Standardized MedDRA Queries (SMQ) (Table 72).

Table 72: GO28141 Exploratory MedDRA-Based Adverse Event Diagnostics (MAED) Analysis for Narrow Standardized MedDRA Queries (SMQ) (Safety Population; Data Cut-off Date: 19 SEP 2014)

SMQ (Narrow Search)			Vem/Placebo (n=246)	Vem/Cobi (n=247)	Vem/Cobi vs. Vem/Placebo		
<i>Level 1</i>	<i>Level 2</i>	<i>Level 3</i>	<i>Proportion (%)</i>	<i>Proportion (%)</i>	<i>OR</i>	<i>OR C.I. (lower bound)</i>	<i>OR C.I. (upper bound)</i>
(1) Retinal disorders			8.94	34.41	5.342	3.143	9.336
(1) Noninfectious diarrhea			30.89	59.92	3.344	2.269	4.934
(1) Gastrointestinal nonspecific inflammation and dysfunctional conditions	(2) Gastrointestinal nonspecific symptoms and therapeutic procedures		55.69	74.9	2.374	1.593	3.547
(1) Gastrointestinal nonspecific inflammation and dysfunctional conditions			57.32	75.3	2.271	1.52	3.4
(1) Malignancies *	(2) Malignant or unspecified tumors *	(3) Malignant tumors *	22.36	10.93	0.426	0.248	0.72
(1) Malignancies *			25.61	13.77	0.464	0.283	0.752
(1) Malignancies *	(2) Malignant or unspecified tumors *		22.76	11.74	0.451	0.267	0.754
(1) Premalignant disorders *	(2) Skin premalignant disorders *		12.6	4.86	0.354	0.162	0.732
(1) Premalignant disorders *			12.6	5.26	0.385	0.18	0.783
(1) Hypertension			8.13	15.79	2.119	1.161	3.961
(1) Hyponatremia/SIADH			1.22	5.26	4.5	1.212	24.865
(1) Skin neoplasms, malignant and unspecified			15.45	8.91	0.535	0.291	0.965
(1) Pregnancy and neonatal topics	(2) Congenital, familial and genetic disorders *		4.47	1.21	0.263	0.047	1.014
(1) Hepatic disorders			30.89	40.08	1.496	1.015	2.208

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(1) Hepatic disorders	(2) Drug related hepatic disorders - comprehensive search		30.89	40.08	1.496	1.015	2.208
(1) Skin neoplasms, malignant and unspecified	(2) Skin malignant tumors		15.04	8.91	0.552	0.3	0.999
(1) Cardiomyopathy			4.07	8.91	2.308	1.02	5.577
(1) Angioedema			5.28	10.53	2.109	1.014	4.582
(1) Peripheral neuropathy			4.88	1.62	0.321	0.075	1.081
(1) Hepatic disorders	(2) Drug related hepatic disorders - comprehensive search	(3) Liver related investigations, signs and symptoms	30.89	39.68	1.471	0.998	2.172
(1) Hemorrhages			7.32	12.96	1.885	0.992	3.676
(1) Hemorrhages	(2) Hemorrhage terms (excl laboratory terms) *		7.32	12.96	1.885	0.992	3.676
(1) Hyperglycemia/new onset diabetes mellitus			1.22	4.45	3.775	0.978	21.286
(1) Cerebrovascular disorders	(2) Central nervous system hemorrhages and cerebrovascular conditions	(3) Hemorrhagic cerebrovascular conditions *	0	2.02	11.181	0.615	203.311
(1) Cardiac failure			4.47	8.91	2.089	0.944	4.88

*Ranked in order of the p-value for the Likelihood Ratio Test (LRT). Terms with P-value for relative Risk ≤ 0.05 .
Source: NDA206192/0036(37): GO28141:adae.xpt

In addition to the previously noted flag for cerebrovascular disorders, exploration of SMQ (Narrow) terms suggested a possible increase in the risk of hemorrhagic events and hyperglycemia. The per-patient incidence of hemorrhagic events in the GO28141 is shown in Table 53. While the incidence of hemorrhagic events was increased in the Vem/Cobi treatment group compared to the Vem/Placebo treatment group, most events were assessed as CTCAE Grade 1 or 2. One Grade 5 event of cerebral hemorrhage was reported in the Vem/Cobi treatment group but this was assessed as related to the underlying disease.

The distribution of patients included in the Hyperglycemia SMQ (Narrow) by maximum CTCAE Grade is shown below in Table 53.

9.5 Literature Review/References

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RUTHANN M GIUSTI
10/31/2015

MARC R THEORET
11/01/2015

Sponsor Proposal for Content and Timing of Submission of Ocular Information

The Sponsor proposes to provide a retrospective collection of OCT scans and any associated reports as an amendment to NDA 206192 in conjunction with the planned NDA Safety Update which will be submitted by March 11, 2014. Due to the challenges of scan collection previously discussed, the Sponsor has focused on providing a high-quality subset of OCT scans and reports to the FDA. In keeping with the Agency's stated desire to review serial OCT scans (baseline and on-study), the Sponsor is prioritizing serial OCT scan collection from sites who participated in the NO25395 and GO28141 studies who are able to provide source OCT imaging files and reports in English in time for the planned March 11th submission.

The Sponsor has conducted a thorough and robust site-by-site feasibility assessment and anticipates that serial OCT imaging studies will be available and provided for evaluation from approximately 55 melanoma patients treated on Studies NO25395 and GO28141. This represents a total of approximately 150 scans and reports that would be collected from these patients. Since sites remain blinded to study treatment, the current approximation is that 40 of the 55 patients are anticipated to have been treated with cobimetinib and vemurafenib. The Sponsor believes that providing high quality, serial assessments, albeit from a subset of patients, will provide the FDA with the information they have requested for their assessment.

OCT scans and associated reports will be collated, de-identified and uploaded by ophthalmologists who evaluated patients on study to a validated central repository. The Sponsor has engaged the services of The Digital Angiography Reading Center (DARC) to operationalize and manage the central repository, in part since the Sponsor understands that the ophthalmic branch of the Agency has worked with DARC previously and the Sponsor hopes this will help facilitate the Agency's review. FDA reviewers will be able to access and read the OCT scans through direct access to the central repository using a secure VPN connection provided by DARC.

In addition, the Sponsor will provide a brief report summarizing the imaging findings. This report will be provided to the FDA by March 11, 2014 in conjunction with the planned NDA Safety Update.

March 10, 2015 Submission

The Sponsor retrospectively collected serial OCT scans and reports from selected 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. The image files and associated study ophthalmic reports were collated, de-identified and uploaded directly into a secure central repository operated and managed by an ophthalmology reading center with expertise in evaluation of OCT scans - The Digital Angiography Reading Center (DARC). This reading center has been used by Genentech for prior ophthalmology sponsored trials. All OCT scans received were reviewed by qualified personnel at the reading center. The review focused on evaluating the clinical characteristics of abnormal fluid accumulation on OCT scans and quantitative analysis of central foveal thickness over time.

Reviewer's Comment: *The applicant should have prospectively planned to collect OCT images and analyze them.*

The study protocols did not specifically require collection of ophthalmic images. Therefore, the source file formats of this retrospective collection of images and reports were specific to each site and could not be standardized.

Reviewer's Comment: *The drug's potential to cause serious detachments was known prior to the initiation of the study. The protocols should have required the collection and analysis of the ophthalmic images.*

The Sponsor focused on collecting sets of imaging studies and reports that could meet the agreed upon timelines (by March 11, 2015 to coincide with the submission of the NDA Safety Update). As anticipated, due to the country- and site-level feasibility challenges of retrospective scan collection, and as previously discussed with the FDA, the size of this archive is a modest but representative subset of the clinical studies supporting the NDA. In addition, given the added complexities and time required in translating non-English reports, study sites with reports available in English were also prioritized.

Reviewer's Comment: *The images are not language specific. Non-English reports should also have been collected.*

Best-corrected visual acuity results were converted to logarithm of the minimum angle of resolution (logMAR) in order to facilitate statistical manipulation.

Serial OCT scans, defined as baseline plus at least one on-treatment scan, were retrospectively collected from 47 patients in the United States, Canada, Australia, New Zealand and the United Kingdom. Serial OCTs were obtained from 35 patients (74%) in Study GO28141 and 12 patients (26%) in Study NO25395. In total, 35/47 patients (74%) were treated with cobimetinib plus vemurafenib in studies GO28141 and NO25395 and 12 patients were treated with vemurafenib plus placebo in study GO28141.

Patient Demographics of Patients with Serial OCT Scans

Patients with serial OCT scans, n	47
Study and Treatment	
NO25395, n (%)	12 (26%)
- cobimetinib + vemurafenib, n	12
GO28141, n (%)	35 (74%)
- placebo + vemurafenib, n	12
- cobimetinib + vemurafenib, n	23
Median age, years (range)	55 (19 – 82)
Gender, n	
- male	26 (55%)
- female	21 (45%)

Baseline OCT Evaluation

At the baseline OCT evaluation, no patients had evidence of serous fluid accumulation within or under the retinal layers.

Thirty-four patients had a normal macular appearance at baseline OCT scan.

In 13/47 patients, a macular pathology was detected on baseline OCT scan;

10 patients had evidence of non-exudative age-related macular degeneration (AMD),

1 had single choroidal fold within the macula,

1 had an epiretinal membrane,

1 had a lamellar macular hole.

Clinical Features of Serous Retinopathy during Cobimetinib and Vemurafenib Treatment

Out of the 47 patients with serial OCT scans, 9 patients were found to have developed sub-retinal fluid accumulation while receiving cobimetinib and vemurafenib treatment.

	No serous retinopathy	Serous retinopathy
N	38	9
Median age (range)	52.5 (19-82)	64 (31 – 70)
Male	22	4
Female	16	5
Study		
NO25395 - cobimetinib + vemurafenib	8	4
GO28141 - placebo + vemurafenib	18	0
- cobimetinib + vemurafenib	12	5
Mean baseline central foveal thickness (range), μm	196.6 (156.8, 239.5)	204.8 (186.0, 229.5)
Laterality		
- Unilateral	N/A	1
- Bilateral		8

There were 5 patients (3 males, 2 females) from Study GO28141 and 4 patients (1 male, 3 female) from Study NO25395 with an abnormal OCT scan consistent with serous retinopathy, and all patients were treated with cobimetinib 60 mg daily 21 days on / 7 days off in combination with vemurafenib 960 mg twice daily.

In Study NO25395, serial surveillance complete ophthalmic examinations were performed only if clinically indicated during the course of study treatment. Patients found to have abnormal OCT scan consistent with serous retinopathy in Study NO25395 were generally diagnosed later than patients on Study GO28141 where surveillance complete ophthalmic examinations were performed every 3 months after the first month on treatment.

Patient number	Study	Age & Gender	Study day of abnormal OCT scan
1022 Phase 1b	NO25395	69 female	22
1261 Phase 1b	NO25395	64 female	210
1262 Phase 1b	NO25395	70 female	9
1266 Phase 1b	NO25395	70 male	111
2006 Phase 3	GO28141	31 male	34
2099 Phase 3	GO28141	64 male	14
2211 Phase 3	GO28141	64 female	10
2213 Phase 3	GO28141	65 female	198
2257 Phase 3	GO28141	55 male	69

Reviewer's Comment: *As noted, routine monitoring is required to detect many of the cases.*

Study	Subretinal fluid						Intra-retinal/Sub- RPE fluid	
	Count		Focality*		Location*			Count
	Patients	Eyes	focal	multifocal	foveal	extrafoveal		Patients
NO25395	4	8	3	5	6	2	0	
GO28141	5	9	5	4	9	0	0	
Total	9	17	8	9	15	2	0	

RPE – Retinal pigment epithelium

*number of eyes

Reviewer's Comment: *Non-foveal cases are likely to be missed without routine OCT screening, but they can still cause visual field defects.*

Sponsor's Conclusion

This is a retrospective collection and analysis of ophthalmic data (primarily OCT scans) from patients treated with cobimetinib and vemurafenib to better elucidate the clinical features of serous retinopathy events. Baseline clinical characteristics of this subset of patients derived from sites that were able to provide high-quality serial OCT images and that use English as the primary language of medical documentation is consistent with and representative of the advanced BRAF-mutated melanoma patients studied in Studies NO25395 and GO28141.

In this retrospective analysis of 47 advanced BRAF-mutated melanoma patients, subretinal fluid developed during treatment in 9 patients (19% of cases), a frequency consistent with that observed in the overall population treated with vemurafenib and cobimetinib from study GO28141 (24%). Interestingly, sub-RPE and intraretinal fluids did not develop in any patient in this subset during treatment, although we cannot exclude the possibility that such findings may be observed. Almost all cases of subretinal fluid accumulation were bilateral and subfoveal, and in around 50% of the cases was multifocal. Collectively, the clinical features noted in this analysis are similar to literature reports of serous retinopathy in melanoma patients treated with other MEK inhibitors, notably early onset, balanced gender distribution and often involving both eyes (McCannell et al, Urner-Bloch et al). MEK inhibitor-induced serous retinopathy appears to be different from classical central serous retinopathy that has a predisposition for young men, unilateral eye involvement and in acute cases, typically presents with a single collection of sub-retinal fluid secondary to a sole leaking point at the level of the RPE (Nicholson et al, 2013).

The OCT scan findings reported here are consistent with the clinical analysis of serous retinopathy reported in cobimetinib treated patients in Study GO28141. Serous retinopathy tends to occur early in the treatment course and is usually reversible without compromising visual acuity.

Based on the data on serous retinopathy reported in the GO28141 clinical study report and of the findings presented in this report, the Sponsor believes that the dose modification strategy proposed in the Warnings and Precautions is appropriate to manage these events.

Reviewer's Comment: *The reported cases are consistent with those seen in patients treated with other MEK inhibitors. The frequency of macular reports may be under reported because of relatively infrequent OCT monitoring.*

Ocular Adverse Events from Safety Update:

		Placebo+ Vemurafenib		Cobimetinib+ vemurafenib		Cobimetinib+ vemurafenib		Integrated Safety Population	
		SCS n=239	safety update n=246	SCS n=254	safety update n=247	SCS n=129	safety update n=129	SCS n=383	safety update n=376
Patient experiencing events by									
NCI-CTCAE Grade, n (%)	All	5 (2.1)	7 (2.8)	61 (24.0)	63 (25.5)	8 (6.2)	7 (5.4)	69 (18.0)	70 (18.6)
	1	5 (2.1)	6 (2.4)	32 (12.6)	33 (13.4)	6 (4.7)	4 (3.1)	38 (9.9)	37 (9.8)
	2	0	1 (0.4)	22 (8.7)	23 (9.3)	2 (1.6)	3 (2.3)	24 (6.3)	26 (6.9)
	3	0	0	6 (2.4)	6 (2.4)	0	0	6 (1.6)	6 (1.6)
	4	0	0	1 (0.4)	1 (0.4)	0	0	1 (0.3)	1 (0.3)
	5	0	0	0	0	0	0	0	0
Patients experiencing event (preferred term), n (%)									
Chorioretinopathy	All	1 (0.4)	1 (0.4)	30 (11.8)	31 (12.6)	3 (2.3)	3 (2.3)	33 (8.6)	34 (9.0)
Retinal detachment	All	0	1 (0.4)	21 (8.3)	21 (8.5)	2 (1.6)	1 (0.8)	23 (6.0)	22 (5.9)
Detachment of retinal pigment epithelium	All	1 (0.4)	1 (0.4)	8 (3.1)	8 (3.2)	0	0	8 (2.1)	8 (2.1)
Macular edema	All	0	1 (0.4)	4 (1.6)	5 (2.0)	1 (0.8)	1 (0.8)	5 (1.3)	6 (1.6)
Retinopathy	All	0	0	2 (0.8)	2 (0.8)	2 (1.6)	2 (1.6)	4 (1.0)	4 (1.1)

Reviewer's Comment: *As described in these studies, it is likely that chorioretinopathy, retinal detachment, detachment of retinal pigment epithelium, macular edema and retinopathy were all used to describe serious retinal detachments.*

Adverse Events of Special Interest	GO28141 placebo + vemurafenib		GO28141 cobimetinib + vemurafenib		NO25395 cobimetinib + vemurafenib		Integrated Safety Population	
	SCS n=239	safety update n=246	SCS n=254	safety update n=247	SCS n=129	safety update n=129	SCS n = 383	safety update n = 376
Patient experiencing event, n (%)								
Ocular events		76 (30.9)		124 (50.2)				
RVO, all grades	0	1 (0.4)	0	1 (0.4)	0	0	0	1 (0.3)
Serous retinopathy, all grades	5 (2.1)	7 (2.8)	61 (24.0)	63 (25.5)	8 (6.2)	7 (5.4)	69 (18.0)	70 (18.6)
Visual disturbances (not including RVO or serous retinopathy)		73 (29.7)		93 (37.7)		43 (33.3)		136 (36.2)
Grade \geq 2 visual disturbances (not including RVO or serous retinopathy events)	16 (6.7)	20 (8.1)	19 (7.5)	25 (10.1)	12 (9.3)	12 (9.3)	31 (8.1)	37 (9.8)
Vision Blurred		6 (2.4)		25 (10.1)	13 (10.1)	16 (12.4)		41 (10.9)
Visual impairment		0		7 (2.8)		8 (6.2)		15 (4.0)
Uveitis		7 (2.8)		6 (2.4)		4 (3.1)		10 (2.7)
Dry Eye		7 (2.8)		6 (2.4)		2 (1.6)		8 (2.1)

Proposed Labeling:

5.3 SEROUS (b) (6) RETINOPATHY

(b) (6)

(b) (6)

Manage serous retinopathy with treatment interruption, dose reduction or with treatment discontinuation [*see Dosage and Administration (2.2)*].

(b) (6)

Summary:

Based on the submitted clinical studies, retinal pigment epithelial detachments, also known as serous detachments or serous retinopathy have occurred following the use of cobimetinib in at least 25% of treated patients. While these detachments would be expected to result in permanent visual field defects if they remain unresolved, it is expected that most will resolve with temporary discontinuation of therapy and some will resolve while treatment is continued. At present, it is not known how frequently the detachments will resolve with continued treatment or how frequently they will resolve after discontinuation of treatment.

In addition to the serous detachments, approximately 10% of patients reported blurred vision while taking cobimetinib. Other clinically significant ocular events, uveitis/iritis, dry eye and retinal vein occlusions occurred in a small percentage of patients (0.4-2.4%)

Recommendations:

1. It is recommended that the proposed labeling be revised as identified above in this review.
2. It is recommended that additional information be collected to permit better characterization of the frequency, time course and if needed, dose alternation required to minimize the impact of retinal pigmented epithelial detachments in patients taking cobimetinib. The following information is recommended to be collected, but not necessarily prior to approval:

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), 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.

Wiley A. Chambers, M.D.
Supervisory Medical Officer, Ophthalmology

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/s/

WILEY A CHAMBERS
06/03/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 206192

Applicant: Genentech

Stamp Date:

Drug Name: Cobimetinib

NDA/BLA Type: 505(b)(1)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	X			505(b)(1)
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?			X	
15.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: NO25395 Study Title: A Phase Ib, open label, dose-escalation study evaluating the safety, tolerability and pharmacokinetics of vemurafenib in combination with GDC-0973 (cobimetinib) when administered in BRAFV600E mutation-positive patients previously treated (but without prior exposure to BRAF or MEK inhibitor therapy) or previously untreated for locally advanced/unresectable or metastatic melanoma	X			

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?		X		Ocular toxicities have not been adequately evaluated. Additional studies may be requested as a PMR.
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?		X		Ophthalmic scans were requested for review. These are not available on most study patients.
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	6% of participants in t GO28141 and 23% of patients in the ISS were enrolled in the US.
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an	X			

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	IRB and with adequate informed consent procedures?				

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? YES

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

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

Ruthann M. Giusti, M.D. January 27, 2015

 Reviewing Medical Officer Date

Marc Theoret, M.D. _____
 Clinical Team Leader Date

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

/s/

RUTHANN M GIUSTI
02/04/2015

MARC R THEORET
02/06/2015