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*APPLICATION NUMBER:*

**202806Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	May 15, 2013
<b>From</b>	Suzanne G. Demko
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/Supplement#</b>	202806/0
<b>Applicant</b>	GlaxoSmithKline (GSK)
<b>Date of Submission</b>	July 30, 2012
<b>PDUFA Goal Date</b>	May 30, 2013
<b>Proprietary Name / Established (USAN) names</b>	Tafinlar® / Dabrafenib
<b>Dosage forms / Strengths</b>	Capsules/50 mg, 75 mg
<b>Proposed Indication(s)</b>	Indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA approved test.
<b>Recommended:</b>	<i>Approval</i>

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## Abbreviations

%CV	inter-subject variability
AR	adverse reaction
CDRH	Center for Devices and Radiological Health
CMC	Chemistry, Manufacturing and Controls
Cmax	maximum plasma concentration
Cmin	minimum plasma concentration
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte associated antigen 4
DSI	Division of Scientific Investigations
DTIC	dacarbazine
ERK	extracellular signal-related kinases
EOP2	end of phase 2
E-R	exposure-response
GCP	Good Clinical Practices
GSK	GlaxoSmithKline
IR	information request
IRC	independent review committee
IRC IR	Independent Review Committee-Independent Radiologist
IRC IR+IO	Independent Review Committee- Independent Radiologist and Independent Oncologist
IUO	investigational use only
IV	intravenous
MAPK	mitogen-activated protein kinases
MG	Medication Guide
NCI	National Cancer Institute
OC	Office of Compliance
ORR	objective response rate
OS	overall survival
OSI	Office of Scientific Investigations
PDUFA	Prescription Drug User Fee Act
PFS	progression-free survival
PMA	premarket approval
PMC	Postmarketing Commitment
PMR	Postmarketing Requirement
PS	Performance Status
REMS	Risk Evaluation and Mitigation Strategy
RGI	Response Genetics, Inc.
SAE	serious adverse event
(b) (4)	
TEAE	treatment emergent adverse event
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal

## Cross Discipline Team Leader Review NDA 202806 Dabrafenib (Tafinlar®)

### 1. Introduction

GlaxoSmithKline (GSK) completed a rolling submission for NDA 202806 under section 505(b)1 of the Federal Food, Drug, and Cosmetic Act on July 30, 2012. The submission was initiated on June 21, 2012 with filing of the Chemistry, Manufacturing and Controls (CMC) modules of the eCTD. In addition, data were submitted on June 29, 2012 which responded to a request from the Office of Scientific Investigations (OSI) to assist in choosing sites for inspections.

The indication proposed by GSK is: [REDACTED] (b) (4)

The initial submission included a request for priority review; however, GSK withdrew the request when multiple issues with data structure, quality and integrity arose. Therefore, this application was assigned a regular review status and has a Prescription Drug Users Fee Act (PDUFA) action date of May 30, 2013. Data-related issues have been identified throughout the conduct of the review and 21<sup>st</sup> Century Review timelines were missed for the majority of primary reviews as well as the current Cross Discipline Team Leader Review.

The major safety and efficacy data supporting the proposed indication for this application were derived from trial BRF113683, a single, multi-center, international, open-label, randomized, active-controlled trial comparing single agent dabrafenib to dacarbazine (DTIC) in patients with histologically confirmed, cutaneous unresectable or metastatic melanoma (Stage IIIc or Stage IV) determined to be BRAF V600E mutation-positive based upon centralized testing. Testing was conducted with the Response Genetics, Inc. (RGI) investigational use only (IUO) assay. A total of 250 patients were randomized (3:1) to receive dabrafenib 150 mg orally twice daily (n=187) or DTIC 1000 mg/m<sup>2</sup> intravenously (IV) once every 3 weeks (n=63). Treatment in both arms continued until disease progression, death, or patient withdrawal from study. There was one randomization stratification factor, stage of disease (unresectable stage III plus IVM1a plus IVM1b vs. stage IVM1c). The trial permitted patients with progression of disease receiving DTIC to crossover to receive dabrafenib (n=28). The major efficacy outcome measure of the trial was a comparison of investigator-assessed progression-free survival (PFS). Analyses of PFS assessed by independent, blinded, central review were also performed. Secondary endpoints included overall survival (OS) and objective response rate (ORR).

Patients enrolled on Study BRF113683 had the following demographic and baseline entry characteristics: median age was 50 years, 60% were men, 99% were White, and the majority had an ECOG performance status of 0 or 1 (dabrafenib 99%, DTIC 85%). Patients with BRAF V600E mutations were the only patients eligible for this trial.

There was a statistically significant improvement in PFS based on investigator assessments for patients treated with dabrafenib compared with those treated with DTIC [HR 0.33 (95% CI: 0.20, 0.55); p < 0.001 (stratified log-rank test)]. The median PFS was 5.1 months for patients treated on the dabrafenib arm compared with 2.7 months for those treated on the DTIC arm.

The results of PFS assessed by independent, blinded, central review were similar to and supportive of the primary analysis.

Investigator-assessed and confirmed objective response rates (ORR) were 52% (95% CI: 45%, 59%) for dabrafenib-treated patients, including 3% with complete responses, and 17% (95% CI: 9%, 29%) for DTIC-treated patients, all partial responses. There was no statistically significant difference in OS estimates for patients treated with dabrafenib versus DTIC, although median survival was not estimable for either trial arm. The OS data were not mature, but do not reflect a detriment in survival for dabrafenib-treated patients.

Overall, the size of the integrated safety database (n = 586) and duration of dabrafenib exposure (median = 4.9 months) were deemed sufficient by the clinical review team to characterize the safety of dabrafenib for treatment of patients with metastatic melanoma. The rate of treatment withdrawals, dose reductions, and dose interruptions were similar between treatment groups.

Serious adverse events (SAE) occurred in 23% of dabrafenib-treated patients, and in 22% of DTIC-treated patients. The most significant SAEs experienced by dabrafenib-treated patients were second primary malignancies, including cutaneous squamous cell carcinoma/keratoacanthoma, new primary melanomas, as well as febrile drug reactions. Grade 3 or 4 AEs occurred in 33% of dabrafenib-treated patients and 42% of patients treated with DTIC; the most frequent for patient treated with dabrafenib were pyrexia (3%), squamous cell carcinoma (3%), and back pain (3%).

The most frequent adverse reactions reported with dabrafenib were hyperkeratosis (37% dabrafenib vs. 0 DTIC), hypophosphatemia (35% vs. 14%), headache (32% vs. 9%), pyrexia (28% vs. 10%), arthralgia (27% vs. 2%), skin papilloma (24% vs. 2%), alopecia (22% vs. 2%), palmar-plantar erythrodysesthesia syndrome (20% vs. 2%), rash (17% vs. 0), cough (12% vs. 5%), back pain (12% vs. 7%), myalgia (11% vs. 0), and nasopharyngitis (10% vs. 3%).

A Risk Evaluation and Mitigation Strategy (REMS) for this product was not recommended by the clinical reviewer; however a Medication Guide was recommended based on the risk of cutaneous squamous cell carcinoma and other new primary malignancies. I concur with these recommendations.

The most significant issue arising during the review of this application related to the quality and integrity of the data submitted. This pertains especially to datasets required for the primary clinical and statistical reviews. A total of 36 separate information requests (IR) were sent to the GSK from each of the major review teams as of April 9, 2012. Additional requests were also sent after this date. In addition, the clinical and statistical teams required a number of teleconferences and face-to-face meetings with GSK to be able to confirm the results and analyses reported in the application and to be able to utilize the data provided in the application to perform their own analyses. As noted above, because of the poor quality of the submission, data discrepancies, errors, missing data, reviewer inability to confirm the applicant's results, and the amount of time reviewers were required to take in order to rectify

these problems, 21<sup>st</sup> Century Review timelines were not met for the majority of the reviews for this application.

Other significant issues noted in this review are:

- Data from trial BRF113929, (b) (4) for the effectiveness of dabrafenib in patients with brain metastases, are insufficient to support a finding of effectiveness in this population of patients. (b) (4)
- A final determination of acceptability for the facilities inspections was not made until late in the review. GSK had agreed to perform replicate (b) (4) testing going forward and submitted a proposal for doing so to the NDA on April 26, 2013 for review. The proposal was reviewed and deemed adequate by the Office of Compliance (OC) on May 3, 2013, and an overall recommendation of “acceptable” for the facilities inspection for this NDA was communicated to the review team on that date. When this issue arose, the CMC product reviewer did not agree that there was a significant risk posed (b) (4) but agreed to defer to OC on the issue.
- A premarket approval application (PMA) for the bioMerieux THxID BRAF Kit (P120014) is currently under review in the Center for Devices and Radiological Health (CDRH). The kit is intended for use as an in vitro companion diagnostic assay to detect BRAF V600E or V600K mutations in melanoma tissue to aid in the selection of patients for treatment with dabrafenib. Deficiencies remain in the application as of the date of this review. Responses to rectify the deficiencies are expected by the CDRH review team and final approval is expected.
- (b) (4) In early phase trials, objective response rates (ORR) in patients with BRAF V600K mutation-positive metastatic melanoma did not suggest the level of anti-tumor activity with dabrafenib as observed in patients with BRAF V600E mutation-positive metastatic melanoma.
- Labeling will include a limitation of use for patients with wild-type BRAF, for whom treatment with dabrafenib is not recommended.
- Insufficient data were included in the application to adequately characterize the effects of dabrafenib on the QTc and are the subject of a postmarketing requirement.
- No data were included in the application to enable dose recommendations for patients with moderate and severe hepatic impairment. This issue is the subject of a postmarketing requirement.
- No data were included in the application to enable dose recommendations for patients with severe renal impairment. This issue is the subject of a postmarketing requirement.

- Insufficient data were included in the application to adequately characterize the effects of other drugs on dabrafenib pharmacokinetics. This issue is the subject of postmarketing requirements.
- Insufficient data were included in the application for the identification and characterization of adverse reactions that occur at 1% or greater incidence rate that are associated with longer durations of exposure to dabrafenib. This issue is the subject of a postmarketing requirement.
- Additional data are needed to better characterize the incidence rates and natural history for cardiac valvular abnormalities associated with dabrafenib. This issue is the subject of a postmarketing requirement.
- Additional follow-up data are needed to better characterize the incidence rates for new primary malignancies associated with dabrafenib. This issue is the subject of a postmarketing requirement.

## 2. Background

### *Metastatic Melanoma*

As noted in the primary clinical review of Dr. Marc Theoret, melanoma is the fifth most common cancer in men and seventh most common cancer in women in the United States. Approximately 76,690 new melanoma cases will be diagnosed in the U.S. in the current year, with 9,480 deaths estimated. Melanoma develops at a relatively early age and the incidence of melanoma continues to increase with age. Metastatic melanoma accounts for approximately 4% of all newly diagnosed melanoma cases. Once metastasized, the five year survival rate for patients with melanoma is less than 10%.

BRAF gene mutations are commonly identified in human cancers including colorectal (~10%), papillary thyroid (35-70%), and melanoma. BRAF mutations are identified in 40 to 60% of patients diagnosed with melanoma. The most common mutation accounting for 75-80% of BRAF mutations in melanoma results in an amino acid conversion from valine to glutamate at amino acid residue 600 (V600E) resulting in constitutive extracellular signal-related kinase (ERK) signaling. Suppressing an activating BRAF mutation in human melanoma cells inhibits the mitogen-activated protein kinase/extracellular signal-related kinase (MAPK/ERK) pathway leading to cell growth arrest and apoptosis.

### *FDA-approved Treatment Options*

Until recently, FDA-approved treatment options for metastatic melanoma were limited to dacarbazine and interleukin-2. Hydroxyurea is also FDA-approved for melanoma, but has historical significance only. Neither dacarbazine nor interleukin-2 demonstrated an improvement in overall survival for patients treated. In clinical trials, dacarbazine has consistently demonstrated objective response rates in the 5% to 20% range, mostly partial objective responses. High-dose interleukin-2 has demonstrated similar response rates as dacarbazine, approximately 15%, but complete responses (5%) with interleukin-2 may be prolonged with median duration of response extending beyond five years.

In 2011, FDA approved ipilimumab and vemurafenib for patients with unresectable or metastatic melanoma based on demonstration of improvements in overall survival. These approvals are discussed in detail below.

### Ipilimumab

FDA approved ipilimumab (BLA 125377) on March 25, 2011 for the treatment of patients with unresectable or metastatic melanoma. Ipilimumab is a recombinant human IgG1 immunoglobulin monoclonal antibody which binds to the cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), a negative regulator of T-cell activation. Data supporting approval were from clinical trial MDX010-20, a multicenter, placebo-controlled, double-blind clinical trial that randomized 676 HLA-A2\*0201 positive patients with previously treated unresectable stage III or IV malignant melanoma in a 3:1:1 ratio to receive (a) ipilimumab in combination with gp100 peptide vaccine (b) ipilimumab plus gp100 placebo or (c) ipilimumab placebo plus gp100 peptide. Patients randomized to the ipilimumab-containing arms had a significantly longer median overall survival than the gp100 vaccine arm.

Ipilimumab prescribing information includes a warning that administration of ipilimumab may result in severe and fatal immune-mediated reactions due to T-cell activation and proliferation including enterocolitis, hepatitis, dermatitis, neuropathies, endocrinopathies, and ocular manifestations, among others. The most common adverse reactions ( $\geq 5\%$ ) observed in the supporting trial were fatigue, diarrhea, pruritis, rash, and colitis.

In addition, trial CA184024, a double-blind, placebo-controlled, multi-center, randomized (1:1) trial evaluating the efficacy and safety of ipilimumab administered in combination with dacarbazine, randomized 502 patients with previously untreated metastatic melanoma unselected by HLA-A subtype. Patients received ipilimumab (10 mg/kg) plus dacarbazine (850 mg/m<sup>2</sup>) or dacarbazine (850 mg/m<sup>2</sup>) plus placebo for 22 weeks. Patients who did not experience dose limiting toxicity and had stable disease or an objective response continued to receive ipilimumab every 12 weeks. Patients randomized to the ipilimumab arm had an improved median overall survival (11.2 months vs. 9.1 months) with a hazard ratio of 0.72 ( $p < 0.001$ , stratified log-rank test). Adverse reactions occurring at a higher incidence in ipilimumab-treated patients included elevated ALT levels (33.2% vs. 5.6%), elevated AST levels (29.1% vs. 5.6%), diarrhea (36.4% vs. 24.7%), pruritis (29.6% vs. 8.8%), and rash (24.7% vs. 6.8%).

### Vemurafenib

FDA approved vemurafenib (NDA 202429) on August 17, 2011 for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. Vemurafenib is a multi-tyrosine kinase inhibitor. The data supporting the approval was based on the results of trial NO25026, a phase III, open-label, active-control trial that randomized (1:1) 675 patients previously untreated for unresectable or metastatic melanoma to vemurafenib 960 mg orally twice daily (n=337) or dacarbazine 1000 mg/m<sup>2</sup> intravenously on Day 1 every 3 weeks (n=338). Patients randomized to the vemurafenib arm had a statistically significant increase in overall survival compared to patients randomized to the dacarbazine arm [HR 0.44 (95% CI 0.33-0.59;  $p < 0.0001$ )]. At the time of the final OS analysis, the median OS for the vemurafenib arm had not yet been reached (95% CI 9.6, NR),

while the median OS for the dacarbazine arm, after censoring patients on dacarbazine who crossed over to vemurafenib, was 7.9 months (95% CI 7.2, 9.6).

The most common NCI CTCAE grade 1 to grade 4 adverse reactions in vemurafenib-treated patients were: arthralgia (49.1%), rash (36%), alopecia (33.3%), fatigue (32.1%), nausea (30.1%), photosensitivity reaction (29.8%), diarrhea (25%), pruritus (21.4%), headache (21.3%), hyperkeratosis (19%), pyrexia (17.9%), skin papilloma (17.6%), and decreased appetite (15.8%). Additional clinically important adverse reactions associated with vemurafenib include second primary malignancies, hypersensitivity reactions, dermatologic reactions, QT prolongation, hepatic laboratory abnormalities, photosensitivity, and ophthalmologic reactions.

The following table, copied from the clinical review of Dr. Theoret, lists the FDA-approved therapies for metastatic melanoma with details on efficacy outcomes for each drug:

Drug <sup>a</sup>	Approval Year	Trial Design	Endpoint(s)	Clinical Benefit/Effect
<b>DTIC (dacarbazine)<sup>b</sup></b>	1975	Single arm	ORR	ORR 10-20%
<b>Proleukin<sup>b</sup> (interleukin-2)</b>	1998	Single-arm, multicenter	ORR	ORR 16% (CR 6%); DOR 9 months (1-122+)
<b>Yervoy<sup>b</sup> (ipilimumab)</b>	2011	Randomized, open-label, active-controlled, 3-arm	OS ORR	<b><u>Ipi vs. gp100:</u></b> OS: HR 0.66 (95% CI: 0.51, 0.87) median 10 vs. 6 months BORR: 10.9% vs. 1.5% mDOR: not reached in either arm <b><u>Ipi+gp100 vs. gp100:</u></b> OS: HR 0.68 (95% CI: 0.55, 0.85) median 10 vs. 6 months Best ORR: 5.7% vs. 1.5% mDOR: 11.5 months vs. not reached
<b>Zelboraf<sup>c</sup> (vemurafenib)</b>	2011	Randomized, active-controlled	OS PFS ORR	mOS: not reached HR: 0.44 (95% CI: 0.33, 0.59) mPFS: 5.3 months HR: 0.26 (95% CI: 0.20, 0.33) BORR: Vemurafenib: 48.4% (95% CI: 41.6%, 55.2%) CR 0.9% PR 47.4% DTIC: 5.5% (95% CI: 2.8%, 9.3%) PR: 5.5%

<sup>a</sup>Hydroxyurea is FDA approved for melanoma but not clinically relevant.

<sup>b</sup>BRAF V600 mutation status unknown

<sup>c</sup>Patient selection based on BRAF V600E mutation-positive tumor

Abbreviations in table: ORR, overall response rate; BORR, best overall response rate; OS, overall survival; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; HR, hazard ratio; CR, complete response; PR, partial response; ipi, ipilimumab

*Pre-submission Regulatory History for Dabrafenib*

The first-in human study for dabrafenib was conducted in Australia, (b) (4)  
 IND 105032 was submitted for dabrafenib on June 26, 2009 and

the proposed trial was allowed to proceed on July 24, 2009. Orphan designation for treatment of BRAF V600 mutation positive Stage IIb through IV melanoma was granted on January 12, 2011 and Fast Track designation was granted February 11, 2011 for treatment of patients with BRAF (V600E (b)(4)) mutation positive advanced melanoma.

The remaining pre-submission regulatory activities and milestones for the development of dabrafenib are discussed in Dr. Theoret's primary clinical review. A summary of these are as follows:

- On July 6, 2010, a Type B, EOP1/Pre-Phase 3 meeting was held with GSK to discuss the development program for dabrafenib for the proposed indication, treatment of patients with BRAF V600E (b)(4) mutation-positive advanced and/or metastatic melanoma. GSK also proposed to conduct two clinical trials: (1) study BRF113710, a Phase 2 single-arm, open label, study of GSK2118436 in 100 patients with BRAF mutant metastatic melanoma (Stage IV) who received prior systemic therapy to evaluate an overall response rate primary endpoint and (2) study BRF113683, a two-arm, open-label, randomized Phase 3 study comparing dacarbazine (DTIC) to the single agent GSK2118436 in 600 patients to evaluate co-primary endpoints of PFS and OS.
- FDA held a Type A Meeting on October 7, 2010 to discuss GSK's revised clinical development plan.
- (b)(4)
- FDA held a Type A meeting on December 6, 2010 to discuss the potential for an accelerated approval for GSK2118436.
- GSK2118436 received orphan designation on January 12, 2011 for the treatment of BRAFV600 mutation positive Stage IIb through IV melanoma.
- FDA granted Fast Track designation for GSK2118436 on February 11, 2011 for the treatment of patients with BRAF mutation positive (V600E (b)(4)) advanced melanoma.
- FDA granted GSK's request, submitted April 25, 2011 for a Type B meeting to discuss revisions to the ongoing Phase 2 study BRF113929 (amendment submitted April 4, 2011) to potentially allow study results to provide evidence of clinical activity in patients with BRAF V600 mutation positive metastatic melanoma with brain metastases. [Dr Theoret's review notes that no meeting minutes were located in FDA's files for this meeting].

- FDA held a Type B, Chemistry Manufacturing, and Controls Pre-NDA meeting on January 31, 2012 to review and agree upon the proposed content for the CMC section of the planned NDA.
- A Type B, Pre-NDA meeting was held on May 9, 2012, to reach agreement on the contents and format of two planned NDA/eCTD submissions [GSK2118436 and GSK112012] and to acquaint the review teams with the information and strategic intent of the information to be included in each application.

#### *NDA Submission History*

A rolling submission for NDA 202806 was completed on July 30, 2012. The submission consisted of the Administrative, Non-clinical and Clinical sections of the application. The submission was initiated on June 21, 2012 with filing of the Chemistry, Manufacturing and Controls (CMC) section of the application. In addition, data were submitted on June 29, 2012 which responded to a request from FDA's Office of Scientific Investigations (OSI) to assist in choosing sites for inspections. Because of significant deficiencies identified by multiple review teams and communicated to GSK prior to filing, GSK withdrew their request for priority review on September 27, 2012. The NDA was filed by FDA on September 28, 2012 and assigned a regular review status. There were multiple amendments to this application as a result of the poor organization and quality of the data submitted and the multiple information requests from review disciplines to the applicant during the review cycle that were necessary.

### **3. CMC/Device**

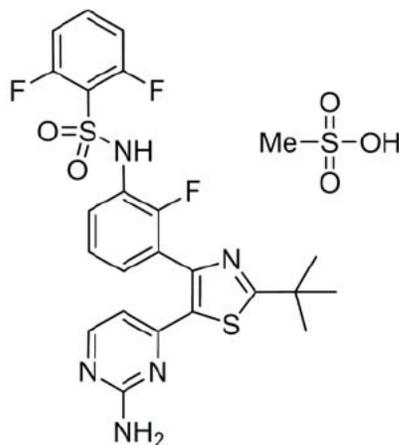
*The information in this section was adapted from the Primary CMC Reviews of Gaetan Ladouceur, Ph.D. (Drug Substance), Amit Mitra, Ph.D. (Drug Product), Akm Khairuzzaman, Ph.D. (Biopharmaceutics), Office of New Drugs Quality Assessment and the Primary Product Quality Microbiology Review of Bryan S. Riley, Ph.D., Office of Pharmaceutical Science, New Drug Microbiology Staff.*

The CMC review team has recommended the approval of this application and I concur with their recommendation.

A final determination of acceptability for the facilities inspections was not made until late in the review cycle for this application. The Office of Compliance was consulted because the inspection team did not believe that (b) (4) testing identified during the inspection allowed for a recommendation of (b) (4). (b) (4) the OC determined that the control strategy for homogeneity of the entire batch was inadequate according to the requirements of 21 CFR 211.110. The CMC product reviewer disagreed that there was a significant risk posed (b) (4) but agreed to defer to OC's determination. The issue was the subject of a teleconference with the applicant, OC and CMC review teams on April 19, 2013. During the teleconference, GSK agreed to perform replicate (b) (4) testing going forward and submitted a proposal for doing so to OC on April 26, 2013 for review. The proposal was reviewed and deemed adequate on May 3, 2013, and an

overall recommendation of “acceptable” for the facilities inspection for this NDA was communicated to the review team on that date.

The chemical name for dabrafenib mesylate is N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzene sulfonamide, methane sulfonate salt. The molecular formula is  $C_{23}H_{20}F_3N_5O_2S_2 \cdot CH_4O_3S$  and the molecular weight is 615.68 g/mol (dabrafenib mesylate). The structural formula of the molecule is shown below:



#### *Drug Product*

The proposed commercial drug product is an immediate release capsule dosage form available in two different strengths. The 50 mg capsules are dark red imprinted with “GS TEW” and “50 mg”; 75 mg capsules are dark pink imprinted with “GS LHF” and “75 mg”. Each 50 mg capsule contains 59.25 mg dabrafenib mesylate equivalent to 50 mg dabrafenib free base. Each 75 mg capsule contains 88.88 mg of dabrafenib mesylate equivalent to 75 mg of dabrafenib free base.

The micronized dabrafenib mesylate drug substance is (b) (4) with microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate (b) (4). (b) (4) hydroxypropylmethylcellulose capsules (b) (4). Dabrafenib capsules, 50 mg and 75 mg, are packed with silica gel desiccant into opaque, white HDPE bottles, and closed with (b) (4) with a (b) (4) induction heat seal liner.

The capsules were developed as simple immediate release capsule formulations. Initially, 1 mg, 5 mg, 25 mg, and 100 mg strengths of drug product were developed to allow dosing flexibility in Phase 1 clinical trials. Later 50 and 75 mg strengths were developed to allow twice a day dosing of (b) (4) 150 mg. The 50 mg and 75 mg strength capsules initially employed hard gelatin capsule shells. The hard gelatin capsule shells were replaced with hypromellose (HPMC) capsule shells because of the enhanced dissolution stability observed with hypromellose capsules. The Phase 3 study (BRF113683) and the Phase 2 study in brain metastases (BRF113929) used only hypromellose capsules.

The specification of the drug product includes: 1) Description, 2) ID for dabrafenib mesylate by UV and HPLC, 3) Content of dabrafenib by HPLC, 4) Uniformity of content by weight variation, and 5) Related substances by HPLC. (b) (4)

(b) (4) The microbial limits are being monitored at the first stability time point.

#### *Drug Substance*

Dabrafenib is a new molecular entity that has no chiral centers and is manufactured as a mesylate salt. (b) (4)

The manufacture of dabrafenib mesylate from starting materials involves (b) (4)

(b) (4) Potential and actual impurities (b) (4) were identified. The critical process parameters were identified and the reaction parameters were controlled to properly minimize the formation of these impurities.

Four related impurities, (b) (4)

The drug substance is stable under long-term and accelerated stability studies. Under forced degradation study, the drug substance was also found stable (b) (4)

(b) (4) No extraordinary storage precautions are required. A retest period of (b) (4) at the recommended controlled room temperature storage conditions is supported by drug substance stability data.

The applicant provided satisfactory information on the manufacturing, control and stability of the drug substance.

#### *Biopharmaceutics*

Dabrafenib mesylate is very slightly soluble at pH 1 and practically insoluble in the pH range of 4 to 8 in aqueous media (b) (4) used for the drug product manufacture). It has high bioavailability and therefore, this drug can be classified as a BCS class II compound. The molecule has a log P value of 2.9 indicating its high lipophilicity and has three different pKa such as 6.6, 2.2 and -1.5. The particle size distribution of micronized dabrafenib mesylate is designated as a drug substance Critical Quality Attributes (CQA) based on its potential impact on bioavailability.

The drug product is a capsule dosage form formulated with excipients such as microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate. Detail studies were conducted to evaluate the impact of variability (coming from formulation and process) on dissolution.

There are no pending biopharmaceutics related issues with this NDA, nor are there microbiological issues with this non-sterile oral dosage form.

#### *Facilities review/inspection*

Inspections were conducted of manufacturing sites for both drug product and drug substance in Ontario, Canada and Singapore, respectively. The status of the facilities inspection reports is “acceptable”.

#### *CDRH Review of the Companion Diagnostic*

The bioMérieux THxID™ –BRAF Kit was submitted to CDRH as PMA120014 on August 31, 2012. The kit is a companion diagnostic test used to select patients with metastatic melanoma for treatment when the test demonstrates that their tumor tissue has mutations in the BRAF gene identified as either BRAF V600E or BRAF V600K mutations. CDRH was first consulted in April, 2010 regarding the companion diagnostic component of this application. Shortly thereafter, GSK submitted a pre-IDE (I100245) to obtain feedback on the development of the companion diagnostic BRAF test. The pre-IDE included information about the test that was applied in Phase I trials. The test was designed and operated by Response Genetics Institute (RGI). This test is referred to as the RGI LDT in the supplements to the pre-IDE. RGI made adjustments to the test based on CDRH feedback and used the revised version of the test in the phase II and phase III trials. This test was referred to as the RGI IUO. GSK partnered with bioMérieux to design and implement the commercial version of the BRAF test to select patients for treatment with dabrafenib and trametinib (NDA 204114 currently under review). Discussions for the co-development project were conducted under pre-IDE number I110489.

The THxID™ –BRAF Kit is an *In Vitro Diagnostic* device intended for the qualitative detection of the BRAF V600E and V600K mutations in DNA samples extracted from formalin-fixed, paraffin-embedded (FFPE) human melanoma tissue. The THxID™ –BRAF Kit is a real-time PCR test on the ABI 7500 Fast Dx system and is intended to be used as an aid in selecting melanoma patients whose tumors carry the BRAF V600E and the BRAF V600K mutation for treatment with dabrafenib or trametinib.

There were significant deficiencies in the original PMA application and as of the date of this review, responses to rectify some of the deficiencies are still expected by the CDRH review team. An approval is expected. Please refer to CDRH’s Summary of Safety and Effectiveness Data for this PMA, which will be filed on the CDRH website after there is an action on the application.

## **4. Nonclinical Pharmacology/Toxicology**

*The information in this section was adapted from the Primary Pharmacology/Toxicology Review of Alexander Putman, Ph.D. and Shawna Weis, Ph.D., Division of Hematology Oncology Toxicology*

The Pharmacology/Toxicology review team has recommended approval for this application. I concur with this recommendation. There are no unresolved issues with this application from a Pharmacology/Toxicology perspective.

*General nonclinical pharmacology/toxicology considerations*

Nonclinical pharmacology studies conducted *in vitro* and *in vivo* demonstrated that dabrafenib is an inhibitor of wild-type BRAF (IC<sub>50</sub> = 3.2 nM), wild-type CRAF (IC<sub>50</sub> = 5 nM), and some mutant forms of BRAF kinases. Specifically, dabrafenib inhibited BRAFV600E, BRAFV600K, and BRAFV600D kinases with IC<sub>50</sub> values of 0.65, 0.5 and 1.84 nM, respectively. Dabrafenib-induced inhibition of BRAF kinases were time-dependent, reversible, and ATP-competitive. *In vitro* incubation with dabrafenib also led to decreased phosphorylation of ERK in cell lines and produced tumor growth inhibition in mice bearing BRAFV600E mutant human tumor xenografts.

Dabrafenib exhibited high oral bioavailability in animals (46-82%), moderate- to low clearance, particularly in dogs (< 12% hepatic blood flow), and strong protein binding (>98% in all species tested, including human). *In vivo* distribution studies indicated that dabrafenib was widely distributed to most major organs. Elimination of dabrafenib in humans occurs predominantly via the fecal route (~71% of administered dose) and in urine (~22%). This elimination profile is distinct from both nonclinical species, which exhibited ~ 1% or less urinary elimination of dabrafenib.

Dabrafenib was a moderate inhibitor of CYP3A4, CYP2C9, and CYP2C19, a weak inhibitor of CYP1A2 and CYP2D6, and a substrate of human P-glycoprotein. The three main dabrafenib metabolites in humans were GSK2285403 (M7; hydroxyl-dabrafenib), GSK2298683 (M4; carboxy-dabrafenib), and GSK2167542 (M8; desmethyl-dabrafenib). Following administration of the recommended twice daily 150 mg dose of dabrafenib, these three metabolites were present at human plasma levels (AUC<sub>0-24</sub>) of approximately 8, 100, and 6 µg h/mL, respectively. All three metabolites were also present in rats and dogs during the 13-week repeat-dose toxicity studies. Specifically, animals tolerated GSK2285403 at plasma levels (AUC<sub>0-24</sub>) ≥ 4 times the level of human exposure following the recommended dose of dabrafenib. At the maximum tolerated dose in animals, GSK2167542 and GSK2298683 plasma exposure levels (AUC<sub>0-24</sub>) were up to approximately 30% and 50% of human exposure levels, respectively. Based on these data and the indicated advanced cancer patient population, the safety of these metabolites is believed to present a minimal risk.

*Carcinogenicity*

Dabrafenib was not mutagenic *in vitro* in the bacterial reverse mutation assay (Ames test) or the mouse lymphoma assay, and was not clastogenic in an *in vivo* rat bone marrow micronucleus test. Carcinogenicity studies were not conducted or required for dabrafenib due to its intended use in patients with advanced cancer.

*Reproductive toxicology*

Dabrafenib was evaluated in a combined fertility and embryo-fetal study in Sprague-Dawley rats. Plasma exposure levels (AUC<sub>0-24</sub>) were up to 3 times the exposure level in humans receiving the recommended dose of dabrafenib. Dabrafenib-induced toxicity included cardiac malformations in developing fetuses (cardiac ventricular septal defects), and a number of visceral and skeletal malformations, including misshapen or split thymuses and decreased skeletal ossification. Dabrafenib also caused a decrease in the number of corpora lutea,

implantations, and live fetuses, an increase in pre- and post-implantation loss, and a reduction in fetal body weights.

## 5. Clinical Pharmacology/Biopharmaceutics

*The information in this section was adapted from the Primary Clinical Pharmacology and Primary Pharmacometrics Reviews of Jian Wang, Ph.D. and Justin Earp, Ph.D., Division of Clinical Pharmacology V, Division of Oncology Products 2.*

The clinical pharmacology review team recommends approval of this NDA and I concur with their recommendation. A number of postmarketing requirements were recommended by the review team and these are listed below in section 13 of this review.

### *General Considerations*

Dabrafenib is a potent, selective, ATP- competitive inhibitor of RAF kinases. The applicant's proposed indication for dabrafenib is for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation. The proposed dose regimen is 150 mg orally twice daily. The development program contains limited data on dose-response and the applicant has not conducted individual dose-response trials. The Clinical Pharmacology review, however, included analyses of exposure-response relationships. The results suggest that for exposures of dabrafenib, including its metabolites, above and below the median active concentration (99.6 ng/mL) there is no trend toward increasing PFS with increasing exposure.

### *Absorption*

After oral administration of dabrafenib, the median time to achieve peak plasma concentration is 2 hours. Mean absolute bioavailability of oral dabrafenib is 95%. Dabrafenib exposure ( $C_{max}$  and AUC) increased in a dose proportional manner between 12 and 300 mg following single-dose administration, but the increase was less than dose-proportional after repeat twice daily dosing. This observed decrease in exposure with repeat dosing is likely because of induction of its own metabolism. Mean accumulation ( $AUC_{Day18/Day1}$ ) ratios averaged 0.73. Following administration of 150 mg dabrafenib twice daily, geometric mean (CV%)  $C_{max}$ ,  $AUC_{(0-\tau)}$ , and predose concentration values were 1,478 ng/mL (37%), 4,341 ng\*hr/mL (38%), and 26 ng/mL (119%), respectively.

### *Food effect*

Administration of a single 150 mg dose of dabrafenib capsules with a high-fat meal decreased its  $C_{max}$  and AUC by 51% and 31%, respectively, when compared to the fasted state.

### *Distribution*

The apparent volume of distribution at steady-state is 70.3 L. Dabrafenib is 99.7% bound to human plasma proteins.

### *Metabolism*

The metabolism of dabrafenib is primarily mediated by CYP2C8 and CYP3A4 to form hydroxy-dabrafenib, which is further oxidized via CYP3A4 to form carboxy-dabrafenib and

is excreted in bile and urine. Carboxy-dabrafenib can be decarboxylated via a non-enzymatic process in the gut to form desmethyl-dabrafenib and reabsorbed. Desmethyl-dabrafenib is metabolized by CYP3A4 to oxidative metabolites. Hydroxy-dabrafenib terminal half-life of 10 hours parallels that of the parent drug while the carboxy- and desmethyl- metabolites exhibited longer half-lives (21 to 22 hours). Mean metabolite to parent AUC ratios following repeat-dose administration were 0.9, 11, and 0.7 for hydroxy-, carboxy-, and desmethyl-dabrafenib, respectively. Based on exposure, relative potency and pharmacokinetic properties, both hydroxy- and desmethyl-dabrafenib are likely to contribute to the clinical activity of dabrafenib; the activity of carboxy-dabrafenib is not likely to be clinically meaningful.

#### *Drug-drug interactions*

Dabrafenib induces cytochrome P450 isoenzyme (CYP) 3A4-mediated metabolism and may induce other enzymes including CYP2B6, CYP2C8, CYP2C9, and CYP2C19. Dabrafenib and its active metabolites are primarily metabolized by CYP2C8 and CYP3A4. Strong inhibitors or inducers of CYP3A4 or CYP2C8 may increase or decrease systemic exposure to dabrafenib, respectively. The effects of strong inhibitors or inducers of CYP3A4 or CYP2C8 on pharmacokinetics of dabrafenib *in vivo* will be studied under postmarketing requirements (PMR).

#### *Elimination*

The elimination half-life of dabrafenib is 8 hours after oral administration and 2.6 hours following an intravenous micro dose with plasma clearance of 12 L/hr. Fecal excretion is the major route of elimination accounting for 71% of a radioactive dose while urinary excretion accounts for 23% of radioactivity.

#### *Intrinsic factors*

Body weight and gender were significant covariates in the population PK model; however, neither affected the clearance sufficiently to warrant dose adjustments. Gender did not decrease clearance by more than 10% for females compared to males. Additionally, no difference was noted by the Clinical Pharmacology reviewer in the median PFS between those with the lowest half of exposures versus those with the highest half of exposures after administration of 150 mg twice daily. Race was not evaluated as a covariate in the population PK analysis because all the patients in the registration trial were white.

#### *Demographic interactions/special populations*

Age was not identified as a covariate on the PK of dabrafenib using a population PK analysis.

The pharmacokinetics, safety and effectiveness in pediatric patients were not studied.

No formal PK study in patients with renal impairment was conducted. The PK of dabrafenib was evaluated using a population analysis in 233 patients with mild renal impairment (GFR 60-89 mL/min/1.73 m<sup>2</sup>) and in 30 patients with moderate renal impairment (GFR 30-59 mL/min/1.73 m<sup>2</sup>) enrolled in clinical trials. Mild or moderate renal impairment has no effect on systemic exposures to dabrafenib and its metabolites. No data are available in patients with

severe renal impairment. As urinary excretion accounts for 23% of total drug elimination, a post-marketing requirement (PMR) was recommended by the Clinical Pharmacology review team for a PK study of dabrafenib to determine the appropriate dose in patients with severe renal impairment. I agree with this recommendation.

No formal PK study in patients with hepatic impairment has been conducted. The PK of dabrafenib was evaluated using a population analysis in 65 patients with mild hepatic impairment enrolled in clinical trials. The effect of mild hepatic impairment (as defined by bilirubin  $\leq$  upper limit of normal [ULN], aspartate aminotransferase [AST]  $>$ ULN, or bilirubin  $>1$  to 1.5 times ULN; AST: any value), had no effect on systemic exposures to dabrafenib and its metabolites.

No data are available in patients with moderate to severe hepatic impairment. As fecal excretion accounts for 71% of the total drug elimination, a post-marketing requirement was recommended by the Clinical Pharmacology review team for a PK study of dabrafenib to determine the appropriate doses in patients with moderate or severe hepatic impairment. I agree with this recommendation.

#### *Genomics*

The Genomics reviewer assessed whether in two Phase 2 studies, BREAK-MB and BREAK-2, BRAF V600E and V600K mutations are associated with distinct clinicopathologic features and whether tumor responses in patients with metastatic melanoma differ by the specific BRAF V600 mutation. The analysis demonstrated an association among BRAF mutation status, age at screening and gender. A greater proportion of patients with BRAF V600K mutations were male and older at screening compared to patients with the V600E mutation suggesting that mutant genotypes may define a subgroup of patients with distinct phenotypes. Although pre-clinical data show similar IC50 values for the V600E and V600K mutations, limited clinical data from Phase 2 studies suggest marginal dabrafenib activity in patients with the BRAF V600K mutation compared to patients harboring the V600E mutation.

Because (1) limited antitumor activity was observed in V600K patients in Phase 2 trials, (2) V600K patients were excluded from Phase 3, and (3) V600K patients may represent a distinct subset of melanoma patients with distinct clinicopathologic features, the genomics reviewer believes it is reasonable to exclude V600K patients from the indication to be granted for this drug. I concur with this recommendation.

#### *QT assessment*

There were inadequate data submitted to rule out the possibility of QT/QTc prolongation associated with dabrafenib. A postmarketing clinical trial evaluating the potential for dabrafenib to prolong the QT/QTc interval in accordance with the principles of ICH E14 is being required of the applicant.

## **6. Clinical Microbiology**

Not applicable to this NDA.

## 7. Clinical/Statistical- Efficacy

*The information in this section was adapted from the clinical review of Marc Theoret, M.D., Division of Oncology Products 2 and the statistical review of Weishi Yuan, Office of Biostatistics*

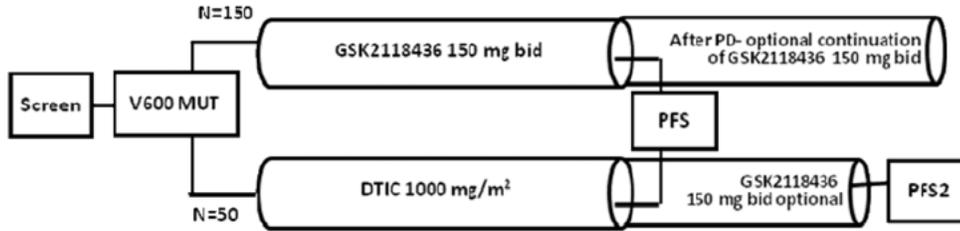
The clinical and statistical reviewers recommend approval for this application and I concur with their recommendations

Submitted with this application were the data from five trials intended to support the proposed indication; however, the primary evidence of efficacy is based on the results of a single randomized, active-controlled trial. The clinical studies of dabrafenib in the melanoma development program submitted with this NDA are listed in the table below which was adapted from Dr. Theoret's clinical review.

Trial ID	Purpose	Formulation	Sites	Countries	Subjects
BRF113683	Efficacy /Safety	HPMC	70	United States, Canada, Australia, Germany, France, Italy, Spain, Poland, Russia, Netherlands, Ireland, Hungary	250
BRF113710	Efficacy /Safety	Gelatin capsule	21	United States, Australia, France, Germany, Italy	92
BRF113929	Efficacy /Safety	HPMC	24	United States, Canada, Australia, France, Germany, Italy	172
BRF113220, Part C	Safety	Gelatin capsule	16	United States, Australia	53 <sup>a</sup>
BRF112680	Safety	Gelatin capsule	8	United States, Australia	184

Study BRF113683 is the trial supporting the assessment of clinical benefit for this application. It was a multi-center, international, open-label, randomized (3:1), active-controlled trial comparing dabrafenib to DTIC in patients with histologically confirmed, cutaneous, unresectable or metastatic melanoma (Stage IIIc or Stage IV), determined to be BRAF V600E mutation-positive based upon centralized testing. There was one randomization stratification factor: stage of disease (unresectable stage III plus IVM1a plus IVM1b vs. stage IVM1c). The primary endpoint of the trial was progression-free survival (PFS) assessed by investigators. Secondary endpoints included overall survival (OS) and objective response rate (ORR). A total of 250 patients were randomized, 187 to the dabrafenib arm and 63 to the DTIC arm. The trial was designed to have > 95% power, at a one-sided alpha level of 2%, to detect a 200% increase in median PFS (HR of 0.33) in patients with BRAF V600E mutation-positive melanoma, assuming a median PFS of 2 months in the DTIC arm and 6 months in the

dabrafenib arm. The primary analysis of PFS was to be estimated using the Kaplan-Meier method and compared using a log-rank test stratified on disease staging. The trial design is included in the figure below, which was copied from the applicant’s submission.



Patient demographics and baseline disease characteristics were balanced as demonstrated in the following two tables copied from Dr. Theoret’s review. Patients were predominantly male, younger than 65 years of age, Caucasian, and enrolled in Europe. At enrollment, the majority of patients had an Eastern Cooperative Oncology Group (ECOG) Performance Status of zero, Stage IV M1c disease, visceral involvement, and normal LDH.

**Trial BRF113683 Demographics**

	<b>Dabrafenib N= 187 n (%)</b>	<b>DTIC N=63 n (%)</b>
<b>Gender</b>		
Male	112 (60)	37 (59)
Female	75 (40)	26 (41)
<b>Race</b>		
Caucasian	184 (98)	63 (100)
Non-Caucasian	3 (2)	0
<b>Age</b>		
< 65	146 (78)	51 (81)
≥ 65	41 (22)	12 (19)
<b>Region</b>		
Europe	140 (75)	44 (70)
North American	36 (19)	14 (22)
Australia	11 (6)	5 (8)

**Trial BRF113683 Baseline Disease Characteristics**

	<b>Dabrafenib N= 187 n (%)</b>	<b>DTIC N=63 n (%)</b>
<b>BRAF V600 Mutation Subtype</b>		
V600E	186 (>99)	62 (98)
V600K	1 (<1)	1 (2)
<b>ECOG Status at Baseline</b>		
0	124 (66)	44 (70)
1	62 (33)	16 (25)
Missing	1 (0.5)	3 (5)
<b>Stratum at Randomization: Disease Staging</b>		
Unresectable III+IVM1a+IVb	63 (34)	21 (33)
IVM1c	124 (66)	42 (67)
<b>Stratum per e-CRF: Disease Staging</b>		
Unresectable III+IVM1a+IVb	63 (34)	23 (37)
IVM1c	124 (66)	40 (63)
<b>Baseline LDH</b>		
Above ULN	66 (35)	17 (27)
Equal to or below ULN	116 (62)	40 (63)
Missing	5 (3)	6 (10)
<b>Visceral disease</b>		
Visceral	22 (12)	8 (13)
Non-visceral	50 (27)	20 (32)
Visceral and non-visceral	115 (61)	35 (56)
<b>Number of disease sites</b>		
< 3	94 (50)	35 (56)
≥ 3	93 (50)	28 (44)
<b>Tumor classification at Initial Diagnosis</b>		
Cutaneous	165 (88)	56 (89)
Non-cutaneous	6 (3)	2 (3)
Other	3 (2)	0
Unknown	13 (7)	5 (8)
<b>Prior Therapy</b>		
Radiotherapy	37 (20)	10 (16)
Surgery	179 (96)	61 (97)

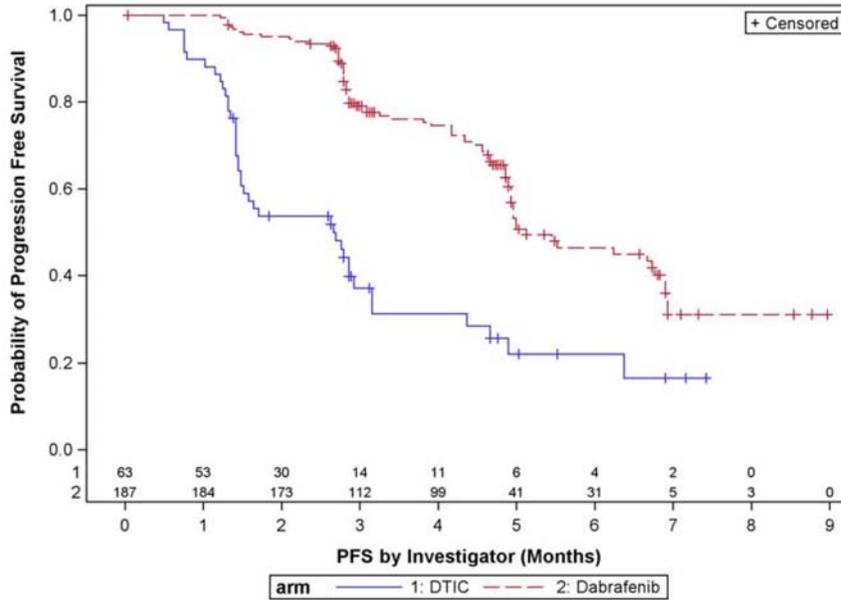
	<b>Dabrafenib</b> N= 187 n (%)	<b>DTIC</b> N=63 n (%)
Immunotherapy	52 (28)	15 (24)
Biologic Therapy	3 (2)	3 (5)
Chemotherapy	1 (0.5)	4 (6)
Hormonal Therapy	0	1 (2)

There was a statistically significant improvement in PFS based on investigator assessment for patients treated with dabrafenib compared with those treated with DTIC [HR 0.33 (95% CI: 0.20, 0.55); p < 0.001]. There was a median PFS of 5.1 months for the dabrafenib arm compared with 2.7 months for the DTIC arm. The results of PFS assessed by independent, blinded, central review were similar to those of the investigator assessment.

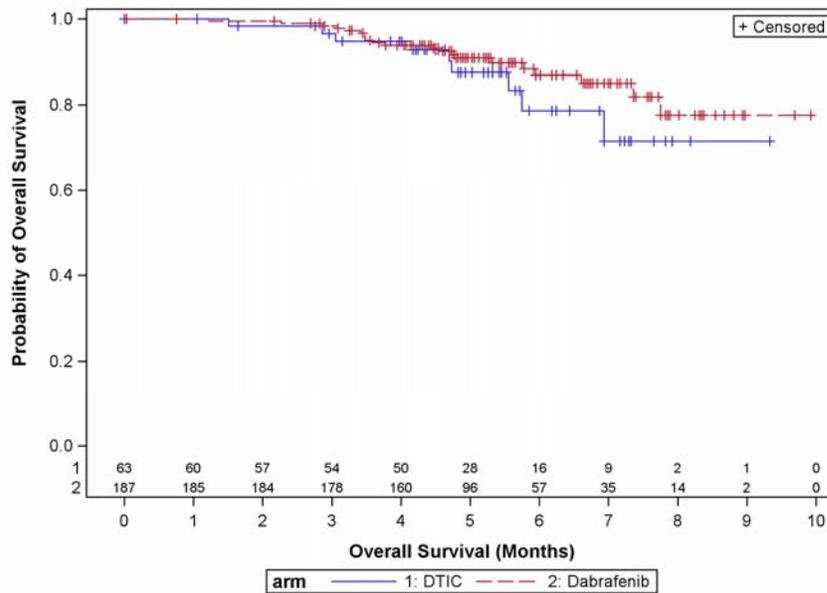
There was no statistically significant difference in OS between the treatment arms. With a total of 30 deaths, median survival for the two arms were not estimable [HR 0.67 (95% CI: 0.28, 1.58); p = 0.31 (based on a Pike unstratified estimating test)] and the OS data were not mature. A comparative analysis of PFS based on different assessment sources and the Kaplan-Meier estimates for the PFS and OS results for trial BRF113683, copied from Dr. Theoret's review, follow:

	Primary Analysis		Blinded, Independent Review Committee			
	INV-PFS		Ind Radiologist-PFS		Ind Radiologist + Oncologist-PFS	
	Dabrafenib N = 187	DTIC N = 63	Dabrafenib N = 187	DTIC N = 63	Dabrafenib N = 187	DTIC N = 63
<b>Number of Events (%)</b>	78 (42)	41 (65)	61 (33)	29 (46)	68 (36)	33 (52)
Progressive Disease	76	41	56	29	63	33
Death	2	0	5	0	5	0
<b>Duration of PFS, months</b>						
Median PFS (95% CI)	5.1 (4.9, 6.9)	2.7 (1.5, 3.2)	6.7 (5.0, 5.9)	4.4 (1.6, NE)	6.5 (4.9, 6.9)	2.9 (1.5, 4.9)
p-value (unstratified log-rank)	< 0.001		<0.001		<0.001	
HR (95% CI)	0.33 (0.20, 0.55)		0.36 (0.20, 0.51)		0.36 (0.21, 0.62)	

### Plots of Kaplan-Meier Estimates for PFS by Treatment Arm, Trial BRF113683



### Plots of Kaplan-Meier Estimates for OS, Trial BRF113683



Investigator assessment of the PFS responses was included in the applicant's original statistical analysis plan and the statistical reviewer has commented that, in general, the analysis plan followed FDA's Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics.

It was noted by Dr. Theoret, that the FDA primary efficacy analysis, as well as the supporting analyses of PFS based on blinded, independent central review, provide numerically different

results than those presented in the clinical study report for Trial BRF113683. In spite of this discrepancy, these analyses confirmed the treatment effect for dabrafenib.

The clinical and statistical reviewers could not validate the derivations of tumor response data based on raw tumor measurements because of the submission quality issues discussed previously. Their analyses of PFS re-derived tumor response data according to RECIST version 1.1 using raw datasets containing tumor measurements as documented by the investigator or the independent radiologist rather than the derived overall tumor response assessment (e.g., complete response, partial response, stable disease, etc.). The raw data provided to support each tumor assessment by the independent oncologist in the datasets was inadequate to permit verification of the PFS endpoint using a blinded independent central review assessment which included tumor assessments performed by the independent oncologist.

The investigator-assessed, confirmed objective response rate (ORR) was 52% (95% CI: 45%, 59%) for patients on the dabrafenib treatment arm and 17% (95% CI: 9%, 29%) for those on the DTIC treatment arm. The median duration of response was 5.6 months (95% CI: 5.4, not estimable) on the dabrafenib treatment arm and was not estimable on the DTIC arm. The ORR rates and duration of responses as assessed by the IRC were similar to those based on investigator assessment.

As discussed previously, both the statistical and clinical reviewers found the quality of the original data submission to be inadequate to evaluate and review the submission. Problems included poor data organization and management, missing data variables, data sets and documents, un-executable SAS programs, and lack of documentation throughout the entire data submission. Numerous formal data quality related information requests were sent to the applicant to request additional data, documentation, and programs. The reviewers had multiple face-to-face meetings, telephone-conferences and email communications with the applicant. As a result, the applicant withdrew the priority review request voluntarily and a standard review was conducted. The final analysis data included in the primary reviews were derived by the reviewers from raw data. For a full evaluation of the quality issues with this application, please refer to the primary clinical and statistical reviews.

## **8. Safety**

*The information in this section was adapted from the Primary Clinical Review of Marc Theoret, M.D., Division of Oncology Products 2.*

The size of the integrated safety database and duration of dabrafenib exposure were deemed acceptable by the clinical reviewer to characterize the safety of dabrafenib for treatment of patients with advanced cutaneous melanoma.

The primary review of safety focused on analyses of data for trial BRF113683 because it was the only randomized, comparative trial submitted to support the safety of dabrafenib and the trial also administered the dabrafenib formulation intended for marketing (HPMC formulation). Other trials submitted in support of the application were conducted with the

gelatin capsule formulation which demonstrated decreased exposure compared to the HPMC formulation.

The safety of dabrafenib in trial BRF113683 was evaluated in 250 patients with BRAF V600E mutation-positive, advanced (unresectable, stage III) or metastatic (stage IV) melanoma, previously untreated, who received either dabrafenib 150 mg orally twice daily or DTIC 1000 mg/m<sup>2</sup> IV every 3 weeks until disease progression or unacceptable toxicity. The median duration of treatment was 4.9 months for dabrafenib-treated patients (n=187) and 2.8 months for DTIC-treated patients (n=59). The mean daily dose intensity for dabrafenib was 95% and the mean relative weekly dose intensity (mg/m<sup>2</sup>/week) for DTIC was 93%. Eighteen percent of dabrafenib-treated patients required at least one dose reduction and permanent discontinuation of study medication was 3% for patients in both arms of the trial.

The most frequent (≥2%) adverse reactions leading to dose reduction were pyrexia (9%), palmar-plantar erythrodysesthesia syndrome (PPES) (3%), chills (3%), and fatigue (2%). Grade 3-4 adverse reactions which occurred in ≥ 2% of dabrafenib-treated patients were hyperglycemia, hypophosphatemia, cutaneous squamous cell carcinoma, pyrexia, back pain, and PPES.

The following table copied from Dr. Theoret’s review lists adverse reactions occurring in ≥ 5% of patients treated with dabrafenib in trial BRF113683.

	<b>Dabrafenib N=187 n (%)</b>		<b>DTIC N=59 n (%)</b>	
	<b>All Grades</b>	<b>Grades 3-4</b>	<b>All Grades</b>	<b>Grades 3-4</b>
Hyperkeratosis	69 (37)	2 (1)	0	0
Headache	59 (32)	0	5 ( 9)	0
Pyrexia	52 (28)	6 (3)	6 (10)	0
Arthralgia	51 (27)	2 (1)	1 ( 2)	0
Papilloma <sup>a</sup>	51 (27)	0	1 ( 2)	0
Alopecia	41 (22)	0	1 ( 2)	0
PPES	37 (20)	4 (2)	1 ( 2)	0
Fatigue	36 (19)	2 (1)	14 (24)	0
Nausea	35 (19)	1 (1)	29 (49)	0
Asthenia	33 (18)	1 (1)	9 (15)	1 (2)
Rash	31 (17)	0	0	0
Vomiting	23 (12)	2 (1)	15 (25)	0
Cough	23 (12)	0	3 ( 5)	0
Back pain	22 (12)	5 (3)	4 ( 7)	0
Constipation	21 (11)	3 (2)	8 (14)	0
Diarrhea	20 (11)	1 (1)	7 (12)	0
Myalgia	20 (11)	0	0	0
Nasopharyngitis	19 (10)	0	2 ( 3)	0

	<b>Dabrafenib N=187 n (%)</b>		<b>DTIC N=59 n (%)</b>	
	<b>All Grades</b>	<b>Grades 3-4</b>	<b>All Grades</b>	<b>Grades 3-4</b>
Chills	17 ( 9)	0	1 ( 2)	0
Pain in extremity	16 ( 9)	1 (1)	7 (12)	0
Decreased appetite	16 ( 9)	0	5 ( 9)	2 (3)
Dry skin	16 ( 9)	0	0	0
Erythema	14 ( 8)	0	1 ( 2)	0
cuSCC <sup>b</sup>	14 ( 7)	8 (4)	0	0
Musculoskeletal pain	13 ( 7)	0	2 ( 3)	0
Dyspnea	12 ( 6)	2 (1)	2 ( 3)	0
Actinic keratosis	12 ( 6)	0	0	0
Paraesthesia	11 ( 6)	1 (1)	2 ( 3)	0
Seborrheic keratosis	10 ( 5)	0	0	0
Pruritus	10 ( 5)	0	1 ( 2)	0
Upper abdominal pain	9 ( 5)	0	1 ( 2)	0
Peripheral edema	9 ( 5)	0	5 ( 9)	0
Weight decreased	9 ( 5)	0	1 ( 2)	0
Acrochordon	9 ( 5)	0	0	0
Melanocytic nevus	9 ( 5)	0	0	0
Oropharyngeal pain	9 ( 5)	0	1 ( 2)	0
Skin lesion	9 ( 5)	0	0	0

Abbreviations in Table: PPES, palmar-plantar erythrodysesthesia syndrome

<sup>a</sup> Composite term including skin papilloma, papilloma

<sup>b</sup> Composite term including squamous cell carcinoma of the skin, squamous cell carcinoma, keratoacanthoma

The integrated safety database included adverse event data from five trials and included 586 patients. The applicant's integrated summary of safety presented the most common ( $\geq 10\%$  of patients) treatment-emergent adverse events (TEAE) occurring in dabrafenib-treated patients on BRF113683 as well as in the entire ISS database. Fatigue, nausea, vomiting, diarrhea, extremity pain, and decreased appetite occurred at a higher incidence ( $\geq 5\%$  difference) in the integrated safety database than in BRF113683.

Overall, 21 patients randomized to the dabrafenib arm (11%) and 9 patients (11%) randomized to the DTIC arm (4 patients after initial progression on DTIC and cross-over to treatment with dabrafenib) died by the time of the clinical data cut-off for trial BRF113683. Advanced melanoma was the most commonly reported cause of death and accounted for all but one death in the dabrafenib-treatment group and all deaths in the DTIC-treatment group. Overall, the occurrence of treatment-emergent deaths (within 30 days of investigational product dosing) in trial BRF113683 was 4.3% and 6.8% of the patients in the dabrafenib-treatment and DTIC-treatment groups, respectively.

Non-fatal serious adverse events (SAE) occurred in 23% (42/187) of patients in the dabrafenib treatment group and 22% (13/59) of patients in the DTIC treatment group in trial BRF113683. The most frequently reported, non-fatal SAEs in the dabrafenib treatment group compared to the DTIC treatment group were squamous cell carcinoma (4% vs. 0), pyrexia (4% vs. 0), squamous cell carcinoma of skin (2% vs. 0), and melanoma (2% vs. 0). The table below, copied from Dr. Theoret's safety review, lists the non-fatal SAEs reported in the randomized trial.

	<b>Dabrafenib N=187 n (%)</b>	<b>DTIC N=59 n (%)</b>
<b>PATIENTS WITH AT LEAST ONE SAE</b>	<b>42 (22.5)</b>	<b>13 (22.0)</b>
<b>NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)</b>	<b>12 (6.4)</b>	<b>0</b>
Squamous cell carcinoma	7 (3.7)	0
Malignant melanoma	3 (1.6)	0
Squamous cell carcinoma of skin	3 (1.6)	0
Basal cell carcinoma	1 (0.5)	0
<b>GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS</b>	<b>8 (4.3)</b>	<b>1 (1.7)</b>
Pyrexia	7 (3.7)	0
Chills	1 (0.5)	0
Influenza like illness	1 (0.5)	0
<b>GASTROINTESTINAL DISORDERS</b>	<b>6 (3.2)</b>	<b>2 (3.4)</b>
Vomiting	2 (1.1)	1 (1.7)
Constipation	1 (0.5)	1 (1.7)
Hemorrhoidal hemorrhage	1 (0.5)	0
Ileus	1 (0.5)	0
Nausea	1 (0.5)	1 (1.7)
Pancreatitis	1 (0.5)	0
Small intestinal perforation	1 (0.5)	0
<b>METABOLISM AND NUTRITION DISORDERS</b>	<b>5 (2.7)</b>	<b>0</b>
Dehydration	1 (0.5)	0
Diabetes mellitus	1 (0.5)	0
Diabetes mellitus inadequate control	1 (0.5)	0
Hyperlipasemia	1 (0.5)	0
Hyponatremia	1 (0.5)	0
Hypophosphatemia	1 (0.5)	0
<b>CARDIAC DISORDERS</b>	<b>4 (2.1)</b>	<b>1 (1.7)</b>
Atrial fibrillation	2 (1.1)	0
Cardiac failure congestive	1 (0.5)	0
Myocardial infarction	1 (0.5)	0

	<b>Dabrafenib N=187 n (%)</b>	<b>DTIC N=59 n (%)</b>
<b>INFECTIONS AND INFESTATIONS</b>	<b>3 (1.6)</b>	<b>2 (3.4)</b>
Erysipelas	1 (0.5)	0
Localized infection	1 (0.5)	0
Pleural infection	1 (0.5)	0
Sepsis	0	1 (1.7)
<b>INVESTIGATIONS</b>	<b>3 (1.6)</b>	<b>1 (1.7)</b>
Ejection fraction decreased	2 (1.1)	0
Blood creatinine increased	1 (0.5)	0
<b>MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS</b>	<b>3 (1.6)</b>	<b>0</b>
Back pain	1 (0.5)	0
Joint effusion	1 (0.5)	0
Muscular weakness	1 (0.5)	0
Pain in extremity	1 (0.5)	0
<b>NERVOUS SYSTEM DISORDERS</b>	<b>3 (1.6)</b>	<b>1 (1.7)</b>
Presyncope	1 (0.5)	0
Syncope	1 (0.5)	0
Transient ischemic attack	1 (0.5)	0
<b>RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS</b>	<b>3 (1.6)</b>	<b>1 (1.7)</b>
Hypoxia	1 (0.5)	0
Pleural effusion	1 (0.5)	0
Pleuritic pain	1 (0.5)	0
Pulmonary embolism	1 (0.5)	1 (1.7)
Pulmonary edema	1 (0.5)	0
Respiratory distress	1 (0.5)	0
<b>VASCULAR DISORDERS</b>	<b>3 (1.6)</b>	<b>0</b>
Hypotension	2 (1.1)	0
Hemorrhage	1 (0.5)	0

The most common ( $\geq 10\%$ ) laboratory abnormalities representing an increase in toxicity grade from baseline in dabrafenib-treated patients compared to DTIC-treated patients were hyperglycemia (50% vs. 42%), decreased phosphorus (35% vs. 14%), anemia (21% vs. 36%), increased alkaline phosphatase (19% vs. 14%), decreased lymphocyte count (18% vs. 27%), decreased WBC count (11% vs. 44%), and increased ALT (11% vs. 22%). Grade 3 or 4 laboratory abnormalities occurring more frequently in dabrafenib-treated patients include hyperglycemia (6% vs. 0) and decreased phosphorus (5% vs. 2%).

#### *Malignancies*

Based on preclinical evidence as well as clinical data with vemurafenib and dabrafenib, second primary malignancies are a concern with BRAF inhibitors. Cutaneous squamous cell carcinoma/keratoacanthoma developed in 24% of patients receiving vemurafenib. Nine

patients (5%) in the dabrafenib-treatment group compared to no patients in the DTIC-treatment group developed cutaneous squamous cell carcinoma. The median time to onset was 12 weeks (range 3.3 to 21 weeks). No patient required dose interruptions or dose reductions and all patients had their lesions resolved by the end of the trial. An additional five dabrafenib-treated patients developed keratoacanthoma.

New melanoma lesions occurred in three (1.6%) dabrafenib-treated patients compared to none of the DTIC-treated patients. All lesions resolved with excision and no dabrafenib dose modifications or interruptions were required.

One patient (BRF113683.0001488), a 67 year old Caucasian man with melanoma metastatic to the liver and soft tissue and no other significant past medical history developed Stage I mycosis fungoides (MF) on the upper arms and trunk 44 days after initiating dabrafenib. The patient was also diagnosed with Grade 1 PPES. Topical methylprednisolone was initiated as treatment and the adverse reaction was ongoing at the time the trial concluded.

No patients randomized to DTIC developed a treatment-emergent, non-epithelial malignancy in the randomized phase or cross-over phase of the trial.

Basal cell carcinoma was reported in five (2.7%) of dabrafenib-treated patients compared to none of the DTIC-treated patients. Three of the five patients were diagnosed in the first month of treatment (minimum 22 days, maximum 87 days). All resolved and none required treatment modification.

#### *QTc Effects*

For patients treated with dabrafenib and DTIC, 159 (85%) and 43 (73%) respectively had a corrected QT interval assessed based on Bazett's formula (QTcB). Six patients (4%) in the dabrafenib-treatment group and two patients (5%) in the DTIC-treatment group developed a QTcB value greater than 480 msec and less than 500 msec. No patient in either treatment group developed a QTcB value > 500 msec. In addition, no patients with a corrected QT interval using methods other than QTcB were reported to be elevated.

Of the 130 patients with a QTcB measured at baseline and on-treatment in the dabrafenib-treatment group, three patients (2%) developed a post-baseline increase in QTcB of > 60 msec. Of the 37 patients with a QTcB measured at baseline and on-treatment in the DTIC-treatment group, one patient (2%) in the DTIC-treatment group developed a post-baseline increase in QTcB of > 60 msec.

The effects of dabrafenib on the QT interval are considered inconclusive by the primary clinical and clinical pharmacology reviewers. The applicant is performing a dedicated, placebo-controlled, blinded trial to evaluate the effect of dabrafenib and its metabolites on cardiac repolarization, and an adequately designed trial to evaluate the effects of dabrafenib on cardiac repolarization and submission of the final study report with the primary data is among the post-marketing requirements for this drug.

#### *Cardiac Valvular Disease*

In a nonclinical toxicology study of dogs administered dabrafenib at doses of 50 mg/kg/day or greater for up to four weeks (approximately 9 times the human exposure at the recommended dose based on AUC), cardiac atrioventricular valve hypertrophy/hemorrhage was observed. Trial BRF113683 excluded patients with abnormal cardiac valve morphology ( $\geq$  grade 2) or moderate valvular thickening as documented by echocardiogram.

Four adverse reactions related to cardiac valvular abnormalities occurred in three patients (2%) in the dabrafenib-treatment group compared to none in the DTIC-treatment group.

A worst-case analysis of valvular regurgitation by toxicity severity grade demonstrated that, of the 38 patients with baseline and follow-up assessments of valvular regurgitation, 21 patients had a post-baseline increase ( $\geq$  1 grade) in toxicity grade in at least one cardiac valve. Of these, the safety reviewer identified 6 events in four patients with a  $\geq$ 2 grade increase from baseline in valve regurgitation. Confounders include valvular disease at baseline (n=2) and prior use of potentially cardiotoxic chemotherapy (n=1).

The applicant did not include valvular abnormalities in its risk management proposal based on the observation of these abnormalities in a minority of subjects in the integrated safety population, and their determination that the central analysis of echocardiograms in trial BRF113710 was not representative of a drug effect. The results of the centralized analysis of valvular abnormalities in BRF113710 may not be extrapolated to the to-be-marketed formulation of dabrafenib (HPMC formulation) based on its increased bioavailability compared to the gelatin capsule formulation of dabrafenib, the formulation administered in trial BRF113710.

The clinical reviewer is of the opinion that the data submitted are insufficient to conclude that dabrafenib causes valvular toxicities. However, Dr. Theoret also believes that the non-clinical toxicology findings of valvular abnormalities in dogs, the increased incidence in valvular toxicities in dabrafenib-treated patients in trial BRF11368, the results of the centralized analysis of BRF113710, and the serious nature of cardiac valvular toxicity support the requirement for a PMR to further evaluate this potential risk as a serious adverse reaction.

#### *Other Cardiac Effects*

Overall, cardiac disorders were reported in 18 (10%) patients treated with dabrafenib compared to 3 (5%) patients treated with DTIC. These adverse reactions were serious in four (2.1%) dabrafenib-treated patients and in one (1.7%) DTIC-treated patient. Two cases of decreased ejection fraction (1.1%), both Grade 2 and considered important medical events, and one case of congestive cardiac failure ( $<$ 1%) requiring hospitalization occurred in the dabrafenib-treatment group compared to no cases of either type of event in the DTIC-treatment group. In addition, two cases of serious atrial fibrillation (1.1%) and one case of myocardial infarction ( $<$ 1%) were reported in the dabrafenib-treatment group, with no cases of either were reported in the DTIC-treatment group. There was one case of Grade 3 angina pectoris requiring hospitalization reported in the DTIC treatment group.

### *Renal Failure*

The applicant identified renal failure as an adverse reaction of special interest. The incidence of renal events was not increased among patients treated with dabrafenib compared to patients treated with DTIC in trial BRF113683; no dabrafenib-treated patients or DTIC-treated patients experienced renal failure and neither treatment group developed Grade 3 or 4 elevations in creatinine based on laboratory monitoring. In an analysis of the Integrated Summary of Safety (ISS) for the 120-Day safety update, the applicant identified seven patients (1.2%) with renal failure. Review of the narratives for these cases by Dr. Theoret suggested that most were confounded (e.g., underlying risk factors, intercurrent illnesses, concomitant medications). The review of renal failure as an adverse drug reaction for dabrafenib rather than as sequelae of other adverse reactions (e.g., serious febrile drug reactions) was considered inconclusive by Dr. Theoret.

### *Pyrexia*

The incidence of pyrexia, serious as well as non-serious, was increased in dabrafenib-treated patients compared DTIC-treated patients, 28% (53/187) vs. 10% (6/59), respectively. Serious adverse events of pyrexia developed in seven (3.4%) patients in the dabrafenib-treatment group and in none of the patients in the DTIC-treatment group. The median time to onset of first occurrence of pyrexia was two weeks in dabrafenib-treated patients and three weeks in DTIC-treated patients with a median duration of 3 and 4 days, respectively. No cases of pyrexia led to treatment withdrawal; however, 16 (8.6%) and 12 (6.4%) dabrafenib-treated patients required either dose reductions or dose interruptions for pyrexia, respectively. Pyrexia resolved in 52 of 53 dabrafenib-treated patients and 6 of 6 patients treated with DTIC.

### *Palmar-Plantar erythrodysesthesia Syndrome (PPES)*

PPES was reported in 37 (20%) dabrafenib-treated patients compared to 1 (2%) DTIC-treated patient. There were no cases of serious or Grade 4 adverse reactions. Four dabrafenib-treated patients (2%) compared to no DTIC-treated patients experienced Grade 3 PPES. The median time to onset was 22 days (range 1 to 100 days) in dabrafenib-treated patients. No cases of PPES led to treatment withdrawal. Dose reduction was required in six patients (3.2%) whereas the remaining patients continued on the same dose of dabrafenib uninterrupted. The outcome of PPES in dabrafenib-treated patients was not resolved in 62% (23/37).

### *Uveitis*

One patient treated with dabrafenib developed iritis compared to no patients treated with DTIC. In addition, blurred vision occurred in three dabrafenib-treated patients and in none of the DTIC-treated patients. In the ISS as reported in the 120-Day safety update, there were six (1%) patients treated with dabrafenib who developed uveitis.

### *Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency*

Because dabrafenib is a sulfonamide, patients with known G6PD deficiency were excluded from all clinical studies because of the theoretical risk of hemolytic anemia. However, the proposed labeling of dabrafenib does not communicate this potential risk based on the justification that, unlike sulfamethoxazole, primaquine, and dapsone, dabrafenib does not contain an aryl amine that can undergo oxidation to hydroxylamine and potentially cause hemolytic anemia. The applicant further notes that amino-pyrimidine nitrogen of dabrafenib does not readily undergo oxidation and there has been no evidence of metabolic oxidation or

other metabolism at this position *in vitro* or *in vivo*. The clinical review team disagrees with the applicant and believes information on this risk should be provided in the dabrafenib label.

## 9. Advisory Committee Meeting

No Oncologic Drugs Advisory Committee meeting was held for this application. Dabrafenib is not the first drug in its class. Additionally, no Special Government Employees were consulted for this application.

## 10. Pediatrics

A pediatric waiver was granted by the Pediatric Review Committee based on dabrafenib's orphan drug status (orphan designation granted January 12, 2011). Dabrafenib has not been studied in the pediatric population.

### *PMHS-MHT Consult*

The Pediatric and Maternal Health Staff-Maternal Health Team (PMHS-MHT) was consulted by DOP2 on September 18, 2012 to attend milestone meetings during the review cycle of this application and provide labeling comments. They provided the following information which was copied from their review.

“Dabrafenib is a NME and there are no human pregnancy data available. In animal developmental reproductive studies, dabrafenib was teratogenic and embryotoxic. Developmental toxicity consisted of embryo-lethality, ventricular septal defects, and variations in thymic shape. There were also delays in skeletal development and reduced fetal body weight. These data are reported in current dabrafenib pregnancy labeling.

### Dabrafenib and Lactation

It is not known if dabrafenib is present in human milk. A search of the Micromedex database resulted in no human or animal data available regarding dabrafenib and lactation. In addition, there are no available human lactation data available for other BRAF kinase inhibitors.

The Proposed Pregnancy and Lactation Labeling Rule (PLLR) published in May 2008. While still complying with current regulations during the time when the Final Rule is in clearance, PMHS-MHT is structuring the Pregnancy and Nursing mothers label information in the spirit of the Proposed Rule. The first paragraph in the pregnancy subsection of labeling provides a risk summary of available data from outcomes of studies conducted in pregnant women (when available), and outcomes of studies conducted in animals, as well as the required regulatory language for the designated pregnancy category. The paragraphs that follow provide more detailed descriptions of the available human and animal data, and when appropriate, clinical information that may affect patient management. The goal of this restructuring is to provide relevant animal and human data to inform prescribers of the potential risks of the product during pregnancy. Similarly for nursing mothers, human data, when available, are summarized. When only animal data are available, just the presence or absence of drug in milk is noted and presented in the label, not the amount. Additionally, information on pregnancy testing, contraception, and infertility that has been located in other sections of labeling are now presented in a subsection, Females and Males of Reproductive Potential.”

The PMHS-MHT reviewed the proposed dabrafenib labeling, and labeling recommendations were provided to the Division and incorporated into labeling negotiations with the applicant.

## **11. Other Relevant Regulatory Issues**

### *Patent Information*

There were no patent issues identified with this application.

### *Exclusivity*

The application requests orphan drug exclusivity for a 7-year period from the date of approval pursuant to Section 527 of the Federal Food, Drug, and Cosmetic Act and Sections 316.31 and 316.34 of Title 21 of the Code of Federal Regulations. In addition, the applicant requests 5 years of exclusivity from the date of approval as a new chemical entity pursuant to Sections 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the Federal Food, Drug, and Cosmetic Act and Section 314.108(b)(2) of Title 21 of the Code of Federal Regulations.

### *Financial disclosures*

In accordance with 21 CFR 54.2, GlaxoSmithKline submitted a list of all trial investigators with certification that the investigators had no financial arrangements as defined in 21 CFR 54.2 that could affect the outcome of the studies submitted to support this application. The disclosure was certified by Randal Batenhorst, Pharm.D, Vice President, Global Regulatory Affairs. Where there were financial arrangements with investigators and based on the information reported by the applicant, no questions were raised by the reviewers with regard to the integrity of the trial data.

### *Other GCP issues*

The applicant includes a statement that all studies were undertaken in accordance with standard operating procedures of the GlaxoSmithKline Group of Companies, which comply with the principles of Good Clinical Practice. In addition, the applicant stated that all studies were conducted with the approval of Ethics Committees or Institutional Review Boards and informed consent was obtained for all subjects. It was also noted that studies were performed in accordance with the version of the Declaration of Helsinki that applied at the time they were conducted, and where regulatory approval was required, this was obtained from the relevant health authority.

### *DSI audits*

Two clinical sites and the applicant were identified for inspection. One of the clinical sites was issued Form FDA 483 classified as Voluntary Action Indicated (VAI). The observations noted for this site were considered to be minor and unlikely to significantly impact the results of efficacy and safety analyses reported in the application. The final classifications for the inspections of the second clinical site and the applicant were No Action Indicated (NAI). Based on the inspectional findings, the data submitted in support of NDA 202806 is deemed reliable.

## 12. Labeling

### *Proprietary Name*

The original request for the proprietary name (b) (4) was denied by the Division of Medication Error Prevention and Analysis on October 27, 2012 (b) (4)

Subsequently, a new request was submitted on November 27, 2012 for the proprietary name "Tafinlar", which was approved on February 12, 2013.

### *Physician labeling*

Labeling negotiations are ongoing as of the filing of this review. The proposed labeled indication is: "Tafinlar is a kinase inhibitor indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test." The label includes a limitation of use: "Tafinlar is not recommended for use in patients with wild-type BRAF melanoma". Labeling comments were last sent to the applicant for review and concurrence on April 12, 2013.

### *Carton and immediate container labels*

A consultant review was obtained for the carton and container labels for dabrafenib by the Division of Medication Error Prevention and Analysis (DMEPA). In general, recommendations were made to increase readability and prominence of important information in the labels and to promote safe use of the product. These recommendations were sent to the applicant and are under negotiation as of the filing of this review. For the detailed recommendations, please see the review of James Schlick, RPh, MBA.

### *Medication guide*

A consultant review was obtained for the non-REMS Medication Guide (MG) from the Division of Medical Policy Programs (DMPP) who made recommendations to the applicant to simplify wording and clarify concepts for the MG where possible, ensuring that the MG is consistent with the Prescribing Information (PI), removing unnecessary or redundant information, and ensuring that the MG meets the Regulations as specified in 21 CFR 208.20. These recommendations were sent to the applicant and are under negotiation as of the filing of this review. For the detailed recommendations, please see the review of LaShawn Griffiths, MSHS-PH, BSN.

## 13. Recommendations/Risk Benefit Assessment

### *Recommended Regulatory Action*

All disciplines have recommended approval for this application and I concur with these recommendations.

### *Risk Benefit Assessment*

Approval is recommended for Tafinlar (dabrafenib) as a new molecular entity and small molecule oral inhibitor of BRAF kinases for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.

Melanoma is the fifth most common cancer in men and seventh most common cancer in women in the United States. Approximately 76,690 new melanoma cases will be diagnosed in the U.S. in the current year, with 9,480 deaths estimated. Melanoma develops at a relatively early age and the incidence of melanoma continues to increase with age. Metastatic melanoma accounts for approximately 4% of all newly diagnosed melanoma cases. The five year survival rates are less than 10% for patients with metastatic disease.

There are few FDA-approved treatments for metastatic melanoma, vemurafenib, ipilimumab, aldesleukin, and dacarbazine. Only vemurafenib, an inhibitor of BRAF kinases, was specifically studied in patients with BRAF V600E mutation-positive melanoma. In this molecularly defined subgroup of patients, vemurafenib demonstrated a prolongation of investigator-assessed PFS from a median of 1.6 months (95% CI: 1.5, 1.7) with DTIC to 5.3 months (95% CI: 4.8, 6.6) with vemurafenib with a hazard ratio of 0.26 (95% CI: 0.20, 0.33). Vemurafenib also demonstrated improved overall survival compared to dacarbazine with a HR of 0.44 (95% CI: 0.33, 0.59;  $p < 0.0001$ ).

Approval for dabrafenib is recommended based on the statistically significant and robust results of a single, open-label, multicenter, international clinical trial of 250 patients with unresectable or metastatic, BRAF V600E mutation-positive melanoma randomized to receive dabrafenib (n=187) or DTIC (n=63). The trial, BRF113683, was initiated prior to FDA approval of vemurafenib. The trial results demonstrated a 67% reduction in the hazard rate of investigator-assessed progression of disease or death from any cause for patients treated with dabrafenib [HR 0.33 (95% CI: 0.20, 0.55)]. The median PFS for dabrafenib-treated patients was 5.1 months (95% CI: 4.9, 6.9) compared to 2.7 months (95% CI: 1.5, 3.2) for DTIC-treated patients ( $p$ -value  $< 0.001$ , stratified log-rank test). This is a highly statistically significant and clinically meaningful prolongation in PFS for this patient population.

The robust nature of the primary analysis was confirmed by analyses based on blinded, independent, central review of PFS which supported the primary efficacy analysis that was based in investigator assessments. The investigator-assessed, confirmed objective response rates (ORR) were 52% (95% CI: 45%, 59%) for dabrafenib-treated patients, including 6 (3%) complete responses, and 17% (95% CI: 9%, 29%) for DTIC-treated patients, all partial responses. Overall survival data available at the time of the primary analysis were immature.

Earlier trials evaluating dabrafenib in patients with BRAF V600 mutation-positive metastatic melanoma that did not exclude patients with tumors containing BRAF V600K mutations did not support the same level of anti-tumor activity with dabrafenib for these patients as was observed in patients with BRAF V600E mutation-positive disease. No effectiveness-estimating trials for dabrafenib were conducted by the applicant in patients with BRAF V600K mutation-positive melanoma. (b) (4)

The most serious safety risks associated with dabrafenib are second primary malignancies, including cutaneous squamous cell carcinoma/keratoacanthoma (cuSCC) and new primary melanomas, as well as serious febrile drug reactions, defined as fever complicated by hypotension, dehydration, severe rigors/chills, or renal failure in the absence of another

identifiable etiology (e.g., infection). The rate of cuSCC was 11% across clinical trials and 7.5% in dabrafenib-treated patients and zero in DTIC-treated patients in the main supporting trial for this application, Trial BRF113683. In addition, new primary melanoma lesions occurred in three (1.6%) dabrafenib-treated patients while none were observed in DTIC-treated patients in the same trial. Cutaneous malignancies were manageable when identified early.

The most common ( $\geq 20\%$ ) safety risks associated with dabrafenib were hyperkeratosis, hypophosphatemia, headache, pyrexia, arthralgia, skin papilloma, alopecia, and palmar-plantar erythrodysesthesia syndrome. Approximately 3% of dabrafenib-treated patients experienced safety events leading to treatment withdrawal. Dose reductions occurred in 18% of dabrafenib treated patients, most frequently for pyrexia (9% in the dabrafenib-treatment group vs. 0 in the DTIC-treatment group), palmar-plantar erythrodysesthesia syndrome (3% vs. 0), chills (3% vs. 0), fatigue (2% vs. 0), and headache (2% vs. 0). Safety events led to withholding treatment without dose reduction in 16% of dabrafenib-treated patients, most commonly for pyrexia (6% vs. 0). Grade 3 or 4 adverse reactions occurred in 33% of dabrafenib-treated patients (42% of DTIC); most frequent were pyrexia (3%), squamous cell carcinoma (3%), and back pain (3%).

In spite of the observed toxicities over the course of the development program, dabrafenib has a favorable benefit: risk assessment for treatment of patients with BRAF V600E mutation-positive unresectable or metastatic cutaneous melanoma when compared to other available treatment. Approval of this drug, which demonstrated statistically significant and robust results in a well-conducted, randomized, active-controlled clinical trial, offers another treatment option for a group of patients for whom the prognosis is grave in a disease with limited options for treatment. A companion diagnostic test, the bioMerieux THxID BRAF Kit, is currently under review by CDRH to assist in patient selection for the use of dabrafenib.

The reservations that arose during the review of this application were prompted by data that were poorly organized and of poor quality. However, the results of the trial submitted to support the effectiveness of dabrafenib, the supporting materials and the opportunity to approve another drug for patients with advance melanoma were compelling.

*Recommendation for Postmarketing Risk Evaluation and Management Strategies*  
No REMS is recommended for this drug.

*Recommendation for other Postmarketing Requirements and Commitments*  
I concur with the following postmarketing requirements proposed by the Clinical Pharmacology and Clinical Review Teams under the Food and Drug Administration Amendments Act of 2007 (FDAAA).

*Clinical Pharmacology*

- Complete a clinical trial evaluating the potential for dabrafenib to prolong the QT/QTc interval in accordance with the principles of the FDA Guidance for Industry entitled “E14 Clinical Evaluation of QT/QTc Interval Prolongation”. Submit the final report that includes central tendency, categorical and concentration-QT analyses, along with a thorough review of cardiac safety data.

- Complete a clinical pharmacokinetic trial to determine the appropriate dabrafenib dose in patients with moderate to severe hepatic impairment in accordance with the FDA Guidance for Industry entitled “*Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*”.
- Complete a clinical pharmacokinetic trial to determine the appropriate dabrafenib dose in patients with severe renal impairment in accordance with the FDA Guidance for Industry entitled “*Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*”.
- Conduct a drug interaction trial to evaluate the effect of rifampin (a strong CYP3A4 and CYP2C8 inducer) on the repeat dose pharmacokinetics of dabrafenib in accordance with the FDA Guidance for Industry entitled “*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*”. The results of this clinical trial should allow for a determination on how to dose dabrafenib with regard to concomitant strong CYP3A4 and CYP2C8 inducers.
- Complete a clinical trial evaluating the effects of repeat doses of oral ketoconazole on the repeat dose pharmacokinetics of dabrafenib in accordance with the FDA Guidance for Industry entitled “*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*”. The results of this clinical trial should allow for a determination on how to dose dabrafenib with regard to concomitant strong CYP3A4 inhibitors.
- Complete a clinical trial evaluating the effects of repeat doses of oral gemfibrozil on the repeat dose pharmacokinetics of dabrafenib in accordance with the FDA Guidance for Industry entitled “*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*”. The results of this clinical trial should allow for a determination on how to dose dabrafenib with regard to concomitant strong CYP2C8 inhibitors.
- Complete a clinical trial evaluating the effects of repeat doses of dabrafenib on the single dose pharmacokinetics of warfarin (CYP2C9 substrate) in accordance with the FDA Guidance for Industry entitled “*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*”. The results of this clinical trial should allow for a determination on how to dose dabrafenib with regard to concomitant sensitive CYP2C9 substrates and CYP2C9 substrates with a narrow therapeutic window.
- Conduct a clinical trial to evaluate if proton pump inhibitors, H2 antagonists and antacids alter the bioavailability of dabrafenib. You may study the worst case scenario first, and then determine if further studies of other drugs are necessary. The study results should allow for a determination on how to dose dabrafenib with regard to concomitant gastric pH elevating agents.

*Clinical*

- Submit the final analyses of safety from all ongoing randomized controlled clinical trial(s) using the hydroxypropyl methylcellulose formulation of dabrafenib as monotherapy to identify and characterize unexpected serious risks from longer duration of exposure.
- Submit cumulative safety analyses annually, and for one year after the last patient has completed clinical trial treatment, to identify and characterize the risk of new primary malignancies, including cutaneous squamous cell carcinoma, in all ongoing and subsequently initiated randomized controlled clinical trials through 2020 that use dabrafenib alone or in combination. In addition to a cumulative listing of all cases, include the following summary analyses as well as any additional informative analyses of new primary malignancies in each report:
  - Incidence rates, overall and stratified by tumor type, for each arm of the trial(s)
  - Timing of onset in regard to exposure to dabrafenib (i.e., timing from first and last dose)
  - Prognostic features relevant to each tumor type (e.g., clinicopathological features, including pertinent molecular characteristics, as well as disease staging information)
  - Treatment(s) administered by tumor type
  - Outcome
- Submit integrated safety analyses of cardiac valvular abnormalities based on centralized, blinded, independent review assessment of all echocardiograms from an adequate number of randomized controlled clinical trials that use dabrafenib as monotherapy or in combination to inform the label regarding incidence rate and natural history of the safety signal.

Submit the first interim report within six months of the date of FDA-approval of NDA 202806 and every two years thereafter until FDA determines that the final report submission fulfills this postmarketing requirement.

*Recommended Comments to Applicant*

Future applications should be quality controlled for data uniformity and consistency across trials, or be submitted utilizing a standard data format acceptable to FDA.

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/s/  
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SUZANNE G DEMKO  
05/16/2013