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APPLICATION NUMBER:

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CLINICAL REVIEW(S)

Clinical Review
Patricia Oneal, MD
NDA 202429
Zelboraf™ (vemurafenib) for the treatment of patients with Erdheim Chester Disease with the BRAF V600 mutation

**Amendment to Clinical Review of NDA202429
Division of Hematology Products**

NDA # / SDN #	NDA 202429/ SDN 16
Application Type	Amendment to Clinical Review on Postmarket Requirements and Commitments
Protocol Number	MO28072 (Version 07)
Protocol Title	An Open-Label, Phase II Study Of Vemurafenib In Patients With BRAF V600 Mutation-Positive Cancers
IND Sponsor	Hoffmann-La Roche, Inc.
Primary Reviewer	Patricia Oneal, MD
Team Leader	Virginia Kwitkowski, MS, ACNP-BC
Date	13 October 2017

(b) (5), (b) (4)



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/s/

PATRICIA A ONEAL
10/13/2017

VIRGINIA E KWITKOWSKI
10/13/2017

CLINICAL REVIEW

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(Proposed) Trade Name	ZELBORAF®
Therapeutic Class	Kinase inhibitor
Applicant	Hoffmann-La Roche, Inc.
Formulation(s)	Oral
Dosing Regimen	960 mg twice daily
Indication(s)	Treatment of patients with Erdheim Chester Disease (ECD) with BRAF V600 mutation
Intended Population(s)	Erdheim Chester Disease patients (ECD) with BRAF V600 mutation

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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 supplemental new drug application for vemurafenib (NDA 202429), the reviewers recommend regular approval of vemurafenib for the following indication:

Zelboraf (vemurafenib) is indicated for the treatment of patients with Erdheim-Chester Disease (ECD) with BRAF V600 mutation.

1.2 Risk Benefit Assessment

The recommendation for approval is based on a single-arm, open-label cohort in which vemurafenib monotherapy in a population of patients with Erdheim-Chester Disease with the BRAF V600 mutation did show an objective response rate of 54% (12/22) assessed by the investigator using RECIST v1.1. This trial, which enrolled 22 patients, demonstrated that 50% of the patients either achieved a partial response or stable disease. The improvement in disease-related symptoms and physical function was also documented in 15 of 22 patients and supports the clinical benefit of using vemurafenib in patients with ECD.

There are several safety signals that emerged from this single-arm, open-label clinical trial including cutaneous malignancies (squamous cell carcinoma of skin, keratoacanthoma and basal cell carcinoma), hypertension, QT prolongation and infection. However, with appropriate monitoring and management, these adverse reactions do not outweigh the overall clinical benefit demonstrated in this trial. Vemurafenib has a favorable benefit/risk evaluation for patients with ECD.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

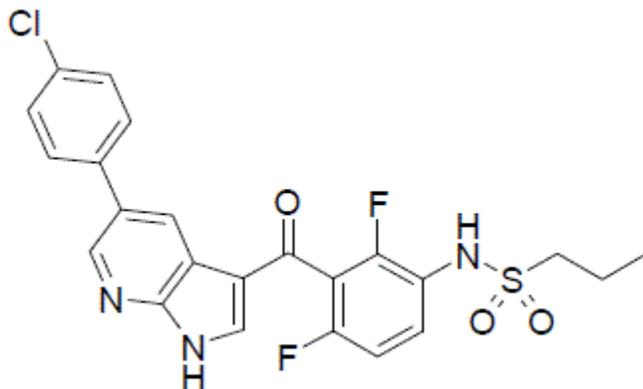
(b) (4), (b) (5)

2 Introduction and Regulatory Background

2.1 Product Information

Vemurafenib is chemically designated as Propane-1-sulfonic acid {3-[5-(4-chlorophenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluoro-phenyl}-amide. The molecular formula is C₂₃H₁₈ClF₂N₃O₃S and the molecular weight is 391.55. The structural formula is shown in **Figure 1**.

Figure 1 Structural Formula of Vemurafenib



2.2 Tables of Currently Available Treatments for Proposed Indications

Erdheim-Chester disease (ECD) is a rare, non-Langerhans Histiocytosis described by Jakob Erdheim and William Chester in 1930¹. Although 600 to 700 cases have been reported, the number has dramatically increased in the last 10 years due to increased recognition of the disease. ECD primarily affects adults between their 5th and 7th decades of life. A slight male predominance is noted amongst patients. The etiology of the disease is unknown and there is no evidence that ECD is an inheritable genetic disorder^{1,2,3,4,5,6}.

Erdheim-Chester disease has various phenotypes. The most common characteristic is bone involvement along with infiltration of at least one more organ system. Bilateral symmetric sclerosis of peripheral long bones is frequently observed. Central axial bone involvement is less common. Skeletal localizations have been described in 74% of patients during the entire course of their disease. Neurological symptoms occur in approximately 25%-50% of patients at onset or during the course of the disease. The most recurrent manifestations include exophthalmos, gaze disturbances, diabetes insipidus, cerebellar syndromes, seizures and focal mass-lesions related radiculopathy. Exophthalmos can present itself unilaterally or bilaterally with a clinical appearance of a retro-orbital mass in 98% of cases. One third of all deaths have been associated with central nervous system (CNS) involvement. CNS involvement has been identified as an independent predictive factor of poor prognosis. Up to 72% of ECD patients with diabetes insipidus have other CNS sites involvement including visual disturbances, diplopia and blurred vision. Persons presenting with ataxia have lesions involving the retrobulbar fat, optic chiasm and cerebellar lobes. Headaches, dysarthria, and cognitive function deterioration has been observed in less than 10% of patients with neurological involvement. The known involved sites would include the cerebral lobes. Hypopituitarism has been documented in about 6% of ECD patients where intracranial hypertension along with nausea, vomiting and papilledema has been reported in 2.5% of patients. The most common endocrinopathy is diabetes insipidus (DI) and occurs in about 25% of patients with ECD.

Retroperitoneal involvement has been reported in about 33% of patients and is found incidentally on radiological scans without symptoms. This finding can appear as a perirenal fat infiltration on radiological scans. Renal disease can manifest as obstructive uropathy due to retroperitoneal fibrosis or renal histiocytic infiltration.

1 (Chester, W, 1930)

2 (Haroche J, 2013 May)

3 (Veyssier-Belot C, 1996)

4 (Cavalli, 2013 October)

5 (Tan AC, 2017 April)

6 (Diamond EL D. L., 2014 July 24)

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Cutaneous manifestations can be found in about 27% of patients. Xanthelasmas are the most commonly reported skin lesions and is typically more commonly seen in older patients. Xanthelasmas of the eyelids or the periorbital spaces are found in up to 18% of patients.

Lung infiltration and cardiovascular involvement have also been reported. In about 18% of patients presenting with cough and dyspnea, they may have infiltration of the lung parenchyma. The most frequent site for cardiovascular involvement is the thoracic and abdominal aorta with extension to the main aortic branches. “Pseudo-tumoral” infiltration of the heart (i.e. right atrium or atrio-ventricular sulcus) and coronaries as well as pleural and pericardial involvement have been reported in 11% and 9% of patients, respectively. Most notably, the occurrence of cardiovascular involvement is higher among older patients. Cardiovascular involvement, along with pulmonary and neurological, is associated with poor prognosis. Sixty percent of patients with cardiac involvement are at high risk of death^{6,7,8}.

The correct diagnosis is made by the distinct histological pattern seen in a respective organ(s) infiltrated by the non-Langerhans foamy histiocytes which are characterized by immunohistochemistry stains that are positive for CD68, CD163, and Factor XIIIa and negative for CD1a and Langerin (CD207) along with the radiological findings and clinical sequela of the patient. Tissue biopsy, preferably of an osteosclerotic bone lesion, is crucial for diagnosis. This differentiates ECD from Langerhans cell histiocytosis in which the Langerhans cells are positive for CD1a, S100 and Langerin.

Laboratory workup, including complete blood count and chemistries, are usually nondescript for this diagnosis unless urine electrolytes highlight evidence of diabetes insipidus. There is no universally accepted staging, prognostic or scoring system for ECD. It has been suggested that imaging studies including MRI of the brain, CT scan or MRI of the heart and aorta, CT scan of the chest, abdomen and pelvis and PET/CT, echocardiogram (if heart involvement is suspected), MRI of the spine (if spine involvement is suspected) should be done at initial staging. The most specific imaging findings would be symmetrical diaphyseal and metaphyseal osteosclerosis of long bone on plain radiographs, increased radiotracer uptake in the proximal and distal ends of tibia and proximal ends of femurs by bone scan or PET, respectively, and infiltration of perinephric fat and circumferential soft-tissue sheathing of the aorta on CT. It has also been suggested that PET/CT along with C-reactive protein (CRP) elevation may predict disease activity. Therefore, the diagnosis of ECD relies heavily on the established radiological and histological criteria since the clinical picture is variable.

6 (Cives M, 2015 July)

7 (Cavalli, 2013 October)

8 (Diamond EL, 2014 July 24)

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Historically, ECD has been considered a variably aggressive histiocytic disorder of unclear origin with poor response to therapy. Currently, there are no universally accepted guidelines for the diagnosis and treatment of ECD. There are no FDA-approved treatments for Erdheim Chester Disease. Table 1 (below) lists the products that are used frequently in an off-label fashion to treat ECD^{9,10,11,12,13,14,15}.

Table 1 Currently Available Treatments for Erdheim Chester Disease

Drug Name	Drug Type
PEG-IFN α	Immunomodulator
IFN- α	Immunomodulator
Anakinra	Interleukin-1 Receptor Antagonist
Cladribine	Antimetabolite (Purine Analog)
Imatinib	Tyrosine Kinase Inhibitor
Infliximab	Anti-TNF α antibody
Tocilizumab	Interleukin-6 Receptor Antagonist
Sirolimus and Prednisone	mTOR Kinase Inhibitor/ Corticosteroid

Until 2005, the treatment of ECD included steroids, cytotoxic agents, and double autologous hematopoietic stem cell transplantation (autoHSCT). Interferon α (IFN- α) was shown to provide a rapid, substantial, and long-lasting regression of retro-orbital infiltration and gradual improvement in bone lesions, pain, and diabetes insipidus in three patients¹⁶. In 2010, Arnaud et al, demonstrated in a survival analysis of 53 biopsy-proven ECD patients that treatment with IFN- α or PEGylated IFN- α was a major independent predictor of survival (HR = 0.32; 95% CI, 0.14–0.70; P = .006). Multivariate survival analysis showed that central nervous system involvement was an independent predictor of death (HR = 2.51; 95% CI, 1.28-5.52; P = .006)¹⁷.

Recombinant human interleukin 1 (IL-1) receptor, anakinra, has shown some clinical response in three patients with ECD who had poor tolerance or contraindication to IFN- α ; neither of these patients had cardiovascular or CNS involvement. The bone pain,

9 (Mazor RD, 2013 Sep)

10 (Killu AM, 2013 Sep 1)

11 (Myra C, 2004 June)

12 (Haroche J A. Z., 2008 June 1)

13 (Ferrero E, 2014 January)

14 (Ortiz Salvador JM, 2017 June)

15 (Gianfreda D1, 2015 September 3)

16 (Abdelfattah AM, 2014 July)

17 (Arnaud L, 2011 March 10)

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eyelid involvement, as well as the retroperitoneal fibrosis was shown to either completely or partially regress with this treatment¹⁸.

Cladribine has been shown to be beneficial for treating CNS localizations of the disease primarily in a patient with orbital pseudotumors which were refractory to IFN- α , steroids, cyclophosphamide and etoposide while simultaneously presenting with an isolated elevation of monocytes in the peripheral blood. This outcome was not as favorable at institutions that have seen a larger subset of ECD patients; mainly in Europe^{19,20}.

The use of infliximab, with some success after 12 to 18 months of treatment, in two patients with ECD with cardiac involvement was reported in 2012²¹.

Even more encouraging was the demonstration in 2012 of the rapid activity of a BRAF inhibitor (vemurafenib) in three patients. It was in these biopsy-proven ECD patients with multi-systemic (skin and lymph node involvement) and refractory ECD carrying the BRAFV600E mutation that rapid clinical and tumor response by PET/CT was seen in one month and remained effective after four months. Follow-up with PET/CT still showed persistent disease activity primarily in the bones without clinical symptoms and normal CRP levels^{22,23,24,25}. Hence, BRAF inhibition was proven to be an alternative in ECD patients carrying the BRAFV600 mutation.

ECD, and the related histiocytic disorder Langerhans cell histiocytosis, are hematopoietic neoplasms that represent clonal proliferation of myeloid progenitor cells. This was demonstrated by finding the *BRAF* V600E mutation in subsets of dendritic cells, mature monocytes, committed myeloid progenitors, and CD34+ cells of affected ECD and LCH patients. It is an activating mutation of the proto-oncogene *BRAF*, and results in an activation of the RAS-ERK pathway, independently of RAS activation. The RAS-RAF-MEK-ERK (MAPK/ERK pathway) pathway is a cellular signaling pathway, and is involved in diverse tumors. Somatic mutations in components of the MAPK signaling pathway are present in most patients with ECD. *BRAF* V600E has been found in approximately half of ECD cases, and the mutation of this serine-threonine kinase enhances cell proliferation and survival by activating the RAS-RAF-MEK-MAPK signaling pathway²⁶.

18 (Podestà MA, 2014 September)

19 (Myra C S. L., 2004)

20 (Haroche J A. L.-A., 2013 May)

21 (Dagna L, 2012)

21 (Blombery P, 2012 Nov 10)

22 (Chapman PB, 2011)

24 (Emile JF, 2013)

25 (Haroche J C.-A. F., 2013 February 28)

26 (Badalian-Very G, 2010)

Haroche et al demonstrated in 93 samples from 127 patients that BRAF V600E mutations were detected in 13 of 24 (54%) ECD samples, 11 of 29 (38%) LCH samples and none of the other histiocytoses diseases like Rosai-Dorfman disease, disseminated juvenile xanthogranuloma (JXG) and xanthoma disseminatum, interdigitating dendritic cell sarcoma and histiocytic sarcomas through direct pyrosequencing and immunohistochemistry²⁷. However, Cangi et al was able to demonstrate that through the use of ultrasensitive molecular techniques like immunohistochemistry using the specific anti-BRAF V600 monoclonal antibody, VE1 and locked nucleic acid-PCR (LNA-PCR) prior to pyrosequencing, that BRAF V600 mutated histiocytes could be identified in virtually all patients with ECD²⁸. The high sensitivity of LNA-PCR/pyrosequencing allows the identification of one mutated BRAF allele among 10,000 wild type copies²⁹. In understanding the pathogenesis of ECD, BRAF V600E has recently been associated with oncogene-induced senescence (OIS), a protective mechanism against oncogenic events aimed in tumor growth to enlist BRAF V600 mutated histiocytes to attract inflammatory cells to ECD lesions and recruit non-mutated cells to transform into the inflammatory cells unique to ECD. ^{28,30}.

Current reports show that approximately fifty percent of cases of ECD do not harbor a BRAF mutation, but will have NRAS, PIK3CA, KRAS Q61H or mutations of the RAS-PI3K-AKT signaling pathway. A patient who had demonstrated response to another BRAF inhibitor, dabrafenib, and experienced a recurrence 14 months later was started on the MEK inhibitor, trametinib resulting in an excellent response. Meanwhile, the efficacy of the MEK inhibitor, cobimetinib, has been shown in BRAF wild-type ECD³¹. However, the efficacy of combination therapy with BRAF inhibitors with MEK inhibitors remains unknown.

The availability of several drugs selectively inhibiting BRAF or its downstream kinases could represent potential therapeutic tools for severe, refractory forms of ECD since among patients with ECD are mutations in NRAS, KRAS, ARAF, PIK3CA, and MAP2K1as well. The recent report of a patient with BRAF wild type, NRAS-mutated ECD further substantiates the central role of the mitogen-activated protein kinase pathway in this disease, and the need for other therapeutic targeted therapies for this disorder³².

Though, in the current literature, the predominance of V600 mutations is approximately 50%, the Applicant was not required to submit a companion diagnostic to CDRH for the ECD indication because it was believed to be infeasible to obtain enough patients with

27 (Haroche J C. F., 2012)

28 (Cangi MG, 2015 August)

29 (Cavalli G, 2014 Jun 13)

30 (Jacob K, 2011)

31 (Haroche J C. P., 2009 June 30)

32 (Diamond EL A.-W. O., 2013 Aug 8)

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ECD to conduct the testing required for a submission and that with appropriate molecular techniques, the identification of the BRAF V600 mutation can be identified in all patients with ECD. In addition, patients with ECD have no approved effective treatments. Treating a patient with BRAF V600 wild-type ECD with vemurafenib for a few cycles to evaluate for activity would provide minimal risk over other unapproved therapies.

2.3 Availability of Proposed Active Ingredient in the United States

Vemurafenib is now approved in 102 countries including the U.S., EU, Switzerland, Israel, Brazil, New Zealand and Canada.

2.4 Important Safety Issues With Consideration to Related Drugs

To date, dabrafenib is the only other approved agent that has demonstrated activity against BRAF. Dabrafenib (Tafinlar) is labeled with the following warnings:

- New primary malignancies, cutaneous and non-cutaneous
- Tumor promotion in BRAF Wild-Type Melanoma
- Hemorrhage
- (b) (4)
- Cardiomyopathy
- Uveitis
- Serious febrile reactions
- Serious skin toxicity
- Hyperglycemia
- Glucose-6-Phosphate Dehydrogenase Deficiency (risk of hemolytic anemia in patients with G6PD deficiency with dabrafenib use)
- Embryo-fetal toxicity

Trametinib, a mitogen-activated extracellular signal regulated kinase (MEK) inhibitor is FDA approved as a single agent or in combination with dabrafenib, for treatment of patients with unresectable metastatic melanoma with BRAF V600E or V600K mutations detected by an FDA-approved test.

In 55% to 70% of ECD as well as Langerhans cell histiocytosis (LCH) patients, BRAF V600E mutations provide evidence that these diseases represent clonal disorders driven by activated MAPK signaling. Subsequently, activating mutations in MAP2K1, ARAF, and fusions in kinases including BRAF were found in the majority of BRAF V600-wild-type ECD and LCH patients.

Many of these patients had kinase alterations characteristic of both ECD and myeloid neoplasms. Molecular analysis showed that 19 patients had concomitant myeloid

neoplasms and ECD. Twelve patients (63.2%) harbored the BRAF V600E mutation in ECD tissue biopsy material and 7 patients (36.8%) were positive for JAK2V617F in peripheral blood (PB) and/or bone marrow (BM). Four patients (23.5%) had both BRAF V600E and JAK2V617F mutations. One patient with essential thrombocytosis (ET) had a CALR mutation as well as the BRAF V600E mutation, and another had a MAP2K1 mutation in the histiocytic disease associated with a JAK2V617F mutated ET. Unlike BRAF V600E or MAP2K1 mutations, which are detected only in histiocytosis lesions, mutations in NRAS can be found in both histiocytosis and myeloid neoplasms. This was identified in a patient who had the same NRAS mutation in ECD lesions from perirenal tissue as well as the BM and PB following a diagnosis of chronic myelomonocytic leukemia (CMML). In addition to harboring mutations in JAK2 and CALR, patients with myeloid neoplasm-associated histiocytosis also carried additional mutations in transcriptional regulatory genes common in myeloid neoplasms but rare in ECD, such as mutations in TET2, ASXL1, IDH2, U2AF1, and TP53.

Although BRAF inhibition has resulted in remarkable clinical responses for patients with BRAF V600E-mutant histiocytosis, there is a well-described risk of paradoxical activation of cytokine signaling in cells bearing kinase mutations other than BRAF V600E upon exposure to RAF inhibitors. BRAF inhibitors (vemurafenib or dabrafenib) were given to 7/19 patients with BRAF V600E-mutant ECD and coexisting myeloid neoplasms. In 3 cases, vemurafenib treatment resulted in an increase in blood counts, which led to treatment discontinuation. Knowing the presence of an associated myeloid neoplasm in ECD patients has important implications for clinical management of adult histiocytosis patients as well as in the classification and biological understanding of these disorders^{33,34,35,36,37,38}.

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 2**.

Table 2 Major Regulatory Milestones

Milestone	Time	Key Regulatory Activities Related to Clinical Development
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33 (Papo M, 2017 August 24)

34 (Jaiswal S, 2014)

35 (Emile JF D. E.-R., 2014)

36 (Chen W, 2013)

37 (Busque L, 2012)

38 (Jamieson CH, 2006)

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<p>Pre-IND Type C Guidance Meeting (IND 121566)</p>	<p>April 2014</p>	<ul style="list-style-type: none"> • [REDACTED] (b) (4) • Agency suggested development plan for [REDACTED] (b) (4) Erdheim-Chester (ECD) [REDACTED] (b) (4) which harbor BRAF V600E mutation
<p>Pre-IND meeting (INDs 121566 [REDACTED] (b) (4))</p>	<p>February 2016</p>	<ul style="list-style-type: none"> • Joint teleconference meeting with DHP [REDACTED] (b) (4) to discuss top-line results for the ECD, [REDACTED] (b) (4) <p>[REDACTED] (b) (4)</p>
<p>Type C Guidance Meeting under [REDACTED] (b) (4) 121566 [REDACTED] (u) (+)</p>	<p>March 18, 2016</p>	<ul style="list-style-type: none"> • Discussed proposal to submit sNDA seeking approval for [REDACTED] (b) (4) [REDACTED] (b) (4) patients with BRAF V600 mutation-positive ECD). The Agency stated that the preliminary efficacy and safety data for vemurafenib in the ECD cohort appeared reasonable to support an evaluation of the benefit-risk for a new indication in ECD. • FDA agreed with HLR's plan not to submit a companion diagnostic for the ECD indication. • Submission of investigator assessed RECIST based efficacy data would be sufficient and independent review not required
<p>Orphan Designation</p>	<p>August 2, 2016</p>	<p>Orphan drug designation granted for the treatment of Erdheim-Chester Disease (ECD) [designation #16-5296]</p>
<p>IND 121566 Submission</p>	<p>October 2016</p>	<ul style="list-style-type: none"> • IND submitted for the indication

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		<p>the treatment of patients with BRAF V600 mutation positive Erdheim-Chester Disease.</p> <ul style="list-style-type: none">• This submission was an administrative split from the original vemurafenib IND 073620.• Additional requests included IRB waiver request for non-US investigators. This open-label, Phase 2 study in patients with BRAF V600 mutation positive cancers was evaluated and found to be safe to proceed.
preNDA Meeting	March 31, 2017	<ul style="list-style-type: none">• The Agency asked Applicant to include in the sNDA scientific justification on the feasibility and necessity of a companion diagnostic for the proposed ECD indication.• The Sponsor asked whether the data would support full approval; the Agency stated that this decision would be made during the review process. The parties discussed the content and format of the proposed sNDA.• The Agency requested submission of the diagnostic pathology and molecular diagnostic reports for the 22 patients in the ECD cohort.
Breakthrough Therapy Designation	April 2017	<p>The Sponsor request for Breakthrough Therapy designation was granted for “the treatment of patients with ECD with BRAF V600 mutation”.</p>

2.6 Other Relevant Background Information

Zelboraf (vemurafenib) was first granted marketing approval in the United States on 17 August 2011. As of 3 May 2017, Zelboraf has been approved in 102 countries worldwide. Zelboraf is approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.

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Reference is made to the following Investigational New Drug Applications (IND) and New Drug Application (NDA) for Zelboraf (vemurafenib):

- IND 73,620 that is under co-development with Plexxikon Inc. for the treatment of patients with solid tumors (submitted on 29 September 2006 as Serial No. 0000)
- IND 121566 that is under co-development with Plexxikon Inc. for the treatment of patients with Erdheim-Chester Disease (submitted on 24 October 2016 as Serial No. 0000)
- NDA 202429 for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation (submitted on 27 April 2011 as Serial No. 0002, and approved by FDA on 17 August 2011).

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission contains all required components of the eCTD. The overall quality and integrity of the application was acceptable for review.

3.2 Compliance with Good Clinical Practices

Study MO28072 was conducted in accordance with the principles of the “Declaration of Helsinki” and the principles of Good Clinical Practice (GCP). The appropriate Ethics Committees and Institutional Review Boards reviewed and approved all studies. The Roche Clinical Quality Assurance group or designee conducted audits at three investigator sites. No critical audit findings were observed. For all audit findings appropriate corrective and preventive actions were undertaken.

OSI Inspection

OSI was consulted and inspection was request for site 244213 (Memorial Sloan-Kettering Cancer Center) as this site enrolled (b) (6) of 22 enrolled patients with ECD. The findings indicate that the data are reliable for regulatory action.

Table 3 OSI Inspected Site

Site # (Name, Address, Phone number, email, fax #)	Protocol ID	Number of Enrolled Subjects	Number of Evaluable for Response	Number of Subjects with Best Response	Number of SAEs
Site #: 244213 Site Name: Memorial Sloan-Kettering Cancer	MO28072	(b) (6)			

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Center PIs: David Solit & David Hyman Site Address: 300 East 66th Street, Box 22, New York, NY 10065 Email: hymand@mskcc.org & solitd@mskcc.org Phone: +1 646-707- 0763; +1 646-422-4459 Fax: +1 646- 888- 4270			(b) (6)	1: Complete response	56
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The following is excerpted from the OSI review:
 David Hyman and David Solit
 Site# 244213

The site screened 49 subjects and enrolled 47 subjects including the (b) (6) subjects with ECD for Study Protocol MO28072. An audit of all (b) (6) subjects' records with ECD was conducted.

The following observations were noted with a Form FDA 483 issued by the field investigator:

1. Failure to report promptly to the sponsor adverse events that may reasonably be regarded as caused by, or probably caused by, an investigational drug. Specifically, the following adverse events were documented in subject source records, but were not recorded in the subjects' electronic data capture (EDC)/electronic case report forms (eCRF's):
 - Subject (b) (6) sore throat
 - Subject (b) (6) dizziness
 - Subject (b) (6) diarrhea and akathisia
2. Failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation. Specifically, some concomitant medications including pain medication, antibiotics, or sleeping medications were not included in eCRFs for (b) (6) subjects (b) (6)
3. An investigation was not conducted in accordance with the signed statement of investigator and investigational plan. Specifically, protocol-required procedures were not followed for (b) (6) subjects for timely reporting of serious adverse events. According to the IRB-approved study protocol, any serious adverse event or non-serious adverse event of special interest must be reported to the sponsor immediately; under no circumstances should reporting take place more than 24 hours after the

investigator learns of the event. The following deviations from the protocol were observed:

- Subject (b) (6): Squamous cell carcinoma was noted in this subject's source records with a date of onset of (b) (6). According to this subject's source records, the site became aware of this serious adverse event (SAE) on (b) (6) via pathology report. This SAE was reported on (b) (6).
- Subject (b) (6): Keratoacanthoma was noted in this subject's source records with a date of onset of (b) (6). This SAE was reported on (b) (6). Gangliocytic paraganglioma was also noted in this subject's source records with a date of onset of (b) (6). According to this subject's source records, the site became aware of this SAE on (b) (6) via pathology report. This SAE was reported on (b) (6).
- Subject (b) (6): Basal cell carcinoma was noted in this subject's source records with a date of onset of (b) (6). According to this subject's source records, the site became aware of this SAE on (b) (6), via pathology report. This SAE was reported on (b) (6). Basal cell carcinoma was noted an additional time in this subject's source records with a date of onset of (b) (6). According to this subject's source records, the site became aware of this SAE on (b) (6), via pathology report. This SAE was reported on (b) (6).
- Subject (b) (6): Squamous cell carcinoma was noted in this subject's source records with a date of onset of (b) (6). According to this subject's source records, the site became aware of this SAE on (b) (6), via pathology report. This SAE was reported on (b) (6).
- Subject (b) (6): Basal cell carcinoma was noted in this subject's source records with a date of onset of (b) (6). According to this subject's source records, the site became aware of this SAE on (b) (6) via pathology report. This SAE was reported on (b) (6).

OSI Reviewer's comments:

The above observations were shared with DHP. The underreported adverse events were considered to be non-serious adverse events and the missed concomitant medications are supportive medications. For tumor adverse event reporting, most events were reported within 1 or 2 weeks after the site received the pathology reports except one event was reported 3 months later. These observations appear unlikely to have significant impact on the overall efficacy and safety of the study.

3.3 Financial Disclosures

This section provides the required financial disclosure information for clinical investigators that participated and enrolled patients in Study MO28072 entitled "An open-label, phase II study of vemurafenib in patients with BRAF V600 mutation-positive cancers."

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During the study site initiation process, Hoffman La Roche (HLR) provided study-specific financial disclosure forms to all principal investigators and sub-investigators for use in disclosing financial interest in or receipt of significant payments from HLR. During the course of the study, new or revised financial disclosure forms and other essential documents were collected as needed.

Financial disclosure information was separated into three categories:

- Disclosure: Financial information to disclose
- No Disclosure: No financial information to disclose; or
- Unable to Obtain: Demonstration of Due Diligence (Sponsor cannot confirm financial status but has performed due diligence, i.e., Sponsor acts with due diligence to obtain the information required but is unable to do so; therefore, Sponsor shall certify that all attempts were made to obtain the information and shall include the reason).

A total of 544 out of 563 (96.6%) principal investigators and sub-investigators in Study MO28072 responded with financial disclosure information. Of the 544 investigators who responded, 544 (100%) had no financial disclosures to report. Certification of those investigators with no financial disclosures to report was also provided. Positive Disclosure Form 3455 was not been provided as there were no investigators with disclosable financial interest.

A signed financial disclosure was not obtained for 19 sub-investigators in Study MO28072. None of these investigators participated at sites that enrolled patients with Erdheim-Chester Disease (ECD). Hoffman La Roche generated Notes to File detailing the attempts made to collect the financial disclosure information for those investigators.

Reviewer's comments:

Of the 19 sub-investigators in Study MO28072 none participated at sites that enrolled patients with Erdheim-Chester Disease (ECD). Hence, the non-reporting of the financial disclosures did not drive the efficacy or safety conclusions 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

No CMC information was submitted to Module 3 in this sNDA.

4.2 Clinical Microbiology

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

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4.3 Preclinical Pharmacology/Toxicology

No Pharm/Tox information was submitted to Module 4 in this sNDA.

4.4 Clinical Pharmacology

The text below is from the “Recommendations” in the Clinical Pharmacology review archived by Sriram Subramaniam on 10/01/17.

The Office of Clinical Pharmacology’s Division of Clinical Pharmacology V reviewed the information contained in supplement 16. The supplement is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations and comments are summarized below:

The recommended dose of 960 mg BID, with or without food is supported by the limited PK data that indicates that the PK is similar for patients with different diseases. No exposure-response relationship (E-R) can be explored in the ECD population, as PK samples were only collected from one patient with ECD. There is no recommended post-marketing requirement from the Clinical Pharmacology Team.

4.4.1 Mechanism of Action

From the approved Vemurafenib package insert:

Vemurafenib is a low molecular weight, orally available, inhibitor of some mutated forms of BRAF serine-threonine kinase, including BRAFV600E. 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 BRAFV600E.

4.4.2 Pharmacodynamics

No new PD data was submitted with this supplement.

4.4.3 Pharmacokinetics

(The following is excerpted from the Clinical Pharmacology Review)

The applicant conducted population PK analyses using data from Trial MO28072 following oral administration of vemurafenib to confirm if a previously established population PK model of vemurafenib in patients with metastatic melanoma (MM) is able to describe the PK of vemurafenib in patients with non-small cell lung cancer (NSCLC),

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Erdheim-Chester Disease (ECD) and other diseases harboring a V600BRAF mutation and to compute the PK parameters for these diseases within Trial MO28072. In addition, graphical analysis of exposure-efficacy (BOR and change in tumor size from baseline) and exposure-safety (serious AEs and Grade ≥ 3 AEs) in NSCLC and ECD in Trial MO28072 were compared.

The population PK data set contains 147 measurable PK samples from 26 patients that received a dose of 960 mg BID. Data points that were not used in the analysis were 2 (1.3%) post-dose BQL observations and 1 (0.7%) positive pre-dose observation. PK samples were collected from only one patient with ECD.

The previously developed population PK model (Model 001) included a one compartment model with first order absorption and first-order elimination. Only sex was identified as a significant covariate. The results from the population analysis showed that the differences in exposure (in terms of steady-state AUC, C_{max}, and C_{min} following 960 mg BID) between male and female are relatively small, indicating that there is no need to dose adjust based on sex. The results from the previous analysis also showed that the impact of food intake at the time of measurement may have an impact on the PK measurements as food intake was not strictly controlled across all studies. Different relative bioavailability values were estimated in the previous analysis based on differences in the study design to account for this effect. In the final model of the prior analysis all the parameters were fixed (including the effects of gender) and relative bioavailability was constant and equal to 1.

Following investigation of various model refinements during model development, the previously established model (Model 001) was found optimal and was used to compute exposure estimates.

From the Prescribing Information:

Zelboraf (vemurafenib) is an orally available inhibitor of mutated forms of the BRAF serine-threonine kinase, including BRAF V600E. Zelboraf was previously reviewed under original NDA 202429 (DARRTS ID 2968791). The following is a summary of the clinical PK of vemurafenib in metastatic melanoma (MM):

Vemurafenib exhibits linear PK at steady state between a dose of 240 mg and 960 mg. The mean (\pm SD) C_{max} is 62 ± 17 $\mu\text{g/mL}$ and the mean (\pm SD) AUC_{0-12h} is 601 ± 170 $\mu\text{g}\cdot\text{h/mL}$. The median T_{max} is ~ 3 hours following multiple doses. The median accumulation ratio was 7.4 following twice daily administration and steady-state was achieved within 15 days to 22 days. The population apparent oral clearance was 31 L/day (%CV=32%) and the median terminal elimination half-life was 57 hours (5th percentile, 30 hours; 95th percentile, 120 hours).

A high-fat meal increased vemurafenib AUC by ~5-fold and C_{max} by 2.5-fold, and delayed T_{max} by ~4 hours as compared to an overnight fasted state.

The PK was collected as part of an ongoing open-label basket trial (MO28072) designed to evaluate the safety and efficacy of a dose of 960 mg BID, without regard to food, in patients diagnosed with BRAF V600 mutation-positive diseases, including 22 patients with ECD (Cohort 7a). The observed and population PK data following a dose of 960 mg BID appears similar in patients with different diseases, including MM, non-small cell lung cancer (NSCLC) and ECD.

4.5 Companion Diagnostic

Trial MO28072 permitted enrollment of patients diagnosed with ECD based upon local testing for BRAF V600 mutations. The Applicant proposed, in the preNDA meeting, not to develop a companion diagnostic for ECD due to the rarity of the condition. The Division agreed.

In the Application, the Applicant argues that the mutation rate in ECD is very high (50-100%) and the disease is rare; which makes the development of a disease-specific diagnostic challenging.

Source, Clinical Overview, Applicant: *“The established pathway to develop a companion diagnostic test may not be directly applicable to the rare-disease setting. Disease-specific companion diagnostics have been developed in a stepwise approach, from nonclinical characterization of the test in a specific disease, to adaptation of the test platform for the disease, through the evaluation of a large number of patient samples. Finally, validation is performed in prospective clinical trials, where clinical benefit is demonstrated for patients who are selected via the diagnostic test. This process would be prohibitive in the rare-disease setting due to the very large number of patient samples that would need to be acquired and tested. In addition, the development of an in vitro companion diagnostic assay can often take years even in more prevalent diseases, and can therefore be expected to take even longer in the rare-disease setting”*.

“Roche/Genentech is committed to making targeted therapies for rare diseases available to patients as soon as possible. At the same time, Roche/Genentech is committed to accurate identification of mutations in order to ensure patient safety and appropriate drug treatment. Based on these commitments, the use of multiple technologies for the enrollment of ECD patients with a BRAF V600 mutation in the VE BASKET trial (Study MO28072) was allowed. The methodologies employed to identify targetable BRAF mutations in this study represent use of currently available real-world advanced technologies with reasonable sensitivity and specificity to appropriately identify driver mutations. The clinical efficacy observed across BRAF mutation-positive

patients identified by local methods and treated with targeted BRAF inhibition with vemurafenib in the ECD cohort (see Section 4.3) indicates that the selection by local testing was effective in appropriately identifying mutation-driven ECD patients who would respond to vemurafenib treatment. This is consistent with the experience in metastatic melanoma with patient selection via the cobas 4800 BRAF V600 Mutation Test.”

“Given the challenges of validating a companion diagnostic in a rare population like ECD, the local methodologies employed in MO28072 effectively identified BRAF V600 mutation-positive ECD patients for enrollment in the trial and most of these patients experienced clinical benefit from treatment. These methodologies could therefore have utility in testing ECD patients for BRAF mutation in the future.”

Literature review was conducted to clarify the BRAF V600 mutation rate in ECD patient tissue samples.

Reviewer’s Comments:

Haroche et al demonstrated in 93 samples from 127 patients that BRAFV600E mutations were detected in 13 of 24 (54%) ECD samples, 11 of 29 (38%) LCH samples and none of the other histiocytoses diseases. The techniques used were direct pyrosequencing and immunohistochemistry³⁹. Colleagues like Cangj et al. were later able to demonstrate that through the use of ultrasensitive molecular techniques like immunohistochemistry using the specific anti-BRAFV600 monoclonal antibody, VE1 and locked nucleic acid-PCR (LNA-PCR) prior to pyrosequencing, that the BRAFV600 mutated histiocytes could be identified in virtually all patients with ECD. The high sensitivity of LNA-PCR/pyrosequencing allows the identification of one mutated BRAF allele among 10,000 wild type copies⁴⁰. Since ECD lesions composed of BRAFV600E mutated histiocytes are interspersed variably with non-mutated histiocytes, these findings may help to explain why previous clonality studies on ECD have resulted in conflicting results.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 4 Clinical Studies in Support of NDA 202429

39 (Haroche J C. F., 2012)

40 (Cavalli G, 2014 Jun 13)

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Protocol No.	Primary Objective of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Admin	Number of Subjects	Duration of Treatment
Efficacy and Safety Studies					
MO28072 (VE BASKET TRIAL)	Evaluate efficacy using (ORR) as assessed by RECIST v1.1 (Best Overall Response Rate [BORR])	Open label Multi-cohort Nonrandomized	vemurafenib 960 mg twice daily (BID)	Total: 208 patients Cohort 7a: 26 patients (ECD: 22 patients, LCH: 4 patients)	Until patient completed a minimum of 8 weeks of Treatment, progression withdrawal , or death
MO25515	Safety and tolerability of vemurafenib	Open label Multicenter Nonrandomized	vemurafenib 960 mg twice daily (BID)	3224 BRAF V600 positive metastatic melanoma patients enrolled (ITT population) and 3219 patients received at least 1 dose study treatment (safety population)	Until the development of progressive disease or unacceptable toxicity

5.2 Review Strategy

The efficacy review was conducted by both Patricia Oneal (Medical Officer) and Lola Luo (Biostatistician).

The clinical efficacy review is based on review of the clinical study report for the open-label, non-randomized trial in patients with histologically confirmed cancers that harbor BRAFV600 mutation refractory to standard therapy or where standard or curative therapy did not exist (MO28072); including the applicant's orientation meeting presentation slides; case report forms; primary data sets for efficacy and safety submitted by the applicant; clinical study reports for diseases other than ECD; efficacy narratives; and literature review of Erdheim-Chester disease.

The clinical safety review was based on data from both ECD and non-ECD patients in Study MO28072 as well as the BRAF V600 positive metastatic melanoma patients from Study MO25515.

5.3 Discussion of Individual Studies/Clinical Trials

This NDA is based primarily on the objective response rate (ORR) from single arm, open-label, multi-cohort, non-randomized, Phase II study, MO28072 (VE BASKET TRIAL).

Study Title: An Open-Label, Phase II Study of Vemurafenib in Patients with BRAF V600 Mutation-Positive Cancers

Reviewer's comments:

Vemurafenib is also known as RO5185426.

5.3.1 Study Design

Study MO28072 was an open-label, multicenter, multinational, phase II study exploring the efficacy and safety of vemurafenib monotherapy in a diverse population of patients with cancers (excluding melanoma and papillary thyroid cancer) known to harbor BRAF V600 mutations and for whom vemurafenib was deemed the best treatment option in the opinion of the Investigator. Patients with BRAF V600 mutation-positive malignancies were identified through mutation analysis assays as routinely performed at each participating site according to their local procedure. Patients with ECD and/or LCH were entered into Cohort 7a (as shown in **Figure 2**).

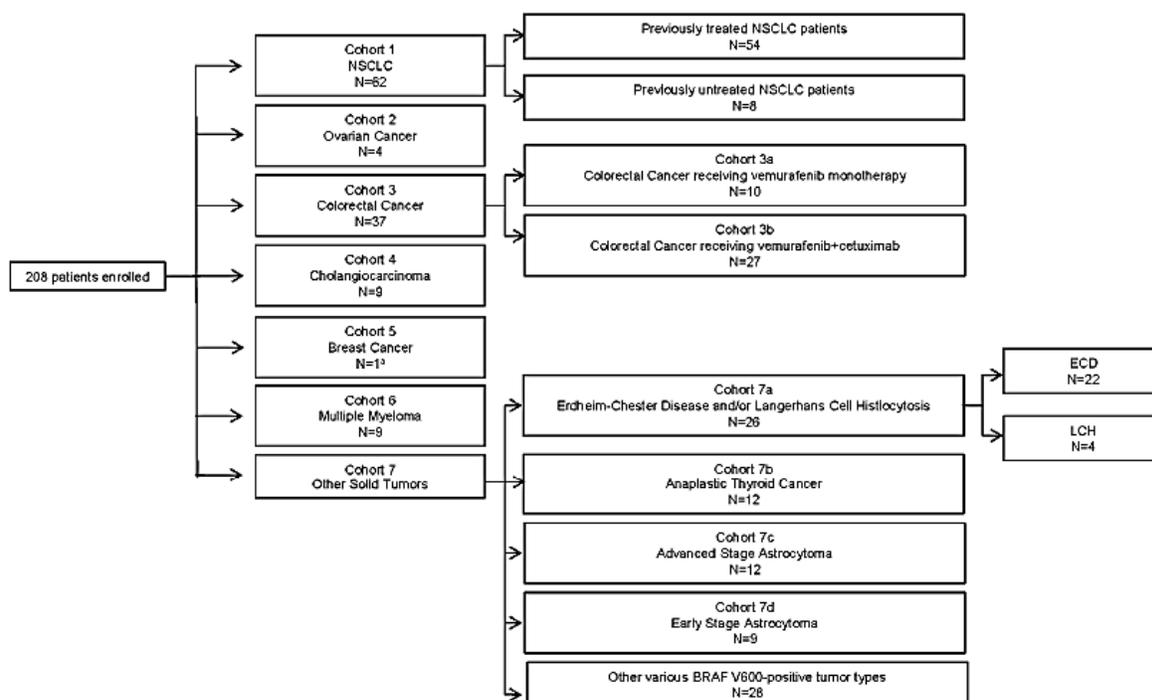


Figure 2 Overall Enrolled Patients – All Cohorts in Study MO28072

(Taken from Applicant Clinical Study Report; vemurafenib; Protocol MO28072; Report Number 1074622, page 117)

^a One breast cancer patient who was screened shortly after the cohort had been closed was allowed to enter the study in Cohort 7 in agreement with the Steering Committee.
 ECD=Erdheim Chester Disease; LCH=Langerhans cell histiocytosis; NSCLC=non-small cell lung cancer

A total up to 170 patients with solid tumors or multiple myeloma were planned to be enrolled in the United States, United Kingdom, Germany, Spain and France. Approximately 13-37 patients per indication (cohort) were included. The maximum number of patients in this study was 490 (7 cohorts up to 70 patients each). The planned trial schema is shown in **Figure 3**.

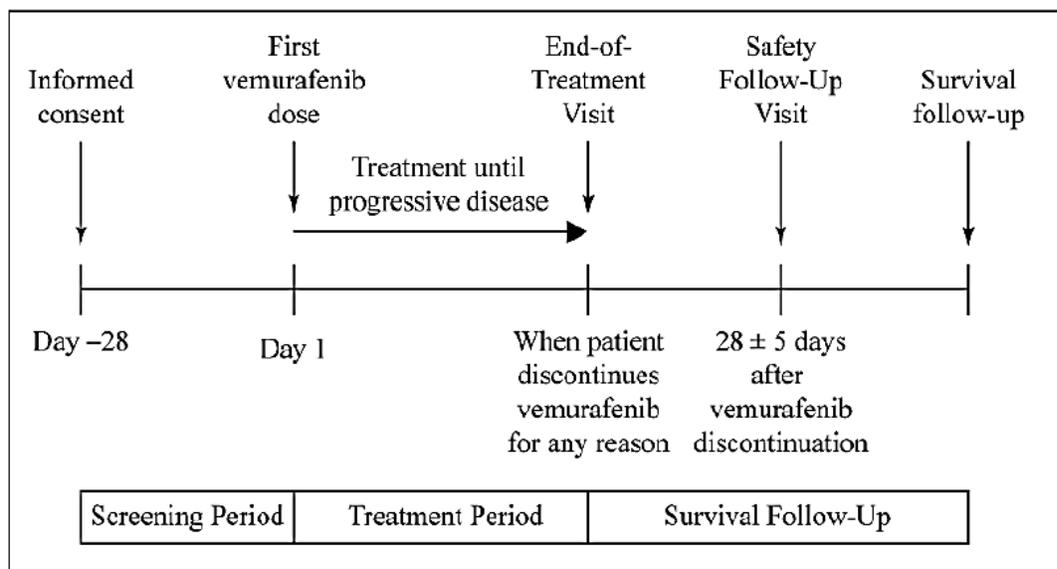


Figure 3 Trial Schema Study MO28072

(Taken from Sponsor's meeting package; Protocol MO28072, Version 7- 24 March 2016, page 69)

- **Study MO28072 included 7 cohorts of patients with the following cancers:**
 - Cohort 1: NSCLC
 - Cohort 2: Ovarian
 - Cohort 3: Colorectal
 - 3a: Monotherapy
 - 3b: Combination therapy with cetuximab
 - Cohort 4: Cholangiocarcinoma/Biliary Tract
 - Cohort 5: Breast
 - Cohort 6: Multiple Myeloma
 - Cohort 7: Other BRAF V600-positive tumor types
 - **7a: ECD and/or LCH**
 - 7b: Anaplastic thyroid cancer
 - 7c: Advanced astrocytoma
 - 7d: Early stage astrocytoma

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Patients with solid tumors were required to have measurable disease according to the Response Evaluation Criteria In Solid Tumors, Version 1.1 (RECIST, v1.1), and adequate hematologic function (absolute neutrophil count $\geq 1.5 \times 10^9/L$ and platelet count $\geq 100 \times 10^9/L$). Those patients with non-measurable disease according to RECIST v1.1 were eligible if the tumor response could be reliably morphologically evaluated by one or more of the following tests (including Brain MRI, Cardiac MRI, Bone scan, 18F-FDG-PET, CT of chest, abdomen and pelvis) depending on the location and extent of disease. Patients with concurrent ECD and LCH were eligible as well as patients with ECD and/or LCH and active or untreated central nervous system involvement were also eligible.

For each cohort or subcohort the study was divided into two stages. Stage I was completed when 7 patients with measurable disease were enrolled and completed a minimum of 8 weeks of treatment, developed progressive disease (PD), were prematurely withdrawn from the study, or died, whichever occurred first. Dependent upon the response rate of patients completing Stage I, more patients could be enrolled to Stage II. In Cohort 7 (other solid tumors including ECD), the possibility of small enrollment levels within each solid tumor type was a concern.

Prior to the closure of the trial or the Sponsor decision of closure of the trial, the Sponsor could offer patients who had completed the protocol-mandated minimum 12-month safety follow-up and who continued to benefit from vemurafenib therapy, the opportunity to receive continued vemurafenib treatment via enrollment in the GO28399 extension trial.

Patients in Study GO28399 trial were followed for survival for a minimum period of 12 months after the last patient has been enrolled or until all patients had died, withdrawn consent or were lost to follow up, whichever occurred first.

5.3.2 Study Drug Administration and Schedule

The patients with ECD received continuous oral dosing of vemurafenib at 960 mg twice daily (BID). Treatment continued until the development of PD (as per Investigator assessment), unacceptable toxicity, withdrawal of consent, protocol violation endangering the patient's safety, death, reasons deemed critical by the treating physician, or study termination by the Sponsor. Patients with ECD/LCH had the option of discontinuing vemurafenib treatment after one year, if the Investigator considered it to be in the best interest of the patient. Patients could then resume vemurafenib treatment if they became symptomatic or if their scans showed worsening of their disease.

The study consists of a Screening Period (Day -28 to -1), a Treatment Period, and an End of Treatment Visit occurring when study medication was discontinued for any reason. One cycle of therapy is defined as 28 days of treatment. A safety follow-up visit

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occurred 28 days (\pm 5 days) after the last dose of study medication along with a survival follow-up period lasting for a minimum of 12 months after the last patient had been enrolled or until all patients had died, withdrawn consent or were lost to follow-up (whichever occurred first). Patients attended clinic visits at regular intervals during the study for safety and efficacy assessments.

Reviewer's Comments:

Given the rarity of the disease, the number of patients enrolled into this clinical trial was adequate to establish the efficacy of vemurafenib in ECD.

5.3.3 Study Endpoints

Primary Efficacy Endpoint

The primary endpoint of the final analysis for the Cohort 7a patients with ECD was the objective response rate (ORR), which was defined as the proportion of patients who had an objective response, which in turn was defined as a complete response (CR) or partial response (PR) on two occasions \geq 4 weeks apart, as assessed by the Investigation using RECIST v1.1.

Secondary Efficacy Endpoints

The following endpoints for Study MO28072 are described below:

- Progression free survival (PFS) is defined as the time from the first day of study treatment until the first documented progression of disease or death from any cause, whichever occurred first.
- Time to tumor progression (TTP) is defined as time from the first day of study treatment to the first occurrence of PD.
- Best overall response (BOR) is defined as the best response recorded from the first day of study treatment until disease progression/recurrence, death, end of study, or data cutoff, whichever occurred first.
- Clinical benefit rate (CBR) is defined as the proportion of patient whose best response was confirmed PR, confirmed CR, or stable disease (SD) that has lasted at least 6 months.
- Time to response (TTR) is defined as the time from the first day of study treatment to the first date the response criteria was met, given they were later confirmed.
- Duration of response (DOR; only for patients show confirmed best response was CR or PR) is defined as the time interval between the date of the earliest qualifying response (according to RECIST, V1.1) and the date of PD or death from any cause, whichever occurred first.
- Overall survival (OS) is defined as time from the first day of study treatment to the date of death of any cause.

Efficacy Assessment in Patients with ECD

These additional assessments were performed on the ECD patients:

- Baseline tumor assessment by CT/MRI of the chest, abdomen and pelvis as well as clinical relevant tumor assessment to define baseline extent of disease (i.e. brain MRI, cardiac MRI/echocardiogram, bone scan, ¹⁸F-FDG-PET).
- Those patients with baseline measurable disease according to RECIST v1.1, the following tumor assessments must consist of the same method used at baseline to determine measurable disease at 8-weekly intervals. Response was assessed by the investigator.
- For all other patients, the same tumor assessments had to consist of the same method used at baseline.
- For assessments of bone lesions, the Prostate Cancer Working Group 2 (PCWG2) guidance for bone lesions was used. For the assessment of ¹⁸F-FDG-PET, the PET response criterion (PRC) was used. C-reactive protein, a tumor marker in ECD, was monitored on Days 1, 29, 57 and every 8 weeks thereafter until discontinuation of study drug.

Reviewer Comment:

PFS and OS are time-to-event endpoints and are not evaluable from this single-arm trial. Per the FDA Guidance for Industry: Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, overall survival should be evaluated in randomized controlled studies. Data derived from historical trials are seldom reliable for time-dependent endpoints (e.g., overall survival, PFS). Apparent differences in outcome between historical controls and current treatment groups can arise from differences other than drug treatment, including patient selection, improved imaging techniques, or improved supportive care. Randomized studies minimize the effect of these differences by providing a direct outcome comparison.

The exploratory endpoints evaluating the clinical benefit response via baseline tumor assessments are relevant in identifying a clinical response to vemurafenib for the treatment of patients with ECD. However, (b) (4), we do not recommend this endpoint for description in labeling.

5.3.4 Eligibility Criteria

The target population was male or female patients ≥ 18 years of age with histologically confirmed cancers (excluding melanoma and papillary thyroid cancer) that harbored BRAFV600 mutation refractory to standard therapy or where standard or curative therapy did not exist. Patients with concurrent ECD and LCH were eligible as well as patients with active or untreated central nervous involvement.

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Solid tumors were required to have measurable disease according to RECIST, v1.1, and adequate hematologic function (absolute neutrophil count $\geq 1.5 \times 10^9/L$ and platelet count $\geq 100 \times 10^9/L$).

Patients with non-measurable disease according to RECIST v1.1 where tumor response is reliably morphologically evaluated by one or more of the tests listed below:

- Brain MRI
- Cardiac MRI
- Bone scan
- ^{18}F -FDG PET
- (CT) of chest, abdomen, and pelvis (C/A/P).

Inclusion Criteria

Patients had to meet the following criteria based on the cohort assigned:

*For solid tumors only**

1. Histologically confirmed cancers (excluding melanoma and papillary thyroid cancer) that harbor a BRAF V600 mutation and are refractory to standard therapy or for which standard or curative therapy does not exist or is not considered appropriate by the Investigator. Note: for the patient to be eligible, they must be able to provide a tumor sample (preferably tissue; alternatively DNA) for retrospective confirmation of the BRAF mutation by a central laboratory. This tumor sample should preferably be from the original specimen used to detect the BRAF mutation. If archival samples are not available, the patient should be biopsied in order to obtain adequate tissue. Exceptions may be considered upon discussion with the Sponsor (e.g. ≥ 250 ng of DNA may be sent instead of tissue samples).
2. Measurable disease according to RECIST, v1.1
3. Adequate hematologic function, as defined by the following laboratory values; test performed within 7 days prior to the first dose of vemurafenib:
 - a. Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$
 - b. Platelet count $\geq 100 \times 10^9/L$

For multiple myeloma (MM) only:

4. Patients with a confirmed diagnosis of MM harboring a BRAF V600 mutation
Note: for the patient to be eligible, they must be able to provide a tumor sample (preferably tissue; alternatively DNA) for retrospective confirmation of the BRAF mutation by a central laboratory. This tumor sample should preferably be from the original specimen used to detect the BRAF mutation. If archival samples are not available, the patient should be biopsied in order to obtain adequate tissue. Exceptions may be considered upon discussion with the Sponsor (e.g. ≥ 250 ng of DNA may be sent instead of tissue samples).

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5. Patients must have received at least one line of prior systemic therapy for the treatment of MM. A line of treatment is sequential treatment without interruption for response and subsequent progression
6. Patients treated with local radiotherapy (with or without concomitant exposure to steroids for pain control or management of cord/nerve root compression); two weeks must have elapsed since the last date of radiotherapy, which is recommended to be a limited field. Patients who require concurrent radiotherapy should have entry into the Study deferred until the radiotherapy is completed and two weeks have passed since the last date of therapy
7. Patients must have relapsed and/or refractory MM with measurable disease, defined as disease that can be measured either by serum or urinary evaluation of the monoclonal component or by serum assay of free light chain (FLC) of at least one of the following three parameters:
 - a. Serum M-protein > 0.5 g/dL
 - b. Urine M-protein > 200 mg per 24 hours
 - c. Involved FLC level > 10 mg/dL (> 100 mg/L) provided serum FLC ratio is abnormal
8. Adequate hematologic function as defined by the following laboratory values performed within 7 days prior to the first dose of vemurafenib:
 - a. Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9/L$
 - b. Platelets count $\geq 50 \times 10^9/L$

For all patients (solid tumors and MM):

9. Signed written informed consent approved by the relevant Independent Ethics Committee (IEC) / Institutional Review Board (IRB) must be obtained prior to performing any study related procedures
10. Male or female ≥ 16 years of age
11. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2
12. Must have recovered from all side effects of their most recent systemic or local treatment
13. Able to swallow pills
14. Adequate hematologic, renal and liver function as defined by the following laboratory values; tests performed within 7 days prior to the first dose of vemurafenib:
 - a. Hemoglobin ≥ 9 g/dL
 - b. Serum creatinine ≤ 1.5 times upper limit of normal (ULN) or creatinine clearance (CrCl) > 50 mL/min by Cockcroft–Gault formula
 - c. Aspartate aminotransferase (AST [SGOT]) and alanine aminotransferase (ALT [SGPT]) ≤ 2.5 times ULN (≤ 5 times ULN if considered due to primary or metastatic liver involvement)
 - d. Serum bilirubin ≤ 1.5 times ULN
 - e. Alkaline phosphatase ≤ 2.5 times ULN (≤ 5 times ULN if considered due to tumor)

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15. Negative serum pregnancy test within 7 days prior to commencement of dosing in premenopausal women. Women of non-childbearing potential may be included without serum pregnancy test if they are either surgically sterile or have been postmenopausal for ≥ 1 year

16. Fertile men and women must use an effective method of contraception during treatment and for at least 6 months after completion of treatment as directed by their physician. Effective methods of contraception are defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly (for example implants, injectables, combined oral contraception or intra-uterine devices). At the discretion of the Investigator, acceptable methods of contraception may include total abstinence in cases where the lifestyle of the patient ensures compliance. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception).

17. Absence of any psychological, familial, sociological, or geographical conditions potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before trial entry

Additional inclusion criteria for patients with ECD and/or LH:

18. Patients with non-measurable disease according to RECIST v1.1 are eligible if in the opinion of the investigator the tumor response can be reliably morphologically evaluated by one or more of the below tests (depending on the location and extent of disease):

- Brain MRI
- Cardiac MRI (or cardiac echography for patients who cannot undergo MRI and have cardiac involvement)
- Bone scan
- ^{18}F -FDG PET
- CT chest/abdomen/pelvis

19. Patients with concurrent ECD and LCH3 are eligible

20. Patients with ECD and/or LCH and active or untreated CNS involvement

Exclusion Criteria

1. Melanoma, papillary thyroid cancer or hematological malignancies (with the exception of multiple myeloma)

2. Uncontrolled concurrent malignancy (early stage or chronic disease is allowed if not requiring active therapy or intervention and is under control)

3. For MM, solitary bone or solitary extramedullary plasmacytoma as the only evidence of plasma cell dyscrasia

4. Active or untreated CNS metastases. Patients with brain metastasis are eligible if asymptomatic, off corticosteroid therapy, and without evidence of disease progression in brain for ≥ 2 months. Patients with incidentally found brain metastases that are asymptomatic and for which no treatment is planned are also eligible.

5. History of or known carcinomatous meningitis

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6. Concurrent administration of any anti-cancer therapies (e.g., chemotherapy, other targeted therapy, experimental drug, etc.) other than those administered in this study
7. Known hypersensitivity to vemurafenib or another BRAF inhibitor. In addition, for Cohort 3b only: known hypersensitivity to cetuximab
8. Prior treatment with a BRAF or MEK inhibitor (prior sorafenib is allowed)
9. Pregnant or lactating women
10. Refractory nausea and vomiting, malabsorption, external biliary shunt or significant bowel resection that would preclude adequate absorption.
11. Any of the following within the 6 months prior to first vemurafenib administration:
 - Myocardial infarction, severe/unstable angina, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack
12. Pulmonary embolism within 30 days prior to first study medication administration
13. Hypertension not adequately controlled by current medications within 30 days prior to first study medication administration
14. History or presence of clinically significant ventricular or atrial dysrhythmias \geq Grade 2 (National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 [NCI CTCAE, v4.0])
15. Corrected QT (QTc) interval \geq 450 msec at baseline or history of congenital long QT syndrome or uncorrectable electrolyte abnormalities
16. Uncontrolled medical illness (such as infection requiring treatment with intravenous [IV] antibiotics)
17. Other severe, acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study medication administration or may interfere with the interpretation of study results which, in the judgment of the Investigator, would make the patient inappropriate for entry into this study
18. Unwillingness to practice effective birth control
19. Inability to comply with other requirements of the protocol

Reviewer's Comment:

These inclusion and exclusion criteria are reasonable for the trial population.

Procedure for Assessing Patients for BRAF V600 Mutations

Patients with BRAF V600 mutation-positive cancers were identified through mutation analysis assays as routinely performed at each participating site (the BRAF V600 mutation and test used for the detection of BRAF mutation assay was recorded in the eCRFs). Sites submitted a tumor sample (preferably tissue; alternatively DNA) for retrospective confirmation of the BRAF mutation using the Roche CoDx cobas 4800 BRAF V600 Test or other standard methodology by a central laboratory. This tumor sample should preferably be from the original specimen used to detect the BRAF mutation. If archival samples are not available, the patient was biopsied in order to

obtain adequate tissue. Exceptions may be considered upon discussion with the Sponsor (e.g. ≥ 250 ng of DNA may be sent instead of tissue samples).

Reviewer's Comment:

The cobas test or any other standard methodology used by a central laboratory for confirmation of the BRAF mutation was allowed. It was agreed during a Type C Guidance meeting (March 18, 2016) between the Applicant and the Agency that a companion diagnostic would not be required.

5.3.5 Duration of Treatment

Treatment continued until the development of PD (as per Investigator assessment), unacceptable toxicity, withdrawal of consent, protocol violation endangering the patient's safety, death, reasons deemed critical by the treating physician, or study termination by the Sponsor. Patients with ECD/LCH had the option of discontinuing vemurafenib treatment after one year, if the Investigator considered it to be in the best interest of the patient. Patients could then resume vemurafenib treatment if they became symptomatic or if their scans showed worsening of their disease.

Prior to the closure of the trial or the Sponsor decision of closure of the trial, the Sponsor could offer patients who had completed the protocol-mandated minimum 12-month safety follow-up and who continued to benefit from vemurafenib therapy, the opportunity to receive continued vemurafenib treatment via enrollment in the GO28399 extension trial.

Patients in Study GO28399 trial were followed for survival for a minimum period of 12 months after the last patient has been enrolled or until all patients had died, withdrawn consent or were lost to follow up, whichever occurred first.

5.3.6 Primary and Secondary Endpoint Evaluations

Primary Endpoint

The primary endpoint was response rate (RR) at Week 8 for each cohort, as assessed by the Investigator using RECIST, v1.1 for patients with solid tumors. For patients with solid tumors, responders at Week 8 will be defined based on tumor assessment status of PR or CR at Week 8.

Secondary Endpoint Evaluation

The secondary efficacy endpoints for each cohort included: best overall response (BOR), clinical benefit rate (CR [or sCR] plus PR [or VGPR] plus SD), duration of response (DOR), time to response, time to tumor progression, progression-free survival (PFS), and overall survival (OS). In addition, secondary endpoints included the assessment of response rates that demonstrate clinically meaningful efficacy as per the investigator's assessment.

Overall Response Rate (ORR) confirmed

The best (confirmed) overall response (OR) was assessed at the end of Stage II for each cohort and considered efficacious if the OR is higher than 15%. OR was defined as the best response recorded, from the first day of study treatment until disease progression, recurrence or death. To be assigned a status of PR or CR (i.e., a responder), changes in tumor measurements were confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met, i.e., patients need to have two consecutive assessments of PR or CR to be a responder. Only patients with measurable disease at baseline were included in the analysis of the OR. Patients without a post-baseline tumor assessment were considered to be non-responders. Duration of confirmed response was defined as the period from the date of initial PR or CR that contributed for the OR status until the date of progressive disease or death from any cause. Patients with no documented progression after CR or PR were censored at the last date at which they are known to have had the CR or PR, respectively. The method for handling censoring is the same as described for the PFS.

For responders in OR, time to response was defined as the time from the first day of study treatment to the date of first CR or PR. The censoring rules will be similar to those of the PFS. The ORR and the associated 95% Clopper-Pearson CI were calculated for each treatment group.

5.3.8 Major Protocol Amendments

Study Design

1. Survival follow-up period and end of study

The protocol was so that the Survival Follow-Up Period will last a minimum of 12 months after the last patient has been enrolled or until all patients have died, withdrawn consent, or are lost to follow-up, whichever occurs first. After study end, no further data would be collected on the clinical database for this study.

The Survival Follow-Up Period was amended to ensure that a minimum of 12 months' patient treatment and follow-up data from enrollment is available to measure study outcomes.

Sample size

1. Cohort 7

It was clarified that the sample size of 19 patients for Cohort 7 (other solid tumors) is not the total sample size for the cohort, but rather it represents the number of enrolled patients of each individual tumor type within the cohort, should a sufficient number of patients with any given individual tumor be enrolled so that the Stage I and II analysis could be performed. This number was to provide sufficient patients to allow the assessment of desirable response for that individual tumor type at the end of Stage Two.

Patient Population

1. CNS metastases

As per the current protocol, patients with active or untreated CNS metastases were not eligible for the study unless they are asymptomatic, off corticosteroid therapy and without evidence of disease progression for ≥ 2 months. However to make this study consistent with other vemurafenib protocols, patients with incidental brain metastases that are asymptomatic and for which no treatment is planned could now be entered into the study.

Additional Guidance for patients in Cohort 7

1. Additional Guidance

As Erdheim-Chester disease (ECD) and/or Langerhans cell histiocytosis (LCH) have some unique characteristics as compared to other types of solid tumors, Appendix 10 was created to provide additional guidance for these patients, including eligibility criteria, duration of treatment, additional efficacy assessments and reporting of results.

Schedule of Assessments

1. Biochemistry

As treatment with vemurafenib might be associated with an increased risk of pancreatitis, amylase and lipase was added to the biochemistry measurements in order to ensure adequate monitoring of the patients.

Safety

1. Dose Interruptions and modifications criteria for vemurafenib

The protocol stipulated a 50% reduction of vemurafenib, depending on the starting dose, at the first appearance of grade 4 toxicities. Vemurafenib is only provided as 240 mg tablets which cannot be divided. The guidelines for dose interruptions/modifications were clarified for patients receiving vemurafenib at a starting dose of 720 mg twice daily (BID). For these patients, treatment was started at a reduced dose of 480 mg twice daily (BID), once the adverse event has resolved to grade 0 or 1.

Informed Consent Form

1. Second primary malignancies

The potential for second primary malignancies were reported as an SAE according to protocol section 7.3.3.2 and added to the synopsis for completeness. Any suspected cutaneous squamous cell carcinoma (SCC) as well as any suspected SCC were reported as an SAE. The protocol was updated to include the information that vemurafenib should be used with caution in patients with prior or concurrent cancers associated with RAS mutation.

6 Review of Efficacy

Efficacy Summary

The initiation date of study MO28072 was April 11, 2012 and the completion date was October 27, 2016. The data cut-off date was Jan 12, 2017. The protocol MO28072 version 1 was finalized on November 30, 2011. The last version, version 6, was finalized on January 13, 2015.

As of this date, all patients had completed treatment with vemurafenib.

On June 7th, 2017, the applicant, Hoffmann-La Roche/Genentech, Inc., submitted a new efficacy supplement for NDA 202429 Zelboraf (vemurafenib). The sponsor is proposing a new indication in patients with Erdheim Chester Disease (ECD) with BRAF V600 mutation.

The supplement is supported by the results of an open-label, multicenter, multinational, phase II study. The trial enrolled 208 patients into 7 different cohorts. Twenty-two subjects enrolled in Cohort 7a had ECD. The proposed indication is based on these 22 ECD patients. The primary efficacy endpoint was the overall response rate (ORR) by

investigator. ORR is defined as a complete response, partial response on two occasions ≥ 4 weeks apart, as assessed by the investigator.

The ORR was 54.5% (12 out of 22 subjects; 95% CI= [32.2, 75.6]). One subject had a complete response and eleven had partial responses. For the rest, nine subjects had stable disease and one patient's outcome was not measurable.

Based on the data submitted, the statistical reviewer confirms the results for patients with ECD known to harbor BRAF V600 mutations.

6.1 Indication

The applicant proposes that vemurafenib is indicated for the treatment of patients with Erdheim Chester disease with BRAF V600 mutation.

Statistical Reviewer's Comment:

This study does not have a formal statistical hypothesis due to the single arm study design and small sample size of 22 patients in the ECD cohort. Based on the data submitted, this reviewer confirms the results for patients with ECD known to harbor BRAF V600 mutations.

Clinical Reviewer's Comment:

The efficacy of vemurafenib was based on the response rate as assessed by the Investigator using the Response Evaluation Criteria In Solid Tumors (RECIST, v1.1) response criteria at week 8. In addition to the overall response rate among the patients with ECD, supportive evidence of symptomatic and physical function improvement was reported in sixty-eight percent (15/22) of the patients after starting treatment with vemurafenib. These results were derived from "efficacy narratives" created from excerpts from the patient medical records. The documented evidence of functional and symptomatic improvement while on vemurafenib does represent a favorable benefit to risk ratio to support regular approval of vemurafenib among patients with ECD. Usually, patient reported outcome data would require a control arm to interpret the results. However, in this case, patients with ECD typically progress (symptomatically, functionally, and radiographically) without treatment. This is particularly true in those with CNS involvement. The symptomatic and functional improvements were also observed in patients who had baseline neurologic involvement. The functional and disease symptom improvements are very likely to be due to vemurafenib treatment, and not a function of disease waxing and waning. [See Section 6.1.10 for results]. The benefit:risk assessment for vemurafenib is favorable for patients with ECD who harbor a BRAF V600 mutation.

6.1.1 Methods

Data were provided electronically with the standard analysis data formats. SAS programs used to create key efficacy and safety endpoints and analyses for Study MO28072 were submitted electronically with this application.

The path to the CDER Electronic Document Room (EDR) data is:
<\\CDSESUB1\evsprod\NDA202429\0186\m5\datasets\mo28072>.

Data from study MO28072 was provided with SDTM and ADAM formats. Documentations on datasets and programming for the key study endpoints were included with sufficient details for verifications.

Efficacy narratives provided in the submission were reviewed.

6.1.2 Demographics

Demographics Characteristics:

The enrolled population in Study MO28072 does adequately reflect the current literature's description on the prevalence of Erdheim-Chester disease. The phenotypes among the patients with ECD included those subjects with cardiovascular involvement, retroperitoneal involvement, CNS involvement resulting in headaches, dysarthria, blurred vision and ataxia as well as skin involvement and most commonly, bone involvement. Fifteen subjects (68.2%) had at least one prior systemic therapy.

Table 5 Demographics of ECD Patients Enrolled to Trial MO28072

	ECD (n=22)
Age (years)	
Mean (SD)	59.9 (11.8)
Median	58.5
Min-Max	(b) (6)
Sex	
Male	(b) (6)
Female	
Race	
White	(b) (6)
Asian	
ECOG Status	
0	4 (18.2%)
1	12 (54.5%)
2	5 (22.7%)

NA	1 (4.6%)
Prior Systemic Therapy	
0	7 (31.8%)
1	7 (31.8%)
2	5 (22.7%)
3 or more	3 (13.7%)

6.1.3 Subject Disposition

As of the data cutoff, all ECD patients (22/22) were no longer receiving study treatment and all patients had discontinued from the study. The most common reason for study discontinuation was “Other” (59.1%), followed by withdrawal by subject (27.3%), loss to follow-up (9.1%), and death (4.5%). The median time to study discontinuation was 26.64 months. The most common reason for treatment discontinuation was “Other” (40.9%) as well, followed by Progressive Disease (31.8%), followed by withdrawal by subject (22.7%), physician decision (4.5%). The median time to treatment discontinuation was 14.16 months.

Table 6 Subject Disposition (ECD Cohort MO 28072)

	ECD (N=22)
Study Discontinuation Reasons	
N	22
Death	1 (4.5%)
Lost to Follow-up	2 (9.1%)
Withdrawal by Subject	6 (27.3%)
Other	13 (59.1%)
Time to Study Discontinuation (months)	
N	22
Mean (SD)	22.7 (12.98)
Median	26.6
Min - Max	3.1 – 44.3
Vemurafenib Discontinuation Reasons	
N	22
Progressive Disease	0
Adverse Event	7 (31.8%)
Death	0
Withdrawal by Subject	5 (22.7%)
Physician Decision	1 (4.5%)
Other	9 (40.9%)

Time to Vemurafenib Discontinuation (months)	
N	22
Mean (SD)	17.2 (13.35)
Median	14.2
Min - Max	1.6 – 44.2

6.1.4 Analysis of Primary Endpoint(s)

Overall Response Rate:

The ORR was 54.5% (12/22) 95% CI (32.21%, 75.61%). One patient had a complete response (4.5%), eleven patients had a partial response (50.0%), nine had stable disease (40.9%), and one patient's disease status was not measurable (4.5%). Out of the twelve responders, the median time to response was ~11 months with 95% CI of 4 and 15 months. The median duration of response was not reached at the time of study cutoff.

Table 7 Overall Response Rate by Investigator (ECD Cohort MO28072)

Efficacy Result	ECD patients (N=22)
Median duration of follow-up (months) (Min, Max)	26.64 (3.0, 44.3)
ORR by Investigator (95% CI)	12 (54.5%) (32.21, 75.61)
Complete response	1 (4.5%)
Partial response	11 (50.0%)
Stable disease	9 (40.9%)
Progressive disease	0
Not Measurable	1 (4.5%)

6.1.5 Analysis of Secondary Endpoints(s)

Table 8 Secondary Efficacy Endpoints DOR and TTR

Efficacy Result	ECD patients (N=22)
Duration of Response	
Number of responders	12 (54.5%)
Median (months) (95%CI)	NE (NE)
Time to Response	
Number of responders	12 (54.5%)
Median (months) (95%CI)	10.97 (3.68, 14.55)

Table 9 Progression Free Survival and Overall Survival Rates by Investigator (ECD Cohort MO28072)

Efficacy Result	ECD patients (N=22)
Median duration of follow-up (months) (Min, Max)	26.64 (3.0, 44.3)
Progression Free Survival (PFS)	
Number of events	3 (13.6%)
Median (months) (95%CI)	NE (NE)
Overall Survival (OS)	
Number of events	1 (4.5%)
Median (months) (95%CI)	NE (NE)

There is no formal statistical hypothesis. The number and percentage of responders with corresponding exact 95% CI are presented.

6.1.6 Other Endpoints

There were no other endpoints explored.

6.1.7 Subpopulations

Subgroup analyses presented in this section are considered exploratory.

Subgroup Analyses by Age, Gender, Race and Region:

The difference of ORR between the subgroups and their associated wide 95% CI are the result of small sample size.

Table 10 Subgroup Analysis (ECD Cohort MO28072)

Subgroup	N	ORR	95% CI for ORR
Gender			
Men	12	5 (41.7%)	(15.17%, 72.33%)
Women	10	7 (70.0%)	(34.75%, 93.33%)
Age (years)			
<65 years old	14	9 (64.3%)	(35.14%, 87.24%)
≥65 years old	8	3 (37.5%)	(8.52%, 75.51%)

Reviewer's Comment:

(b) (6) of twenty-two patients were white and (b) (6) of 22 patients were from the (b) (6). Because the groups are so small, the by- race and by-country subset analyses would not be reasonable and provide any substantial insight.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

All patients with ECD had at least one dose reduction (DR) and one dose interruptions (DI) due to an adverse reaction (AR). The most common ARs leading to DR or DI in patients with ECD were maculopapular rash, fatigue, and arthralgia, palmar-plantar erythrodysesthesia, and increased lipase. The AR associated with a DR or DI in patients with ECD are similar to those associated with dose modification in patients with NSCLC or MM; however, more patients with ECD required a DR and DI due to ARs compared to patients with other diseases (**Table 10 and Table 11**). Also, more patients with ECD (32%) discontinued study drug due to ARs compared to patients with NSCLC (10%) and MM (7%: Study MO25515). Nonetheless, these comparisons can be confounded by factors including limited sample size and longer duration of exposure to vemurafenib in the ECD population compared to the other diseases.

Table 11 Patients (%) with at least one dose reduction (DR) due to adverse reactions

Disease (n)	DR to 720 mg	DR to 480 mg	DR to 240 mg
ECD (n=22)	91%	64%*	0
NSCLC (n=62)	53%	16%	3%
MM (n=3219) †	19%	6%	<0.5%

*includes 2 patients with DR from 960 to 480 mg † Table 27, Study MO25515

ECD and NSCLC results based on analysis of dataset aex.xpt

ECD= Erdheim-Chester Disease, NSCLC=non-small cell lung cancer, MM=metastatic melanoma

Table 12 Patients (%) with at least one dose interruption (DI) due to adverse reactions

Disease (n)	1 DI	2 DI	≥3 DI
ECD (n=22)	32%	36%	32%
NSCLC (n=62)	37%	21%	8%
MM (n=3219) †	28%	13%	NA

† Table 28, Study MO25515. NA=not available

ECD and NSCLC results based on analysis of dataset aex.xpt

ECD= Erdheim-Chester Disease, NSCLC=non-small cell lung cancer, MM=metastatic melanoma

(The following tables are excerpted from the Clinical Pharmacology Review)

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A dose was reduced for a total of 20 patients with ECD from the starting dose of 960 mg to 720 mg and the dose was reduced for 12 patients from a dose of 720 mg to 480 mg due to ARs. The dose for two additional patients was reduced to 480 mg from 960 mg due to ARs. The median treatment duration following a DR to 480 mg was 3-fold longer than following a DR to 720 mg (**Table 10 and Table 12**). Nonetheless, the ORR does not appear to be affected for patients with a DR to 480 mg BID (n=14) as the ORR appears consistent with the total population. The duration of DI across the number of DIs ranged from 1 day to 29 days, with a median of 1 day to 10 days (**Table 13**).

Table 13 Summary results of dose reductions (DR) due to adverse reactions

Dose Reduction	720 mg BID	480 mg BID
%Patients	91% (n=20)	67% (n=14)
Median time to dose reduction (min, max)	33 days (9, 421)	91.5 days (17, 502)
Median treatment duration (min, max)	77 days (4, 1325)	236 days (21, 924)
ORR (95% CI)	n=8 37.5% (8.5, 75.5)	n=14 64.3% (35.1, 87.2)
DOR	NE	NE

ORR=best overall response rates, DOR=duration of response

Table 14 Summary results of dose interruptions (DI) for any reason

	First DI	Second DI	Third DI
% Patients	17%	27%	59%
Median time to dose interruption (min, max)	15 days (1, 190)	48 days (13, 492)	110 days (31, 498)
Median duration for interruption (min, max)	6.5 days (1, 29)	10 days (1, 28)	1 day (1, 29)

(The tables above are excerpted from the Clinical Pharmacology Review)

Dose reduction of vemurafenib due to adverse events among patients with ECD was 4 times higher than in the multiple myeloma group and nearly one times higher among patients with NSCLC in the MO28072 study. Twenty of twenty-two (91%) patients required a dose reduction from the starting dosage of 960 mg twice daily to 720 mg twice daily within a median time to dose reduction of thirty-three days. Sixty-seven percent of patients (14/22) required a second dose reduction to 480 mg twice daily. The exposure-response relationship for efficacy could not be evaluated within this study since the PK sampling was limited to only one patient with ECD. However, symptomatic and functional improvement was still apparent among patients whose dose was at the lowest dose used in ECD patients (480 mg twice daily).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

E-R cannot be explored in the ECD population as PK sampling was limited to one patient with ECD. In the original NDA submission in the untreated MM population, a

statistically significant exposure-response relationships was observed between PFS and vemurafenib exposure (C_{min}) ($p < 0.0001$), as well as between the risk of development of a squamous cell carcinomas and vemurafenib exposure (C_{min}) ($p < 0.0001$) (DARRTS ID 2968791).

6.1.10 Additional Efficacy Issues/Analyses

The Applicant provided efficacy narratives for all patients with ECD enrolled. The medical records were abstracted for these narratives. The narratives provided statements describing in changes in symptomatology, activities of daily living and quality of life while on vemurafenib. Among the 22 patients with ECD treated with vemurafenib, 15 demonstrated improvement in disease-related symptoms and physical function, as documented by the clinician in the medical record, after starting treatment with vemurafenib.

Table 15 Review of Efficacy Narratives (CSR MO28072)

Patient Number Age/Sex (b) (6)	Symptomatic/Functional Improvement Described in Narrative
	He feels really well. Spectacular clinical improvement.
	Improved speech, ataxia, now has legible penmanship, newly independent of most of her activities of daily living since beginning protocol therapy.
	Headache and visual disturbances resolved; ECOG from 1 to 0. Ataxia improved; returned to work.
	Improved ability to ambulate; speech; able to navigate stairs without assistance (previously required significant support); "level of energy is better than it has ever been".
	Reduction in lymphedema (confirmed by weight loss); reduced skin weeping; "reports better energy, strength, ambulation and decrease in her pain"; ECOG from 2 to 0.
	Noted improvement in her periorbital lesions and in the overall redness of her face and chest.
	Improvement in xanthelasmas related to her ECD after 5.5 days of vemurafenib. Improved diplopia, skin lesions orbital pain, arthralgias, energy, burning in feet, and cerebellar signs. Reports "ongoing benefit from treatment per her scans; ECD-related symptoms have essentially resolved".
	Night sweats had resolved for the first time in 20 years.
	Reports "much improved prior to beginning this study".

(b) (6)	<p>The “majority of her previous disease-related symptoms” had resolved entirely”; “feels well and maintains full ADLs”.</p>
	<p>Physical examination “slightly improved”; “patient reports improvement in dysarthria and ataxia”; “speech clearly improved, more able to ambulate without the use of an assistive device”; “...neurologic symptoms continue to improve; dysarthria and ataxia”; “patient reports continued and significant improvement in her disease-related symptoms”. “Arrived to clinic for first time without a wheelchair; ambulating on her own for the first time in months.”</p>
	<p>“Dramatic clinical response to therapy with a significant reduction in the swelling of his left eye”, “vision is back to normal with full range of motion of the eyes bilaterally”. “...quick and dramatic improvement; retroorbital swelling and painful exophthalmos with blurring of vision has fully resolved and his vision is back to normal”. “He is doing extremely well on vemurafenib. His eye ptosis as well as pressure associated with his Erdheim-Chester disease have resolved entirely since beginning protocol therapy.”</p>
	<p>During treatment patient noted improved strength, improvement in mental clouding and fatigue, more energy, and reduction in bone pain and malaise. The patient withdrew from the trial at study day 129; not due to toxicities because he “felt well and the best he has in months”.</p>
	<p>During treatment she reported improvement in chest wall masses, reduction in urinary frequency from 7-8 to 3 times per night, improved skin lesions, reduced pain in chest wall masses, dyspnea improved, walking 2-3 km per day, improved headaches, improved balance and improved headaches.</p>
	<p>During treatment, he reported improvements in his ocular symptoms and arthralgias.</p>
	<p>At enrollment, he had progressive neurologic symptoms. After beginning treatment, he noted improvements in his mood, blurred vision, neuropathies, energy, balance, speech, and positional lightheadedness. He withdrew from the study to pursue off-label vemurafenib.</p>

Reviewer’s Comments:

Fifteen of the 22 ECD patients had symptomatic and functional improvement recorded in their medical records. Many of these symptomatic responses were rapid and not always identified concurrent with radiographic (RECIST) responses. If future trials are

conducted in patients with ECD, the development and use of a patient reported outcome measure to assess symptoms of ECD would be recommended.

The efficacy narratives provide supportive evidence that these patients with ECD experienced an improvement in the way they “feel and function”. These findings are not recommended for inclusion in labeling because the trial did not prospectively evaluate patient symptoms or physical function as a trial endpoint and the trial did not have a control-arm. These results may be used to support the efficacy conclusion made by the Agency but are not adequate for inclusion in the prescribing information.

Trial Conduct

A total of 9 ECD patients (40.9%) were considered to have at least one major protocol deviation, inclusive of:

- Procedural deviations (6 patients)
 - Procedures related to disease assessment
 - Missed electrocardiogram (ECG)
- Medication deviations (3 patients)
 - Use of prohibited concomitant medication
 - Incorrect dose modification/interruption/delay
 - Non-compliance with cuSCC and SCC assessments
- Patients who did not meet eligibility criteria (1 patient)
 - Inadequate baseline/demographic performance status

Of note, the change from manual to electronic reporting prompted new reports of protocol deviations that previously categorized as “noncompliance of cuSCC and SCC assessments” or “missed ECD reporting” in the manual system were categorized as “procedural deviations” in the electronic system. Protocol deviations reported under the manual system were not re-categorized in the electronic system.

There was a discrepancy in local BRAF mutation method eCRF vs BRAF pathology reports. During review, discrepancies were identified for five patients in the US and for patient (b) (6) from (b) (4). Four of the five (b) (4) patients’ eCRF data entry indicated “Sequenom” as the mutation analysis method for BRAFV600E. Further review noted the following:

1. Subject (b) (6) : Pathology report indicated pyrosequencing
2. Subject (b) (6) : Pathology report indicated pyrosequencing
3. Subject (b) (6) : Pathology report indicated PCR-based assay
4. Subject (b) (6) : Pathology report indicated COBAS.

Patient (b) (6), from the (b) (4), initial eCRF data entry indicated ARMS PCR as the mutation analysis used. Further review noted that next generation sequencing using the MSKCC IMPACT panel was used.

Patient (b) (6), from (b) (4), initial eCRF data entry indicated “Sequenom” as the local mutation analysis used. Communication with the site confirmed the COBAS testing assay was used.

The Applicant submitted a note to file to the Agency on 11 July 2017. In their explanation, the Applicant noted that the discrepancy was likely due to how the mutation analysis method was entered into the IWRS at the time of screening before being transferred into the clinical database. This information could not be edited by the clinical site.

7 Review of Safety

Safety Summary

7.1 Methods

The assessment of safety of vemurafenib for the treatment of ECD was based upon a safety population that included:

- 22 patients with ECD who received vemurafenib at 960 mg twice daily including 8 patients with ECD who rolled over from Study MO28072
- 3224 patients with BRAF V600 positive metastatic melanoma.

The pivotal trial MO28072 (Cohort 7a) included safety assessments at baseline, on Day 1, Day 15, Day 29, every 28 days thereafter (defined as one cycle) and at the end of treatment (after 28 days (\pm 5 days) from discontinuation of vemurafenib. Patients were assessed for adverse events at each clinical visit. Serious adverse events reported after last dose which the Investigator considers related to vemurafenib were to be reported indefinitely.

At baseline, safety assessments included medical, oncologic, and surgical history, vital signs, physical exam, laboratories (hematology, chemistries, liver function and pregnancy, if applicable), assessment of ECOG PS, ECG, tumor assessments for patients with solid tumors (CT/MRI of chest, abdomen and pelvis and brain as per standard of care. In addition, dermatology and head & neck evaluations for cutaneous squamous cell carcinoma (SCC) and non-cutaneous SCC, respectively were done. Chest CT for non-cutaneous SCC surveillance and findings on physical examinations while on study treatment were required.

The MO25515 study (Open-label study of safety in patients with metastatic melanoma) included safety assessment at baseline, on Day 1 and every 28 days thereafter for the minimum of 16 weeks. The end of treatment follow-up visit will occur 28 days (\pm 5 days) after discontinuation of vemurafenib. All adverse events including serious adverse events are recorded from the first time of vemurafenib administration. Any adverse

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event or serious adverse events after the last dose of vemurafenib were collected. Those events were primarily from second primary malignancies and survival status for 24 months after the last patient was enrolled, or until occurrence of 1 of the following: death, withdrawal of consent or lost to follow-up. At baseline, safety assessments included medical, oncologic, and surgical history, vital signs, physical exam, laboratories (hematology, chemistries, liver function and pregnancy, if applicable), assessment of ECOG PS, ECG, brain CT/MRI at baseline, PET/CT, if applicable, dermatology evaluation, chest CT for non-cutaneous SCC, and pelvic/anal examinations for women were required.

The ongoing GO28399, open-label, multicenter, non-randomized, Phase IV extension (rollover) study provided eight ECD patients continued access to vemurafenib who rolled over from Study MO28072. The inclusion criteria included patients with BRAFV600 mutation positivity with prior eligibility for and received study treatment in Study MO28072. Treatment began within 15 days following the last day of study treatment in Study MO28072 to minimize interruption. Treatment with vemurafenib in this study continued with progression of disease or as long as the patient was deriving clinical benefit as judged by the investigator, death, withdrawal of consent, unacceptable toxicity, loss to follow-up or decision of the Sponsor to terminate the study, whichever occurred first.

Study evaluation began on Day 1 of the study and continued throughout the study until 28 days after the last dose of drug. Patients who discontinued treatment prior to disease progression were followed for up to 6 months after their last dose, withdrawal of consent, initiation of non-protocol therapy, death, or loss to follow-up, whichever was earliest. The safety population included all patients who received at least one dose of vemurafenib.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The two trials for which the applicant submitted safety data are summarized in Table 5. These two trials (MO28072 and MO25515) were included in the integrated summary of safety (ISS). The 120-day Safety Update Report (SUR) provided updated safety data up to the clinical cutoff date of 16 June 2017 for 8 of the 22 patients with ECD in Study MO28072 who rolled over to Study GO28399 from Study MO28072.

Due to the rarity of ECD, the safety and tolerability was a comparison of the following populations' adverse event data. The safety data also included those non-ECD patients from MO28072. The safety population included all patients who received at least one dose of study medication for both studies.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 16 Studies/Clinical Trials Used to Evaluate Safety

Study #	Population	Design	Dose (mg B.I.D.)	# Any Vemurafenib	# Vemurafenib 960 mg B.I.D.
MO28072	Cancers that harbored BRAF V600 mutation refractory to standard therapy	Open label, non-randomized	960	181	181
MO25515	Histologically confirmed metastatic melanoma with the BRAF V600 mutation positive	Open label, non-randomized	960	3219	3219

Reviewer' Comment:

In both the MO28072 and MO25515 studies, all of the patients received vemurafenib on the 960 mg twice daily dosing schedule.

7.1.2 Categorization of Adverse Events

In general, safety data collection, reporting, and analyses are similar for both studies. However, the coding of AEs for Study MO25515 used MedDRA version 18.1 and Study MO28072 used MedDRA v19.1 while Study GO28399 used MedDRA version 20.0. Adverse event grading was done according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

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

Adverse event data from three trials were included in the Applicant's integrated safety database. The rates of the most common (>15% of patients) treatment-emergent adverse events in vemurafenib-treated patients on Study MO28072 were compared to event rates among non-ECD patients and metastatic melanoma patients in the Study MO25515 database. This analysis is presented in **Table 15** below.

Table 17 Applicant Table Most Common Treatment-Emergent Adverse Events (> 15%)

	MO28072 N = 22		MO28072 (non-ECD) and MO25515 N = 3378	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Actinic Keratosis	7 (32.0)	0	274 (8.1)	2 (<1)
Alopecia	16 (72.7)	0	920 (27.2)	0
Arthralgia	20 (90.9)	0	1424 (42.2)	120 (3.55)
Cough	8 (36.4)	0	214 (6.34)	0
Cyst	6 (27.3)	0	17 (<1)	0
Decreased appetite	4 (18.2)	0	515 (15.2)	5 (<1)
Depression	4 (18.2)	0	1 (<1)	1 (<1)
Diarrhea	11 (50.0)	0	630 (18.7)	5 (<1)
Dry Eye	7 (31.8)	0	4 (<1)	0
Dry Skin	10 (45.5)	0	567 (16.8)	0
Headache	4 (18.2)	0	482 (14.3)	0
Fatigue	15 (68)	0	886 (26.2)	78 (2.31)
Hyperkeratosis	15 (68.1)	0	877 (26.0)	2 (<1)
Hypertension	11 (50.0)	4 (18.2)	285 (8.44)	150 (4.44)
Increased Aspartate Aminotransferase	4 (18.2)	0	11	3 (<1)
Increased Blood Creatinine	7 (31.8)	0	0	0
Increased Lipase	7 (31.8)	0	0	3 (<1)
Insomnia	5 (22.7)	0	163 (4.82)	0
Keratosis Pilaris	7 (31.8)	0	26 (<1)	1 (<1)
Maculopapular rash	15 (68.2)	0	210 (6.21)	11 (<1)
Melanocytic Nevus	5 (22.7)	0	265 (7.84)	0
Nasal Congestion	4 (18.2)	0	171 (5.06)	0
Nausea	7 (31.8)	0	760 (22.5)	5 (<1)
Papular Rash	5 (22.7)	0	16 (<1)	1 (<1)
Palmar-Plantar Erythrodysesthesia Syndrome	11 (50.0)	0	232 (6.87)	2 (<1)
Peripheral sensory neuropathy	7 (31.8)	0	19 (<1)	3 (<1)
Photosensitivity	9 (40.9)	0	711 (21.0)	0
Pruritus	8 (36.4)	0	354 (10.5)	0
QT prolongation	15 (68.1)	0	548 (16.2)	0
Seborrheic Keratosis	11 (50.0)	0	294 (8.70)	2

Skin Papilloma	12 (54.5)	0	661 (19.6)	0
Squamous Cell Carcinoma of Skin	8 (36.4)	8 (36.4)	278 (8.22)	278 (8.23)
Sunburn	5 (22.7)	0	336 (9.94)	0
Urinary Tract Infection	4 (18.2)	0	0	1 (<1)
Vomiting	5 (22.7)	0	495 (14.7)	2 (<1)

The incidence of the most common treatment-emergent adverse events among the ECD could not be compared to vemurafenib-treated patients in the non-ECD study group and metastatic melanoma study group due to the smaller sample size. However, both studies share similar observations among the clinically relevant adverse events.

7.2 Adequacy of Safety Assessments

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

Exposure to vemurafenib in the phase 3 trial MO28072 and the phase 3 MO25525 are summarized in **Table 18** below.

Table 18 Vemurafenib Exposure (mean)

Mean Exposure to Vemurafenib			
	ECD Patients from Study MO28072 (n = 22)	Non-ECD Patients from Study MO28072 (n=159)	Metastatic Melanoma Patients from Study MO25515 (n = 3219)
Number of Months on Treatment Mean (SD)	17.21 (13.35)	7.59 (8.22)	9.72 (9.90)
Total Cumulative Dose Mean (SD)	635.6 (543.4)	328.1 (337.2)	501.28 (510.9)
Relative Dose Intensity (%) Mean (SD)	61.8 (15.9)	80.4 (19.1)	90.2 (14.96)

Table 19 Vemurafenib Exposure (median)

Median Exposure to Vemurafenib			
	ECD Patients from Study MO28072 (n = 22)	Non-ECD Patients from Study MO28072 (n=159)	Metastatic Melanoma Patients from Study MO25515 (n = 3219)
Number of Months on Treatment Median	14.16	5.03	5.91
Total Cumulative Dose Median	531.5	209.3	318.7
Relative Dose Intensity (%) Median	62.2	80.6	98.68

The exposure to vemurafenib among the patients with ECD was approximately two times longer than in the non-ECD patients or metastatic melanoma patients. The longer exposure time among the patients with ECD is most likely due to the heterogeneous nature of the disease which at presentation may vary from an indolent focal disease to a life threatening organ failure and allowing for a longer duration on vemurafenib.

Dose modifications, interruptions, and reductions are summarized in the table below.

Table 20 Dose Modifications, Interruptions and Reductions (ECD Cohort MO28072)

	ECD Patients from Study MO28072 (n = 22)
Any Modification	22 (100%)
Reduction	22 (100%)
Number of Dose Reductions	
1	22(100%)
2	13 (59%)
3	0
Interruption	12 (54%)

All of the ECD patients required a dose modification. Twenty-two (100%) vemurafenib-treated ECD patients underwent dose reduction. The majority of patients required an initial dose reduction. Fifty-nine percent required a second dose reduction.

Table 21 Time to Dose Reduction based on Dosage of Vemurafenib (ECD Cohort MO28072)

Dose Reduction	720 mg	480 mg
Median Time to DR	33 days (9-421)	91.5 days (17-502)
Median Duration	77 days (4-1325)	235.5 days (21-924)
BORR	N=8 37.5% (95% CI 8.5, 75.5)	N= 14 64.3% (95% CI 35.1, 87.2)

DR= Dose reduction

There were more dose reductions in patients with ECD than patients with other diagnoses.

Table 22 Vemurafenib Exposure (mean) on Rollover Study (GO28399)

	Vemurafenib 480 mg BID (N= 5)	Vemurafenib 720 mg BID (N = 3)	Vemurafenib 960 mg BID (N =0)
Number of Months on Treatment Mean (SD)	8.58 (1.43)	9.11(1.59)	0 (NE)
Total Cumulative Dose Mean (SD)	244.1 (45.1)	398.4 (70.4)	0 (NE)
Relative Dose Intensity (%) Mean (SD)	97.2 (2.9)	99.7 (0.5)	0 (NE)

Table 23 Vemurafenib Exposure (median) on Rollover Study (GO28399)

	Vemurafenib 480 mg BID (N= 5)	Vemurafenib 720 mg BID (N = 3)	Vemurafenib 960 mg BID (N =0)
Number of Months on Treatment Median	8.21	8.28	0 (NE)
Total Cumulative Dose Median	224.6	362.9	0 (NE)
Relative Dose Intensity (%) Median	98.6	100.0	0 (NE)

During the rollover study, none of the patients were taking the initial starting dose of 960 mg twice daily. At the time data closeout, the number of months of treatment on the next dose reduction dosages was around 8.2 months. Without additional pharmacokinetic data from the patients with ECD, it is difficult to evaluate the exposure –efficacy relationship in those patients with ECD who were dose reduced. However, it is important to note the dose modifications, in general, are higher among those patients with ECD compared to the non-ECD and metastatic melanoma patients.

Adverse events leading to dose modifications in ≥ 3 patients on either arm are summarized in **Table 24 Error! Reference source not found**.below.

Table 24 Events Leading to Dose Modification (≥ 3 Patients) [ECD Cohort MO28072 and GO28399]

	Vemurafenib (n = 22)	
	All Grades	Grade 3-4 (%)
Arthralgia	17 (77%)	3 (14%)
Maculopapular rash	11 (50%)	4 (18%)
Fatigue	11(50%)	1 (4.5%)
QT prolongation	12 (54.5%)	0

Alopecia	12 (54.5%)	0
Diarrhea	11 (50%)	0
Palmar-Plantar Erythrodysesthesia	9 (40%)	0
Squamous Cell Carcinoma of Skin	8 (36%)	8 (36%)
Pruritus	8 (36%)	0
Hypertension	4 (18%)	4(18%)
Increased Lipase	4 (18%)	4 (18%)
Increased Blood Creatinine	7 (31.8%)	0
Vomiting	5 (22.7%)	0
Headache	4 (18%)	0
Increased Aspartate Aminotransferase	3 (13.6%)	1 (4.5%)
Keratoacanthoma	3 (13.6%)	3 (13.6%)
Hematuria	3 (13.6%)	0
Increase Alanine Aminotransferase	1 (4.5%)	2 (9%)
Increase Alkaline Phosphatase	2 (9%)	1 (4.5%)

All ECD patients (22/22) had an AE leading to a dose modification/interruption. Treatment-related AEs that resulted in dose modification/interruption occurred in 100% patients. The most frequent AEs leading to dose modifications/interruption in these patients including those on the rollover study were arthralgia (77%), rash (50%), and fatigue (50%).

Among the eight patients on the rollover study, GO28399, the adverse events led to discontinuation of the study treatment due to Grade 3 pancreatitis and small bowel obstruction in two patients. Only one patient underwent a dose modification after a resolved upper gastrointestinal hemorrhage.

7.2.2 Explorations for Dose Response

There is evidence of an exposure-response relationship for cuSCCs. Eleven ECD patients (50%) have cuSCC and/or KA. Of these eleven patients, 8 had cuSCC and 3 had KA. These were considered related SAEs events which were listed as Grade 3. One patient (4.5%) required dose modification/interruption as a result.

There is no reported evidence of an exposure-response relationship among the eight patients in rollover (GO28399) study.

7.2.3 Special Animal and/or In Vitro Testing

This was non-applicable to this supplemental.

7.2.4 Routine Clinical Testing

See sections 7.4.2-7.4.4.

7.2.5 Metabolic, Clearance, and Interaction Workup

See the summary of the clinical pharmacology review in section 4.4.

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

See Section 2.6

7.3 Major Safety Results

7.3.1 Deaths

There were no fatal AEs (Grade 5) reported among the ECD patients. One ECD patient (1/22) died of sepsis 194 days after receiving the last dose of vemurafenib. The death was assessed by Investigator as not related to prior study medication and not reported as an AE. This one patient had a splenic infarction in which vemurafenib was discontinued approximately six months after the second reduction in vemurafenib. In addition, this patient was also diagnosed with chronic myelomonocytic leukemia and myelodysplasia five and two years prior, respectively.

This reviewer concurs with the Investigator assessment of unrelatedness to vemurafenib treatment in this patient. However, the medical history of this patient highlights the well-described risk of a paradoxical activation of cytokine signaling in cells bearing kinase mutations other than BRAFV600E upon exposure to RAF inhibitors. This

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is an important implication in clinical management of ECD patients with an associated myeloid neoplasm.

7.3.2 Nonfatal Serious Adverse Events

Non-fatal serious adverse events occurred in 72.7% % of ECD patients in the ECD cohort MO28072 (16/22). The number of patients with ECD with non-fatal serious adverse events in the rollover study was four out of the eight patients (50%).

Table 25 Nonfatal Serious Adverse Events (≥ 1%) [ECD Cohort MO28072 and GO28399]

	Vemurafenib N=22	
	All Grades (%)	Grade 3-4 (%)
All SAE events	61	26
Squamous cell carcinoma of skin	8(36.3%)	8 (36.3%)
Keratoacanthoma	3(13.6%)	3 (13.6%)
Lung Infection	3 (13.6%)	3 (13.6%)
Drug-induced liver injury	1 (4.5%)	1 (4.5%)
Fatigue	15 (68.1%)	1 (4.5%)
Posterior reversible encephalopathy syndrome	1(4.5%)	1 (4.5%)
Hypertension	11 (50.0%)	5 (22.7%)
QT Prolongation	14 (63.6%)	1 (4.5%)
Hypertriglyceridemia	1 (4.5%)	1 (4.5%)
Pancreatitis	2 (9.1%)	1(4.5%)
Small bowel obstruction	1 (4.5%)	1 (4.5%)

There were no Grade 5 SAEs. Four patients had an SAE that led to withdrawal from treatment (15.4%) and 7 patients had an SAE that led to dose modification or interruption (26.9%).

SAEs were more frequently reported in the patients with ECD compared to non-ECD and metastatic melanoma patients. The difference may be due to longer vemurafenib exposure in patients with ECD. Patients with ECD had a median duration of exposure of 14.16 months vs. approximately 5 months for the non-ECD patients.

In the rollover study, Study GO2839, hypertriglyceridemia was reported as an ongoing Grade 1 AE from Study that worsened in intensity to Grade 3 in Study GO28399. Small intestinal obstruction and pancreatitis were newly reported Grade 3 AEs in 2 separate patients in Study GO283999. No Grade 4 or Grade 5 AEs were reported as ongoing from Study MO28072 at the time of enrollment in Study GO28399 or were newly reported in Study GO28399 in these 8 patients.

7.3.3 Dropouts and/or Discontinuations

Among the ECD patients, 59.1% patients (13/22) had an AE leading to withdrawal from study treatment. Those events ranged from arthralgia, increased ALT, diarrhea, fatigue, posterior reversible encephalopathy syndrome, pancreatitis, small bowel obstruction, splenic infarction and vomiting.

Table 26 Reasons for Treatment Discontinuation (ECD Cohort MO28072 and GO28399)

	Vemurafenib (N= 22)
Adverse Event	13
Withdrawal of Consent	5
Death ¹	1
Remain on Treatment	6
Other Reason ²	1

¹ Death occurred 194 days after last dose. Diagnosed with CMML (2009) and MDS (2012). Did have splenic infarction while on treatment.

² Developed posterior reversible encephalopathy syndrome; lost to follow up

7.3.4 Significant Adverse Events

Cutaneous Squamous Cell Carcinoma

There were 11 events of cutaneous squamous cell carcinomas (cuSCCs) in the ECD arm. The median time to onset in the vemurafenib arm was 7.1 weeks. Dose interruptions or reductions were undertaken in response to these events. There were no cases reported after 28 days off treatment or currently during the rollover study, GO28399.

Reviewer comment:

Given the patient population for this application, this reviewer does not view cuSCCs as a safety concern if appropriate monitoring is employed to manage these events. The overall benefit of vemurafenib in this population outweighs the risks of cuSCCs given the overall survival benefit and after examining the details and outcomes of patients who were diagnosed with cuSCCs in this trial.

Liver Toxicity

Liver enzyme elevations on this trial were evident on the ECD vemurafenib arm.

Table 27 Hepatic Toxicity in ECD Cohort of Trial MO28072 and GO28399

	Vemurafenib (n=22)
Alanine Aminotransferase Increased	3 (13.6%)
Blood Alkaline Phosphatase Increased	3 (13.6%)
Amylase Increased	3 (9.1%)
Aspartate Aminotransferase Increased	4 (18.2%)
Blood Bilirubin Increased	2 (9.1%)

On the MO28072 study, there was one case of Grade 1 elevation in alanine transaminase and blood alkaline phosphatase after two dose reductions which progressed to a Grade 3 elevation in alanine transaminase before the patient was permanently discontinued and started on dabrafenib. On the GO28399 study, one patient developed Grade 3 pancreatitis with noted Grade 3 elevation in amylase and Grade 5 elevation in lipase. Vemurafenib was permanently discontinued due to persistent elevation in both amylase and lipase levels.

Reviewer's Comment:

Despite the rare frequency of liver enzyme elevations, drug-induced liver injury was documented in the Phase 3 trial as well as the rollover study. Management with dose modification and/or interruption should be considered in addressing this event in most patients; however, in both the pivotal trial and rollover study, dose interruption and/or modification did not result in resuming vemurafenib in the patients affected. Cases of drug-induced pancreatitis have been reported in clinical studies and in the postmarketing setting, generally occurring within two weeks after initiation of vemurafenib. Given the inclusion of liver enzyme abnormalities in the Warnings and Precautions section of the label with monitoring recommended at baseline and monthly during treatment, I do not recommend labeling changes in regard to this group of adverse events.

New Myeloproliferative Neoplasm

One patient was identified as having both chronic myelomonocytic leukemia and myelodysplasia, both of which were diagnosed prior to starting vemurafenib for management of his ECD. With the Sequenom mass-spectrometry genotyping, the following mutations in eight genes: AKT1, BRAF, EGFR, ERBB2, KRAS, MEK1, (MAP2K1), NRAS, and PIK3CA were analyzed. There were no other mutations than BRAF V600E detected within the testing panel.

RAS mutations, especially KRAS and NRAS, are among the most common somatic mutations in CMML and are therefore believed to play an important role in its pathogenesis. Further supporting this hypothesis, oncogenic NRAS and KRAS mutations have been shown to initiate hematologic malignancies with features of CMML in murine models. Importantly, since RAS_{mut} and BRAF_{mut} tumors appear to regulate MEK activation through distinct mechanisms, distinguishing such subsets in CMML will likely have implications for the selection of MEK inhibitors as part of targeted therapy^{35,41}.

Reviewer's Comment:

In light of this finding, identifying an unexpected occurrence of myeloid neoplasms in older histiocytosis patients is concerning. Among ECD patients who are on vemurafenib, it can result in adverse outcomes to kinase-directed therapies. Hence, the proposal of considering a myeloproliferative workup in any histiocytosis patient with a complete blood count abnormality that cannot be explained by a nonmalignant cause including an expanded mutation analysis of the RAS pathway should be considered (NRAS, KRAS and JAK2).

7.3.5 Submission Specific Primary Safety Concerns

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

All ECD patients had at least one AE (100%, 22/22). The most commonly reported AEs (≥ 50% patients), irrespective of relatedness, were: arthralgia (86.3%), maculopapular rash (68%), alopecia (73%), fatigue (68.1%), electrocardiogram QT prolonged (63.6%), skin papilloma (54.5%), hyperkeratosis (68%), and diarrhea (50.0%). A table of all AEs and a listing of all AEs in ECD patients is provided in **Table 28**.

35 (Zhang L, 2014 May)

41 (Hatzivassiliou G, 2013)

Table 28 Grade 1-4 TEAEs (>5% of Patients) [ECD Cohort Trial MO28072]

	Vemurafenib (N = 22)	
	Grade 1-4 (%)	Grade 3-4 (%)
Any Adverse Event	568	61
<i>Skin and Subcutaneous Tissue Disorders</i>		
Maculopapular Rash	15 (68%)	3 (13.6%)
Alopecia	16 (73%)	0
Hyperkeratosis	15 (68%)	0
Palmar-Plantar Erythrodysesthesia Syndrome	11 (50%)	0
Actinic Keratosis	8 (36.4%)	1 (4.5%)
Keratosis Pilaris	8 (36.4%)	0
Papular Rash	5 (22.7%)	0
Rash	5 (22.7%)	0
Milia	3 (13.6%)	0
Dermatitis	3 (13.6%)	0
<i>Neoplasms Benign, Malignant and Unspecified</i>		
Skin Papilloma	12 (54.5%)	0
Seborrheic Keratosis	11(40.9%)	0
Squamous cell carcinoma of skin	8 (36.4%)	8 (36.4%)
Melanocytic Nevus	6 (22.7%)	0
Keratoacanthoma	3 (13.6%)	3 (13.6%)
Basal cell carcinoma	3 (13.6%)	3 (13.6%)
Dysplastic Nevus	2 (9%)	0
<i>Gastrointestinal Disorders</i>		
Diarrhea	11 (50%)	0
Nausea	7 (31.8%)	0
Vomiting	5 (22.7%)	0
Abdominal Pain	2 (9%)	0
Constipation	3 (13.6%)	0
Dyspepsia	2 (9%)	0
Gastric Ulcer	0	2 (9%)
Gastroesophageal reflux disease	2 (9%)	0
Pancreatitis	2 (9%)	1(4.5%)
Small bowel obstruction	1(4.5%)	1(4.5%)
<i>Investigations</i>		
QT prolongation	14 (63.6%)	1 (4.5%)
Increased blood creatinine	9 (40.9%)	0

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Increased lipase	6 (27.2%)	4 (18%)
Increased aspartate aminotransferase	3 (13.6%)	1 (4.5%)
Increased alanine aminotransferase	2 (9%)	2 (9%)
Increased blood alkaline phosphatase	2 (9%)	1 (4.5%)
Increased amylase	0	3 (13.6%)
Increased bilirubin	3 (13.6%)	0
Increased blood cholesterol	2 (9%)	0
<i>Musculoskeletal and Connective Tissue Disorders</i>		
Arthralgia	19 (86.3%)	2 (9%)
Myalgia	3 (13.6%)	0
<i>General Disorders</i>		
Fatigue	15 (68.1%)	1 (4.5%)
Cyst	7 (31.8%)	0
Peripheral edema	4 (18%)	0
Pyrexia	2 (9%)	0
<i>Infections</i>		
Urinary Tract Infection	4 (18%)	0
Lung Infection	0	2 (9%)
Oral Herpes	2 (9%)	0
<i>Nervous System Disorders</i>		
Peripheral Sensory Neuropathy	9 (40.9%)	0
Headache	4 (18%)	0
Dysgeusia	2 (9%)	0
Posterior reversible encephalopathy syndrome	0	1 (4.5%)
<i>Metabolism and Nutrition Disorders</i>		
Decreased appetite	11 (50%)	0
Dehydration	3 (13.6%)	2 (9%)
<i>Vascular Disorders</i>		
Hypertension	11 (36.3%)	4 (18%)
Hot Flush	3 (13.6%)	0
<i>Renal and Urinary Disorders</i>		
Hematuria	3 (13.6%)	0
Micturition urgency	2 (9%)	0
<i>Injury, Poisoning and Procedural Complications</i>		
Sunburn	5 (22.7%)	0
Scar	2 (9%)	0
<i>Psychiatric Disorders</i>		
Insomnia	5 (22.7%)	0
Depression	5 (22.7%)	0

Eye Disorders		
Dry Eye	7 (31.8%)	0
Cardiac Disorders		
Atrial fibrillation	2 (9%)	1 (4.5%)
Palpitations	2 (9%)	0
Blood and Lymphatic System Disorders		
Anemia	2 (9%)	2 (9%)
Endocrine Disorders		
Hypothyroidism	3 (13.6%)	0
Hepatobiliary Disorders		
Drug-Induced Liver Injury	1 (4.5%)	1 (4.5%)

7.4.2 Laboratory Findings

No clinically meaningful population trends were observed in the safety laboratory results following vemurafenib treatment administration. Changes from baseline above or below the normal range were observed.

Table 29 Laboratory Grade 1-4 Adverse Events in ≥ 10% of Patients [ECD Cohort Trial MO28072 and GO28399]

	Vemurafenib (N = 22)	
	Grade 1-4 (%)	Grade 3-4 (%)
Any Adverse Event	17	4
Investigations		
Increased Blood Creatinine	9 (40.9%)	0
Metabolism and Nutrition Disorders		0
Hypokalemia	3 (13.6%)	2 (9%)
Blood and Lymphatic System Disorders		
Anemia	0	2 (9%)

7.4.3 Vital Signs

Vital signs were recorded at baseline, pre-dose, and post-dose study drug administration. Among 22 vemurafenib-treated ECD patients, none had a recorded temperature >39°C. Aberrations in heart rate, either tachycardia or bradycardia, were not reported. Elevated systolic blood pressures were reported with systolic BP ≥160

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mmHg or diastolic BP \geq 100 mm Hg reported for 4 (18.2%) patients which were reported as serious AEs; none resulted in dose modification or discontinuation; and none of these cases were considered by the investigator to be related to study treatment but secondary to the disease itself where patients have manifested evidence of renovascular hypertension secondary to ostial stenosis of the renal arteries⁴².

7.4.4 Electrocardiograms (ECGs)

Fifteen ECD patients (68.2%) had QT prolongation. Of these, 9 patients had Grade 1 QT prolongation, 5 patients had Grade 2 QT prolongation, and 1 patient had Grade 3 QT prolongation; there were no Grade 4 or Grade 5 events of QT prolongation. Only one event (Grade 3) was considered related to vemurafenib. None of the QT prolongation events in the ECD patients resulted in dose modification/interruption or withdrawal from treatment

7.4.5 Special Safety Studies/Clinical Trials

No organ dysfunction studies have been conducted with vemurafenib to date.

7.4.6 Immunogenicity

The following adverse event preferred terms were considered possibly related to immunogenicity: chills, drug hypersensitivity, hypersensitivity, hypotension, pruritus, and rash. For each of these preferred terms, events that occurred within the first seventy-five days of vemurafenib administration were reviewed.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There is a clear relationship between exposure and the incidence of cuSCCs with an increase in the probability of squamous cell carcinomas. Most ECD patients were identified with cuSCC within the first 100 days of study treatment.

7.5.2 Time Dependency for Adverse Events

There were 12 ECD patients who had at least 12 months of vemurafenib exposure. The most common AEs (incidence rate $>$ 10%) occurring after 12 months of exposure to vemurafenib in ECD patients were, hyperkeratosis, lipase increased, skin papilloma, actinic keratosis, electrocardiogram QT prolonged, cyst, peripheral sensory neuropathy,

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urinary tract infection, basal cell carcinoma, keratoacanthoma, edema peripheral, dry eye, nasal congestion, and rash popular.

The most common SAEs (incidence rate >2%) occurring after 12 months of exposure to vemurafenib in ECD patients were basal cell carcinoma, keratoacanthoma, SCC of skin, paraganglion neoplasm, upper gastrointestinal hemorrhage, bacteremia, and prostatitis.

7.5.3 Drug-Demographic Interactions

Rates of grade 1-4 adverse events were examined by age (<65 years of age versus 65 years of age). Overall, grade 1-4 adverse events rates were similar in patients <65 years old and 65 years old. However, several grade 1-4 adverse events occurred more frequently (5% difference) in older patients, while others occurred more frequently in the younger patients. The grade 1-4 events that occurred more frequently in patients >65 years old were: decreased appetite, squamous cell carcinoma of the skin, keratoacanthoma, arthralgia, infection, nausea, diarrhea and peripheral edema. The adverse events that occurred more frequently in patients <65 years old were dry skin, erythema, maculopapular rash, keratosis pilaris, alopecia, hyperkeratosis, arthralgia, QT prolongation, increase in creatinine and liver enzymes.

7.5.4 Drug-Disease Interactions

N/A

7.5.5 Drug-Drug Interactions

See Clinical Pharmacology review.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

CuSCCs developed in approximately 24% of all patients treated with vemurafenib. Overall, all cases resolved with excision. The applicant also monitored for non-cuSCCs. This drug may accelerate the growth of a subset of cells with changes favorable for development of cuSCC, SCC or melanoma. However, in the population proposed in this NDA, proper monitoring for and treatment of these potential adverse events should mitigate this risk.

No vemurafenib-treated patients developed acute myeloid leukemia or myelodysplastic syndrome.

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The Zelboraf prescribing information states in section 13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility, that “there have been no formal studies conducted assessing the carcinogenic potential of vemurafenib. Zelboraf increased the development of cutaneous squamous cell carcinomas in patients in clinical trials.”

7.6.2 Human Reproduction and Pregnancy Data

The Zelboraf prescribing information states that” There are no available data on the use of ZELBORAF in pregnant women to determine the drug-associated risk; however, placental transfer of vemurafenib to a fetus has been reported. Exposure to vemurafenib could not be achieved in animals at levels sufficient to fully address its potential toxicity in pregnant women. Advise pregnant women of the potential harm to a fetus.”

7.6.3 Pediatrics and Assessment of Effects on Growth

Safety and efficacy in pediatric patients below the age of 18 have not been established.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

No cases of overdose were reported in this application. The Zelboraf PI states that there is no information on over dosage of ZELBORAF. Drug abuse potential is not relevant to Zelboraf as the toxicity would preclude abuse. Vemurafenib has no known psychotropic effects.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

There are no known post-marketing data for the ECD indication.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

The Zelboraf labeling revisions that were submitted by the Applicant were reviewed for accuracy and compliance with current labeling regulations, guidances, and policies.

Section 1: We recommend the addition of a new indication: Treatment of patients with Erdheim Chester Disease (ECD) with BRAF V600 mutation

Section 2: The dose for ECD is the same as for melanoma, so no significant revision of this section is recommended.

Section 6: We recommend the inclusion of an adverse reactions table for the ECD safety data.

Section 14: Headings were revised to clarify the indications they cover.

We recommend inclusion of a description of the study, the dosage administered, demographic information, the overall response rate, (including CR and PR), median time to response, and duration of response (not estimable). We do not recommend inclusion of [REDACTED] (b) (4)

Though symptomatic and functional improvements noted in the efficacy narratives (derived from medical records) lend support to the conclusion of efficacy and the recommendation for approval, we do not recommend the inclusion of these findings in the prescribing information. The rationale for this recommendation is that the assessment of symptoms and functional status were not prespecified endpoints and are based on a single-arm trial (without a control arm).

We recommend the inclusion of dosing and dose reductions in the study in the ECD patients.

9.3 Advisory Committee Meeting

An advisory committee meeting was not convened for this application because there were no clinical questions regarding the benefit of vemurafenib in this population with no available therapies. Due to the rarity of this condition, no clinicians self-identifying with experience in the treatment of ECD or patient representatives are on the SGE list. The priority review clock would not have allowed time to clear a new SGE patient advocate or clinician.

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/s/

PATRICIA A ONEAL
10/09/2017

VIRGINIA E KWITKOWSKI
10/09/2017