CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202806Orig1s000

SUMMARY REVIEW

Division Director Summary Review

Date	May 28, 2013
From	Patricia Keegan
Subject	Division Director Summary Review
NDA #	NDA 202806
Applicant Name	GlaxoSmithKline
Date of Submission	July 30, 2012
PDUFA Goal Date	May 30, 2013
Proprietary Name / Established (USAN) Name	Taflinar/ dabrafenib capsules
Dosage Forms / Strength	oral capsules / 50 mg and 75 mg
Proposed Indication(s)	"(b) (4)™ is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF (b) (4) mutation as detected by an FDA approved test. **Limitation of use:** (b) (4) is not recommended for use in patients with wild-type BRAF melanoma."
Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager Review	Norma Griffin
Medical Officer Review	Marc Theoret
Statistical Review	Weishi (Vivian) Yuan
Non-clinical Pharmacology/Toxicology Review	Alexander Putman
CMC Review	Gaetan Ladouceur (DS), Amit Mitra (DP)
Biopharmaceutics Review	Akm Khairuzzaman
Microbiology Review	Bryan S Riley
Clinical Pharmacology Review	Jian Wang
Pharmacometrics Review	Justin Earp
Pharmacogenomics Review	Christian Grimstein
CDRH/OIVD	Donna Roscoe
OSI	Jean Mulinde
OC	Mahesh Ramandan
CDTL	Suzanne Demko
OPDP	Quynh-Van Tran
OSE/DMEPA	James H. Schlick
OSE/DRISK	Amarilys Vega
Maternal Health Team Consult	Tammie Brent Howard
Office of Medical Policy/Patient Labeling Review	Latonia Ford

CDRH=Center for Devices and Radiologic Health
OIVD= Office of In Vitro Diagnostics
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

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1. Introduction

GlaxoSmithKline submitted NDA 202806 seeking approval of dabrafenib (Taflinar capsules) for the proposed indication of "the treatment of patients with unresectable or metastatic melanoma with BRAF (b) (4) mutation as detected by an FDA approved test." Dabrafenib would be the second drug approved for this patient population; Zelboraf (vemurafenib), another RAF kinase inhibitor, was approved for this indication in August 2011.

Dabrafenib mesylate is a small molecule, RAF kinase inhibitor; based on *in vitro* data, dabrafenib inhibits wild type BRAF, BRAF V600E, BRAF V600K, and BRAF V600D protein kinase activity at clinically relevant concentrations.

The application was supported by a single randomized, open-label, multicenter trial (Protocol PRF113683, also known as the BREAK-3 trial) which compared the safety and efficacy of dabrafenib to dacarbazine in patients with previously untreated, unresectable locally advanced or metastatic cutaneous melanoma with BRAF V600E mutations as detected by a clinical trials assay. The NDA was also included supportive data, i.e., evidence of clinical activity (objective tumor responses) in two non-comparative trials of single agent dabrafenib in patients with previously untreated or previously treated, BRAF V600E or V600K mutation-positive, metastatic melanoma (BREAK –2 and BREAK-MB trials), (b) (4) for patients with unresectable locally advanced or metastatic cutaneous melanoma with BRAF V600K mutations and for treatment of CNS metastases from BRAF V600E primary melanomas.

The results of the BREAK-3 trial demonstrated a statistically robust and clinically important improvement in progression-free survival (HR 0.33 $p<0.001$; median PFS of 5.4 months vs. 2.7 months) and a higher response rate (52% vs. 17%) for patients with previously untreated, metastatic or unresectable, BRAF V600E, cutaneous melanoma who were randomized to dabrafenib as compared to those randomized to dacarbazine. In an immature analysis of overall survival (30 deaths), there was no difference in overall survival and no suggestion of a detrimental effect on overall survival. The most common serious adverse reactions were an increased risk of new cutaneous squamous cell cancers of the skin (7% vs. none in controls), serious non-infectious, febrile drug reactions (3% grade 3 pyrexia vs. none in controls), and severe hyperglycemia (>250-500 mg/dL) resulting in the need for medical management in non-diabetics or change in medical management of diabetic patients. The most common (incidence ≥ 20%) adverse reactions of dabrafenib were hyperglycemia (50%), hyperkeratosis (37%), hypophosphatemia (35%), headache (32%), arthralgia and papilloma (27% each), alopecia (22%), and palmar plantar erythrodysesthesias (20%).

The results of the BREAK-2 and BREAK-MB trials were reviewed and, as discussed in Section 7 of the review, these data did not constitute substantial evidence of effectiveness (b) (4) for BRAF V600K mutation-positive cutaneous melanoma or for treatment of CNS metastases from BRAF V600E or K mutation-positive cutaneous melanoma primaries.

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The major issues identified with this NDA were the lack of executable analysis programs and data quality issues which precluded an efficient review. As noted in the New Drug Guidance Document: Refusal to File (July 12, 1993), "the practice of submitting an incomplete or inadequate application and then 'repairing' it in the course of an extended review period is inherently inefficient and wasteful of agency resources." The Guidance also notes that "An application that has required major repair during review will also usually provide to be one with a prolonged review time, even if the actually agency review was efficient and swift." Based on GSK's submission of 'corrected' datasets in order to address data quality issues during the filing review period, data quality issues persisted and the lack of analysis programs based on GSK's determination that FDA systems could not support their proprietary software programs, resulted in increased burdens on the statistical and clinical reviewers to generate analysis datasets in order to verify the reported results.

Additional issues included resolution of process validation issues, lack of complete pharmacokinetic characterization resulting in the need for multiple post-marketing requirements, (b) (4)

As of the date of this review, agreement on post-marketing required trials and the physician package insert have not been reached.

2. Background

Indicated Population

Cutaneous melanoma, arising from malignant transformation of melanocytes in the skin, is the most aggressive malignancy arising from the skin; based on trend analyses, the incidence of melanoma has been increasing over the past several decades. The National Cancer Institute estimates that in 2013 there will be 76, 690 new cases of melanoma and 9,480 deaths due to melanoma in the United States. [1] While 84% of melanoma presents with localized disease which may be cured with surgical excision alone or with adjuvant interferon or investigational agents and has a 5-year survival rate of 98%, for the 4% who present with metastatic disease and receive systemic treatment, the 5-year survival rates is only 15%. Of patients presenting with cutaneous melanoma, approximately 50% will have melanoma bearing BRAF V600 mutations.

There are five drugs that have been approved by the US FDA for the treatment of metastatic melanoma: vemurafenib, ipilimumab, aldesleukin, dacarbazine, and hydroxurea. Hydroxurea which was FDA-approved in the 1970's, is no longer used or recommended by clinical practice guidelines. Dacarbazine and aldesleukin (interleukin-2) were approved by FDA for the treatment of metastatic melanoma in May 1975 and January 1998, respectively, based on evidence of durable objective tumor responses. Their use for the initial treatment of metastatic melanoma has declined following approval of ipilimumab and vemurafenib.

[1] http://www.cancer.gov/cancertopics/types/melanoma

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Commonly used off-label treatments, whose use has also declined following approval of vemurafenib and ipilimumab, include temozolomide alone or in combination with other drugs, dacarbazine-based combination chemotherapy regimens, and interferon alone or in combination with chemotherapy, as well as investigational immunotherapy treatments. All currently used off-label treatment approaches are characterized by low objective tumor response rates (<20%) and no evidence of improved survival.

On March 25, 2011, FDA approved ipilimumab (Yervoy, Bristol Myers Squibb) for the treatment of unresectable or metastatic melanoma. Ipilimumab is a fully human IgG1 kappa monoclonal antibody that is directed against the human cytotoxic lymphocyte antigen-4 (CTLA-4) present on activated T-cells. The approval of ipilimumab was based on the results of a single, randomized trial which demonstrated a statistically significant improvement in overall survival for patients receiving ipilimumab in combination with a peptide vaccine (gp100 peptides) compared to those receiving peptide vaccine alone [HR 0.66 (95% CI: 0.55, 0.85), p=0.0004] with median survival times of 9.95 months and 6.44 months in the combination and gp100 monotherapy arms, respectively. The application was also supported by the high level results of Protocol CA 184024, a randomized trial of dacarbazine with or without ipilimumab, in which the high level results also demonstrated an improvement in overall survival [HR 0.85 (95% CI: 0.76, 0.93)] with a nominal p-value of 0.001, stratified log-rank test.

On August 17, 2011 vemurafenib (ZELBORAF, Genentech Inc.) an inhibitor of some mutated forms of BRAF serine-threonine kinase, including BRAF V600E, was approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test[2]. At the time of approval, labeling for vemurafenib also carried the following limitation of use: "ZELBORAF is not recommended for use in patients with wild-type BRAF melanoma." The approval was based on the results of a single, multicenter, randomized (1:1), open-label, active-controlled (dacarbazine) trial conducted in 675 patients with treatment naive, BRAF V600E mutation-positive unresectable or metastatic melanoma as detected by the cobas 4800 BRAF V600 Mutation Test. The trial demonstrated a statistically significant improvement in overall survival [HR 0.44 (95% CI: 0.33, 0.59); p < 0.0001] and progression-free survival [HR 0.26 (95% CI: 0.20, 0.33); p <0.0001] for patients in the vemurafenib arm. The median survival time not reached in the vemurafenib arm as compared to 7.9 months in the dacarbazine arm. The median PFS was 5.3 months in the vemurafenib arm compared with 1.6 months in the dacarbazine arm. The confirmed, investigator-assessed best overall response rate was 48.4% (95% CI: 41.6%, 55.2%) in the vemurafenib arm compared to 5.5% (95% CI: 2.8%, 9.3%) in the dacarbazine arm. These data were supported by the results of a single arm trial in 132 patients with previously treated, BRAF V600E mutation-positive, metastatic melanoma. In this trial, the confirmed best overall response rate as assessed by an independent review committee (IRC) was 52% (95% CI: 43%, 61%), with three complete responses. The median duration of response was 6.5 months.

[2]http://www.accessdata fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo

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Pre-Submission Regulatory History

IND 105032: Original IND submission for GSK2118436, a small molecule designed to inhibit BRAF V600 muations. The IND was submitted June 26, 2009 and active as of July 26, 2009.

May 5, 2010: teleconference held and agreement reached on the clinical pharmacology program supporting a planned NDA for dabrafenib monotherapy. GSK confirmed that the dosage form of dabrafenib to be used in dabrafenib monotherapy trials would be the HPMC capsules and agreed to conduct enhanced pharmacovigilance of HPMC capsules due to concerns of increased myelosuppression with this dosage form.

May 5, 2010: The draft Protocol BRF113683 (BREAK-3 trial) was submitted to IND 105032

July 6, 2010: End-of-Phase 1/pre-Phase 3 meeting held to discuss the proposed development program for dabrafenib for treatment of BRAF V600 mutation-positive advanced melanoma, supported by Protocol BRF113710, a single-arm, open-label study of dabrafenib in patients with BRAF mutation-positive, metastatic melanoma who have received prior systemic therapy and Protocol BRF113683, a randomized, open-label, multicenter, Phase 3 trial comparing dabrafenib to dacarbazine in previously untreated patients with BRAF mutation-positive metastatic melanoma. Key agreements reached and comments provided during the meeting are as follows

- Regarding Protocol BRF113683, the proposed co-primary endpoints of PFS and OS were acceptable, with hierarchical testing to preserve Type I error for the co-primary endpoints, however the effect size for the PFS endpoint (difference in median PFS of 2 months) may not be sufficient to demonstrate clinical benefit. FDA and GSK agreed that the final analysis of PFS should occur after 60% of the planned number of OS events had occurred. A preNDA meeting should be requested to discuss the top-line results for PFS when available.
- The primary analysis of PFS based on investigator-determined assessment was acceptable, however the acceptability of a supporting analysis based on a random audit of PFS by an independent review committee could not be determined due to lack of details. GSK confirmed that all patient scans will be obtained to allow IRC review of additional patients. FDA stated that the proposed plan would be assessed when the final protocol/SAP were submitted.
- The proposed control (dacarbazine) and patient population were acceptable for Protocol BRF113683.
- GSK agreed to increase monitoring for secondary malignancies, biopsy of all suspicious lesions, and to provide analysis of second malignancies in BRF113683.
- Regarding Protocol BRF113710, FDA strongly recommended that the design be modified to be a dose-ranging comparison against a low-dose arm (e.g., 35 mg BID). GSK raised concerns regarding suboptimal dosing but agreed to consider this request.
- Regarding Protocol BRF113710, FDA stated that evidence of an overall response rate of sufficient magnitude and duration in patients who have received prior systemic therapy for melanoma may support a request for accelerated approval.

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October 7, 2010:

- FDA advised that if another agent receives approval for the treatment of first-line treatment of BRAF mutation-positive metastatic melanoma based on demonstration of improved survival, an accelerated approval could not be granted for this population.
- GSK noted that following the July 6, 2010 meeting, Protocol BRF113683 was revised such that PFS was the sole primary endpoint. GSK further noted that based on agreements with (b) (4), all patients in the control arm would be allowed to cross-over to dabrafenib at the time of progression. FDA stated that an improvement in PFS of sufficient magnitude may be an appropriate endpoint provided that an improvement in OS is not demonstrated in a prior approval of another drug in GSK's proposed population.
- FDA questioned whether dacarbazine remains an appropriate control and recommended that GSK conduct a 3-arm trial of GSK1120212 alone, dabrafenib alone, and the combination of GSK1120212 and dabrafenib. FDA advised that two pairwise comparisons of monotherapy to combination therapy would allow isolation of the treatment effects (b) (4)
- FDA noted that in the modification of Protocol BRF113710 to a two-arm trial, the low dose arm selected was 50 mg BID (as compared to 150 mg BID). FDA did not object to the low dose selected. FDA noted that the alternative hypothesis (overall response rate of 40%) was lower than that observed in the Phase 1 trials (overall response rate of 60%) and stated that acceptability of the final response rate from the Phase 2 study will be a review issue.
- FDA and GSK agreed on monitoring of special adverse events of interest, which include second malignancies, cutaneous malignancies,
- (b) (4)

October 22, 2010: BREAK-3 protocol (b) (4) Trial design issues that prevented acceptance were the primary endpoint of progression-free survival and concerns regarding the acceptability of the control, dacarbazine. FDA also noted that the trial be designed to assess whether the proportion of BRAF V600 mutation-positive tumor was a determinant of disease progression, in light of the rapid disease progression noted in a subset of patients with BRAF wild-type tumors treated with GSK2118436.

December 30, 2010: Meeting held to discuss the possible submission of an NDA seeking accelerated approval in patients who had received and progressed following prior treatment for BRAF mutation-positive, metastatic melanoma based on evidence of a clinically meaningful response rate, duration of response, and acceptable risk:benefit profile, which would be evaluated in the context of available therapy. FDA stated that a submission containing data on 45 patients, supplemented by additional clinical trial data during the NDA review would be acceptable. FDA also advised that a companion diagnostic test would need to be approved concurrently with the approval of dabrafenib.

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February 11, 2011: FDA designated as a Fast Track program the investigation of GSK2118436 (dabrafenib) for the treatment of patients with BRAF mutation positive (V600E [redacted] (b) (4)) advanced melanoma.

January 12, 2011: FDA granted Orphan Drug designation for dabrafenib for the treatment of BRAF V600 mutation positive Stage IIb through IV melanoma.

January 31, 2012: CMC pre-NDA meeting held.

May 9, 2012: preNDA meeting held. Key agreements reached were

- The design and the reported results of Study BREAK-3 together with the proposed supportive data appear sufficient to support the filing of an NDA from a clinical perspective. The wording of the final indication statement will be determined based on the NDA review.
- Including information from the prespecified, IRC-assessed PFS endpoint in the absence of a pre-specified plan for controlling type I error is not likely to provide additional information useful to prescribing physicians. After review of the data in the NDA, FDA and GSK may discuss the appropriateness of inclusion of IRC determined PFS results.
- FDA agreed to consider labeling [redacted] (b) (4) if safety and efficacy in this subgroup is adequately supported by clinical study results and mechanism of action of dabrafenib.
- GSK agreed to provide interim data for cohort B and complete data for cohort D from Study BRF113771 in the NDA to address drug-drug interactions and also agreed to provide the final study report for Study BRF113771 as a post-marketing requirement addressing potential drug interactions.
- GSK agreed to conduct post-marketing trials for dedicated organ dysfunction studies and evaluation of effects on QTc in Protocol BRF113773.
- GSK agreed to provide the results of the exploratory analysis of efficacy based on the population identified as V600E mutation-positive according to the to-be-marketed diagnostic test in the clinical study report for the BREAK-3 trial. GSK agreed to include information on the mutation status based on the to-be-marketed test in the clinical study datasets to allow FDA to confirm the exploratory analysis.

June 20, 2012: FDA granted approval for submission of the NDA under an agreed-upon schedule for rolling review.

NDA Submission History

June 21, 2012: First module submitted
July 30, 2012: The final components of the NDA were received.
October 12, 2012: The 74-day letter issued, notifying GSK that the NDA had been filed and had been designated as a "standard" review.
October 27, 2012: FDA issued a letter notifying GSK that the proprietary name of [redacted] (b) (4) was denied

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The application was amended 66 times as of the date of this review; the bulk of these amendments were submitted in response to information requests from FDA.

3. CMC/Biopharmaceutics/Device

Chemistry, Manufacturing, and Controls
I concur with the conclusions reached by the chemistry and biopharmaceutics reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months when stored at 25° C with excursions between 15° C and 30 °C. There are no outstanding issues..

Dabrafenib is a new molecular entity that is manufactured as a mesylate salt. Dabrafenib mesylate (b) (4).
The drug product is an immediate release capsule, which will be marketed in two strengths, 50 mg and 75 mg. Each 50 mg capsule contains 59.25 mg dabrafenib mesylate equivalent to 50 mg dabrafenib free base. The major efficacy trial was conducted with the hypromellose (HPMC) capsule shells, which will be marketed.

The CMC and biopharmaceutics reviewers recommended approval and did not request postmarketing commitments.

Device (companion diagnostic)
The NDA contained a letter authorizing CDER to refer to bioMerieux's IDE G120011 for the THxID™ BRAF assay in support of NDA 202806. Concurrent with the review of this NDA, a pre-market application (PMA) was submitted for the companion diagnostic for identification of patients with BRAF V600 mutation-positive melanoma, manufactured by bioMerieux.

I concur with the conclusions reached by the device reviewer regarding the acceptability of the companion diagnostic test kit, manufactured by bioMerieux, for the identification of patients for whom dabrafenib is indicated. Manufacturing site inspections for this test kit were acceptable. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

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

As noted in Dr. Putman's review, nonclinical pharmacology studies demonstrated that dabrafenib is an inhibitor of wild-type BRAF (IC_{50} = 3.2 nM), wild-type CRAF (IC_{50} = 5 nM), and BRAFV600E (IC_{50} =0.65nM), BRAFV600K (IC_{50} =0.5nM), and BRAFV600D (IC_{50} =1.48 nM) kinases. Dabrafenib-induced inhibition of BRAF kinases appeared to be time-dependent, reversible, and ATP-competitive. In vitro incubation with dabrafenib decreased phosphorylation of extracellular signal regulated kinase (ERK) in cell lines. In contrast, in a

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panel of tumor cell lines, the effects on tumor cell growth (gIC_{50}) was limited to cell lines from some primary cancers containing BRAFV600E mutations but was ineffective in cell growth inhibition for cell lines derived from colon cancer (3 of 4 cell lines), sarcomas, ovarian cancers, and lung cancers bearing BRAF V600E mutations. Dabrafenib was also ineffective in suppression of tumor growth in cell lines with wild-type BRAF or cell lines with KRAS, NRAS, or HRAS mutations.

Repeat dose (13-week) toxicology studies in rats and dogs supported the safety of the proposed recommended human dose (animal exposures 4-fold higher than humans) and the major metabolites of dabrafenib in humans (30-50% of human exposures). The rat and dog are acceptable species for assessment of toxicology based on similar inhibition of dog and rat wild-type BRAF in *in vitro* studies. The main target organs of toxicity were the skin manifesting as proliferative skin lesions and papules at exposures achievable with the recommended human dose, male reproductive organs consisting of aspermia and degeneration of the testes at exposures achievable with the recommended human dose, heart with development of marked atrophy and hemorrhage in the right atrioventricular at exposures 5-fold greater than that achieved with the recommended human dose, and stomach manifesting as hyperplasia and infiltration. Specifications for impurities and degradants were qualified by 4-week toxicology studies.

Dabrafenib was not mutagenic in the AmesTest or the mouse lymphoma assay, and was not clastogenic in an *in vivo* rat bone marrow micronucleus test. Carcinogenicity studies were not conducted since the indicated population has advanced cancer and clinical trials demonstrated that dabrafenib is carcinogenic (increased incidence of cutaneous squamous cell cancers). Dabrefenib was shown to impair fertility and to be embryotoxic in a combined fertility and embryofetal study in rats.

The non-clinical reviewer recommended approval and did not request post-marketing commitments or require post-marketing required studies for safety.

5. Clinical Pharmacology

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

The clinical pharmacology program of the NDA included single and multiple-dose pharmacokinetic, food effect, mass balance, absolute bioavailability, and drug-drug interactions studies and the results of population pharmacokinetic (PK) analysis. Formal QT studies, dedicated DDI studies, and evaluation of PK in patients with severe renal or hepatic impairment were not provided in the NDA. The clinical pharmacology reviewer did not identify any exposure-response (progression-free survival) relationships or exposure-toxicity (evaluated for ≥ grade 3 adverse reactions, and for ≥ grade 3 hyperglycemia, hyponatremia, hypophosphatemia, palmar-plantar erythrodysesthesia and ≥ grade 2 fever). There were no intrinsic factors (age, gender, weight, race) identified that resulted in clinically important effects on the pharmacokinetics of dabrafenib.

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Following oral administration of dabrafenib, the median time to achieve peak plasma concentration was 2 hours. Mean absolute bioavailability of oral dabrafenib was 95% in the fasted state however administration of a single 150 mg dose of dabrafenib with a high-fat meal resulted in a 51% reduction in Cmax and 31% reduction in AUC as compared to the fasted state. Dabrafenib is 99.7% bound to human plasma proteins.

The metabolism of dabrafenib is primarily mediated by CYP2C8 and CYP3A4; its active metabolites are hydroxy-dabrafenib and desmethyl-dabrafenib, which are also metabolized by CYP3A4, carboxy-dabrafenib which is excreted in bile and urine or decarboxylated. The terminal half-lives of dabrafenib is approximately 8 hours, that of hydroxy-dabrafenib is approximately 10 hours, while those of the carboxy- and desmethyl-metabolites are longer, (21 to 22 hours). 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. Fecal excretion is the major route of dabrafenib elimination (71%) and urinary excretion accounts for 23%.

Dabrafenib induces cytochrome P450 isoenzyme (CYP) 3A4-mediated metabolism and may induce other enzymes.

The pharmacogenomics reviewer evaluated the treatment effects of dabrafenib by mutation type (BRAF V600E vs. BRAF V600K). His analysis summarized published literature noting that, as compared to patients with BRAF wild-type melanoma, those with BRAF V600 mutation-positive melanoma were younger at diagnosis, are more likely to have primary melanoma at skin sites without chronic sun damage, and had a poorer outcome (shorter progression-free survival). Literature reports assessing characteristics of patients with melanoma bearing BRAF V600E as compared with those bearing BRAF V600K mutations noted that those with BRAF V600K mutations were older and a higher proportion were male. These findings were confirmed in FDA's analysis of the two supportive trials (BREAK-2 and BREAK-MB) which enrolled patients with both BRAF V600 E and BRAF V600K mutation –positive melanoma. In FDA's analysis, the Patients with V600K mutation were more likely to be men compared to patients with V600E mutation [82% vs. 60%, p=0.0048], and patients with BRAF V600K mutation were significantly older at screening [median (min, max): 63 (31, 87)] compared to patients with V600E mutation [median (min, max): 51 (19-79), p<0.0001]. In addition, the pharmacogenomics reviewer noted that although pre- clinical data show similar IC50 values for the V600E and V600K mutations, limited clinical data from Phase 2 studies BREAK-MB and BREAK-2 suggest marginal dabrafenib activity in patients with the BRAF V600K mutation compared to patients harboring the V600E mutation.

Based on the information provided (or not provided) in the application, the following post-marketing requirements have been imposed to address important unresolved potential safety issues

- Assesssment of dabrafenib effects on the QTc interval
- Assessment of pharmacokinetics in patients with severe renal impairment
- Assessment of pharmacokinetics in patients with moderate to severe hepatic impairment

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- Assessment of drug interactions based on metabolism of dabrafenib and on dabrafenib's effects on the cytochrome P450 system.

6. Clinical Microbiology

I concur with the conclusions reached by the clinical microbiology reviewer that there are no sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

Protocol 113683 (BREAK-3)

Protocol History

August 17, 2010: The original version of Protocol 113683 (BREAK-3) trial was submitted to IND 105032, following the July 6, 2010 End-of-Phase 1/pre-Phase 3 meeting with GSK. On October 7, 2010, FDA met to discuss trial design issues and on October 22, 2010 issued an SPA Non-Agreement letter for Protocol 113683.

November 3, 2010: Amendment 1
- Modification to contraception section based upon nonclinical tox;
- Addition of CT for respiratory symptoms to dose modification table;
- Change to slide requirements for tumor tissue testing (20 to 15);
- addition of secondary malignancies as secondary objective;

March 23, 2011 Amendment 3
- Inclusion of serial PK sampling on a subset of patients to further characterize final formulation;
- clarification of crossover eligibility criteria;
- modification to tumor tissue requirements to allow primary tissue for screening,
- addition of statistical objective to analyze at best overall response rate.

June 3, 2011 Amendment 4
- Dose monitoring and management guidelines for neutropenia and fever updated based on grade 4 neutropenia and complicated pyrexia in dabrafenib trial using HPMC capsule dosage form.
- Full body skin photos at baseline have been changed from required to recommended.

November 14, 2011 Amendment 5
- Revised to permit patients with investigator reported disease progression on the dabrafenib arm to continue dabrafenib if investigator determines that the patient is still benefitting from dabrafenib treatment after consultation with the Medical Monitor.
- A guideline for renal insufficiency was added for the management of renal toxicities.
- Added the collection of serum creatinine and BUN laboratory values in febrile patients

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April 20, 2012 Amendment 6

- Based on IDMC determination that the primary endpoint was met, patients randomized to dacarbazine were allowed the option to receive dabrafenib prior to investigator-determined disease progression and requirement for independent review confirmation of disease progression prior to crossover was discontinued.
- Statistics section updated to reflect the current plans for analyses and address multiple testing issues.
- Modified to clarify intent in the collection of events of pyrexia and basal cell carcinoma.

Trial Design

The NDA is supported primarily by the results of a single trial, Protocol 113683 (BREAK-3), which is a randomized (3:1), two-arm, open-label, active-controlled trial conducted in patients with previously untreated, unresectable or metastatic, BRAF V600E mutation-positive melanoma, as determined by an investigational-use only test at a CLIA-certified centralized testing facility. Randomization was stratified for stage (unresectable stage III, stage IV M1a, and stage IV M1b vs. stage IV M1c).

The primary endpoint of the BREAK-3 trial was investigator-assessed progression-free survival (PFS). Key secondary efficacy objectives were comparison of overall survival, investigator-assessed overall response rates and durations of response between the two treatment arm, and validation of a BRAF V600E mutation assay as a companion diagnostic test. Additional endpoints were determination of the response rate and duration in patients randomized to dacarbazine who received dabrafenib as second-line therapy, comparison of changes in patient-reported outcomes between the treatment arms, characterization of the toxicity, notably rate of non-melanoma skin lesions in both arms, and of the pharmacokinetic profile of dabrafenib and several exploratory analyses.

Key eligibility criteria were histologically confirmed, unresectable stage III or metastatic melanoma, BRAF V600E mutation-positive tumor by central testing, no prior systemic treatment for metastatic or unresectable disease <u>except</u> aldesleukin (interleukin-2), measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, ECOG performance status of 0 or 1, and HIV sero-negative. Key exclusion criteria were ocular or primary mucosal melanoma; history or evidence of cardiac metastases or active central nervous system disease; history of other malignancy within the past 5 years; major surgery within 4 weeks prior to entry; history of cardiovascular disease (e.g., acute coronary syndrome, coronary angioplasty, cardiac arrhythmia, or coronary stenting within the past 24 weeks, abnormal cardiac valve morphology, QTc$\geq$480 msec, or New York Heart Association (NYHA) Class II-IV heart failure).

Patients were randomized to receive

- dacarbazine 1000mg/m^2 intravenously on day 1 of each 21-day cycle (control)
- dabrafenib 150 mg orally, one hour before or two hours after eating, twice daily (experimental)

Treatment on both arms was to continue until disease progression, death or an unacceptable adverse event. Patients allocated to dacarbazine were permitted to receive open-label dabrafenib

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following investigator-assessed disease progression and completion of a 21-day washout period from last dose of dacarbazine.

The sample size of 200 patients, with a 3:1 randomization, was based on the ability to detect, with more than 95% power at a one-sided alpha level of 2%, a 67% decrease in the immediate risk of progression or death (HR of 0.33) in patients with BRAF V600E mutation-positive melanoma at 102 PFS events, 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 conducted in the intent-to-treat (all randomized) population and compared using a log-rank test stratified on disease stage (unresectable stage III, stage IV M1a, or stage IV M1b vs. stage IV M1c). For the reasons discussed in the statistical review, the stratification variables were based on those used for randomization assignment rather than those recorded on the case report form for the primary analysis. The hazard ratio (HR) was to be calculated using the Pike estimator and one-sided 98% confidence intervals determined for the HR. The timing of the analysis of OS was not specified in the original protocol and no power calculations were provided. Analyses of secondary efficacy endpoints were to be conducted using a two-sided α of 0.05; no adjustment for multiplicity was specified in the original protocol.

Results

A total of 250 patients were enrolled across 70 investigative sites, with the first patient enrolled on February 2, 2011, and 187 patients assigned to dabrafenib and 63 patients assigned to dacarbazine. The majority, 74%, were enrolled in European study sites, 20% in North America study sites, and 6% in Australian study sites. At the data cut-off date for the key efficacy analyses, 57% of patients in the dabrafenib arm and 22% of patients in the dacarbazine arm remained on assigned therapy. Twenty-eight (44%) of the 63 patients assigned to dacarbazine identified as having disease progression by study investigators had received post-progression dabrafenib treatment.

Baseline demographics were similar in the two treatment arms. Nearly all patients (99%) were White, 60% were male, and 79% were less than 65 years of age. With regard to baseline disease characteristics, 67% had an ECOG PS of 0, 31% had an ECOG PS of 1, and 2% had an ECOG PS of 2; 66% had Stage IV M1c disease, 33% had an LDH value above the upper limit of normal, 60% had both visceral and non-visceral sites of disease while 12% had visceral disease only, and 48% of patients had 3 or more sites of disease. Most (88%) had primary cutaneous melanoma and 3% had non-cutaneous primary sites (a protocol violation), however data were missing on primary site of origin for 7%. Prior surgery was reported for 96% of the population and data on prior surgery were missing for 4%. Information on prior chemotherapy treatment was missing for 70% of the population, while 30% were reported to have had prior chemotherapy. Similarly, information on prior radiotherapy was missing for 81% of the population, while 19% were reported to have had prior radiotherapy.

The trial demonstrated a statistically significant and clinically meaningful improvement in PFS for the dabrafenib arm compared to the dacarbazine arm as well as a higher overall response rate for dabrafenib compared to dacarbazine. The key efficacy endpoints are summarized in the following table and figures.

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TABLE 1: Key Efficacy Outcomes in the BREAK-3 Trial

Efficacy Outcome	Dabrafenib (n=187)	Dacarbazine (n=63)
Progression-free survival[1]		
Number of PFS events	78 (42%)	41 (65%)
Number of disease progression events	76	41
Number of deaths	2	0
Hazard ratio[2] (95% confidence interval) p-value[3]	0.32 (0.19, 0.53) P<0.001	
Median PFS in months	5.1	2.7
Overall survival		
Number of deaths (%)	21 (11%)	9 (14%)
Hazard ratio[2] (95% confidence interval) p-value	0.67 (0.28, 1.58) 0.31	
Overall Response Rate[1] (95% confidence interval)	52% (44%, 59%)	17% (9%, 29%)
Complete responses (rate)	6 (3%)	0
Partial Responses (rate)	91 (49%)	11 (17%)

[1] Investigator-assessed
[2] Pike estimator, unstratified
[3] Unstratified log-rank test

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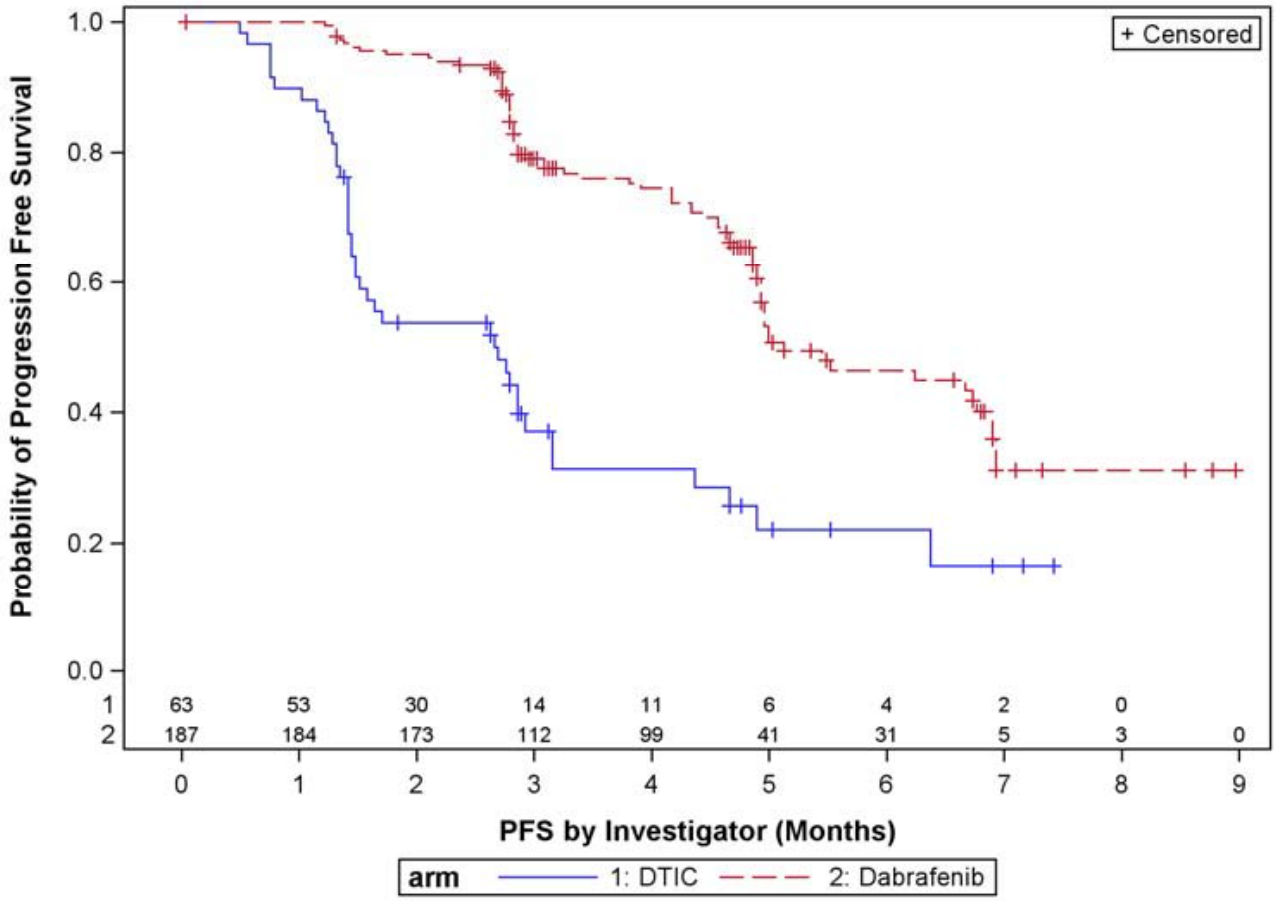
Figure 3. K-M Curves of PFS by investigator (from statistical review)



The results for independent review committee (IRC)-determined PFS using radiologic imaging review alone (IRC IR) or radiologic review combined with an independent oncologist's review of photographic images (IRC IR IO) based on FDA's analysis program were similar to those obtained with investigator-determined PFS. However, FDA did not agree that the point estimates obtained for IRC review be included in product labeling because the "primary" IRC analysis (with or without the oncologist's input) was not specified and because FDA was unable to replicate the GSK's reported results, likely due to differences in programming to generate the analysis dataset.

The analysis of overall survival, provided in the NDA at FDA's request, was not mature. At the time of the analysis, there were 30 deaths, constituting 12% of the study population. There was no evidence of a detrimental effect of dabrafenib treatment of survival in this assessment.

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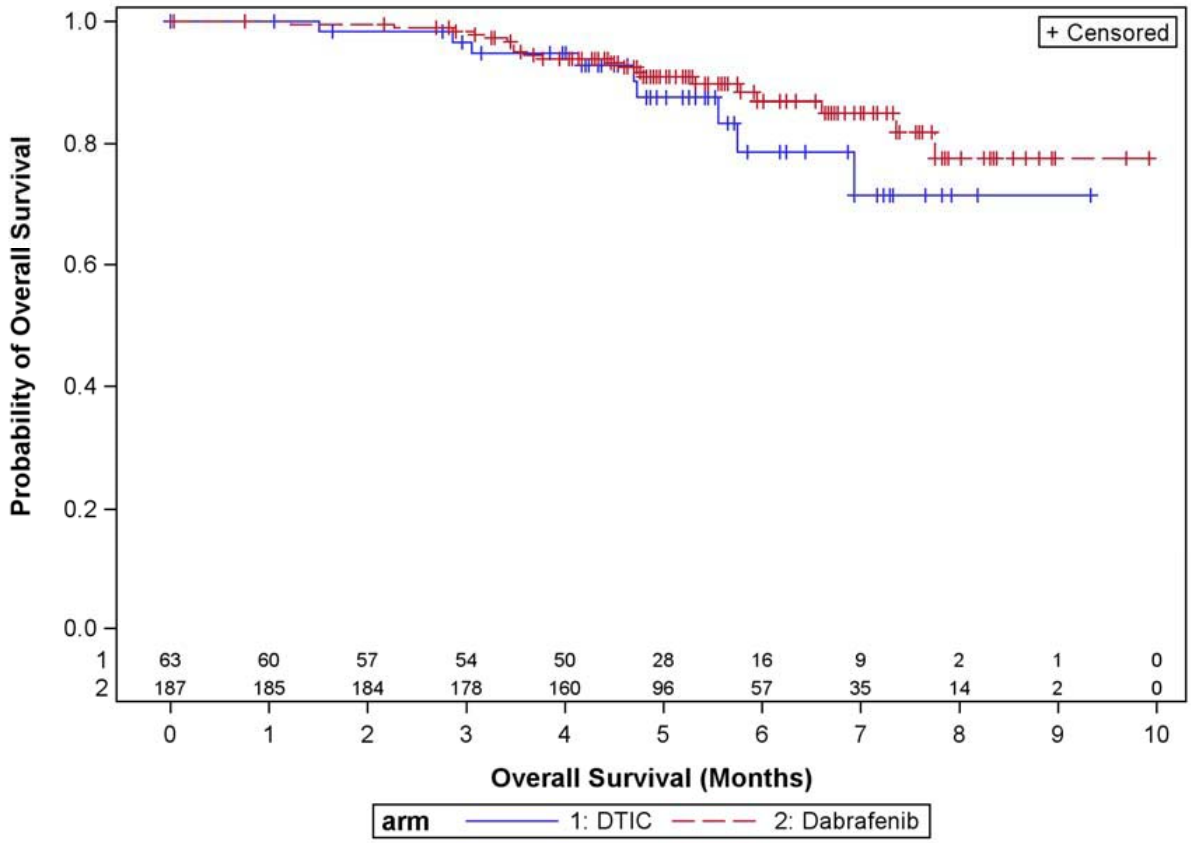
Figure 6. K-M Curves of OS



The overall response rate (ORR) was also higher in the dabrafenib arm as compared to dacarbazine by all assessors (investigator, IRC IR and IRC IR IO), however for those did respond, response durations were similar for patients in both treatment arms. Given the absence of a prespecified plan for multiplicity adjustment and the absence of a statistically significant effect on survival at this time, formal statistical comparisons are not appropriate for secondary outcomes including ORR.

Supportive trials

The NDA contained two supportive trials, intended to provide supportive evidence of anti-tumor activity (objective response rate) for BRAF V600E mutation-positive melanoma (BREAK-2), to provide data supporting anti-tumor activity directly and by relying on the results of BREAK-3 for extrapolation of anti-tumor activity to efficacy to support approval for patients with BRAF V600K mutation-positive melanoma (BREAK-2 and BREAK-MB), (b) (4) . The design and key results of these trials are summarized below:

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Protocol BRF113929 (BREAK-MB Trial)

Study Design
BREAK-MB was an open-label, two-cohort, Phase II study designed to evaluate the activity of dabrafenib in subjects with BRAF-mutation positive (BRAF V600E or BRAF V600K) melanoma metastatic to the brain in 2 cohorts:

- Cohort A (subjects with no prior local therapy for brain metastasis) or
- Cohort B (subjects who received prior local therapy for brain metastasis).

The rationale for conducting this trial was based on the observation of activity against CNS metastases observed in the first-in-human trial, Protocol BRF112680. In this trial, investigators reported that nine of the 10 patients with asymptomatic, untreated, brain metastases had reduction in the CNS metastases, with complete resolution of all brain lesions in four of these patients for a complete response rate of 40% for CNS metastases/

Key inclusion criteria for all subjects included:

- Histologically confirmed metastatic melanoma (Stage IV) with BRAF (V600E or V600K) mutation
- Up to 2 previous treatment regimens for extracranial metastatic melanoma including chemo-, cytokine-, immuno-, biological- and vaccine-therapy
- At least 1 measurable intracranial target lesion for which all of the following criteria had to be met:
  - previously untreated or progressive according to RECIST 1.1 (≥20% increase in longest diameter on baseline scan) after previous local therapy
  - immediate local therapy clinically not indicated or subject is not a suitable candidate to receive immediate local therapy
  - largest diameter of ≥0.5cm but ≤4 cm as determined by contrast-enhanced magnetic resonance imaging (MRI)
  - for target lesions with diameter of >0.5 cm but ≤ 1cm documented measurement by a neuroradiologist was required.
  - for all lesions with diameter of ≥3 cm but ≤4 cm documented measurement by a neuroradiologist was required.
- Subjects receiving concomitant corticosteroids were to be on a stable or decreasing dose for at least 3 weeks (Cohort A) or 2 weeks (Cohort B) prior to first dose of study treatment
- ECOG PS of 0 to 1.

Specific key inclusion criteria: for Cohort A:

- No prior local therapy for brain metastases
- No prophylactic or preventative anti-epileptic therapy (Exception: anti-epileptic therapy indicated in order to prevent neurologic symptoms caused by a preexisting condition and not related to brain metastasis was allowed).

Specific key inclusion criteria for Cohort B:

- At least 1 local therapy for brain metastases including but not restricted to brain surgery, Whole Brain Radiotherapy (WBRT) or Stereotactic Radiosurgery (SRS e.g. gamma knife,

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linear-accelerated-based radiosurgery, charged particles, and CyberKnife). Multiple local therapies or combinations of local therapies were allowed. For subjects receiving local therapy to all brain lesions (including WBRT), progression of pre-existing lesions based on RECIST 1.1 (> 20% increase in longest diameter on baseline scan) or new measurable lesions were required. For subjects receiving local therapy for some but not all lesions, disease progression based on RECIST 1.1 was not required as long as there were remaining brain lesions that were measurable and not previously treated
- Prophylactic or preventative anti-epileptic therapy was permitted.

Neurological symptoms related to brain metastases was a key exclusion criteria for both cohorts.

All subjects in the study received oral dabrafenib 150 mg BID until evidence of disease progression, death, or unacceptable AEs.

RECIST 1.1 Modifications:
Contrast-enhanced MRI was the only imaging modality accepted for the assessment of intracranial lesions throughout the study. Measurable lesions were defined as those that could be accurately measured in at least 1 dimension with the longest diameter ≥5 mm when evaluated with contrast-enhanced MRI. For lesions ≥5 mm but <1 cm, contiguous slices of 1 mm were to be used. For single intracranial lesions ≥1 cm, or for multiple intracranial lesions of which at least 1 was > 1cm, contiguous slices of a thickness corresponding to half the size of the lesion were to be used. Up to 5 lesions were to be selected as target lesions; all brain lesions in excess of these 5 lesions were regarded as non-target lesions.

Confirmation of intracranial response and overall CR and PR was required per protocol.

Efficacy Objectives
Primary: The primary objective of the study was to evaluate the OIRR, assessed by investigators, in Cohort A (treatment naïve) and Cohort B (at least 1 prior local treatment) subjects with BRAF V600E mutation positive metastatic melanoma to the brain treated with oral dabrafenib.

Secondary efficacy objectives for this study included:
- To estimate the ORR in subjects with BRAF V600E mutation positive melanoma
- To estimate duration of OIRR and ORR in subjects with BRAF V600E mutation positive melanoma
- To estimate the OIRR and ORR in subjects with BRAF V600K mutation positive melanoma
- To estimate duration of OIRR and ORR in subjects with BRAF V600K mutation positive melanoma
- To estimate PFS in subjects with BRAF V600E and BRAF V600K mutation positive melanoma
- To estimate OS in subjects with BRAF V600E and BRAF V600K mutation positive melanoma.

Criteria for Overall Intracranial Response Rate (OIRR)
Definitions for assessment of response for ***intracranial target*** lesion(s) are as follows:
- Complete Response (CR): Disappearance of all target lesions.

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- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as a reference, the baseline sum of the diameters (e.g. percent change from baseline).
- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as a reference, the smallest sum of diameters recorded since the treatment started (e.g. percent change from nadir, where nadir is defined as the smallest sum of diameters recorded since treatment start). In addition, the sum must have an absolute increase from nadir of 5mm.
- Not Evaluable (NE): Cannot be classified by one of the four preceding definitions

Note: If an intracranial target lesion disappears and reappears at a subsequent time point it should continue to be measured. The response at the time when the lesion reappears will depend upon the status of the other lesions. For example, if the disease had reached a CR status then PD would be documented at the time of reappearance. However, if the response status was PR or SD, the diameter of the reappearing lesion should be added to the remaining diameters and response determined based on percent change from baseline and percent change from nadir.

Definitions for assessment of response for intracranial non-target lesions are as follows:
- Complete Response (CR): The disappearance of all non-target lesions.
- Non-CR/Non-PD: The persistence of 1 or more non-target lesion(s) identified as a site of disease.
- Progressive Disease (PD): Unequivocal progression of existing non-target lesions.
- Not Applicable (NA): No intracranial non-target lesions at baseline
- Not Evaluable (NE): Cannot be classified by one of the four preceding definitions

Note: Intracranial non-target lesions, which are not assessed at a particular timepoint based on the assessment schedule, should be excluded from the response determination (e.g. non-target response does not have to be "Not Evaluable").

Table 8 presents the overall intracranial response at an individual time point for all possible combinations of tumour responses in target and non-target intracranial lesions with or without the appearance of new lesions for subjects with measurable intracranial disease at baseline.

Table 8 Evaluation of Overall Intracranial Response for Subjects with Measurable Intracranial Disease at Baseline

Target Lesions	Non-Target Lesions	New Lesions	Overall Intracranial Response
CR	CR or NA	No	CR
CR	Non-CR/Non-PD or NE	No	PR
PR	Non-PD or NA or NE	No	PR
SD	Non-PD or NA or NE	No	SD
NE	Non-PD or NA or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=complete response, PR = partial response, SD=stable disease, PD=progressive disease, NA= Not applicable, and NE=Not Evaluable

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Confirmation criteria:

- To be assigned a status of intracranial or overall PR or CR, a confirmatory disease assessment should be performed not less than 4 weeks after the criteria for response are first met.

Statistical Methods (Taken from the analysis plan in the original version of the protocol)

"The primary efficacy objective of this study is to assess the overall intracranial response rate (OIRR) assessed by Investigators using modified RECIST 1.1 criteria for each of two cohorts:

- Cohort A: Subjects who have not received any local therapy for brain metastases
- Cohort B: Subjects who have received prior local therapy for brain metastases including but not restricted to brain surgery, Whole Brain Radiotherapy (WBRT) or Stereotactic Radiosurgery (SRS e.g. gamma knife, linear accelerated-based radiosurgery, charged particles, and CyberKnife)

The study is designed to provide evidence to support the null hypothesis H0: OIRR ≤ 0.10 or to reject it in favor of the alternative hypothesis HA: OIRR ≥ 0.25 in each of the cohorts.

The null hypothesis is based on a study of patients with histologically confirmed metastatic melanoma to the brain (Agarwala 2004), which treated two cohorts with single agent temozolomide. The OIRR in patients with no prior systemic chemotherapy was 7%; in patients with prior chemotherapy the OIRR was 1%. Note that RECIST response criteria were not used in this study: a complete response (CR) was defined as the disappearance of all clinically detectable malignant disease; a partial response (PR) was defined for bidimensionally measurable disease as a decrease of at least 50% in the sum of the products of the largest perpendicular diameters of all measurable lesions, and for unidimensionally measurable disease as at least a 50% decrease in the sum of the largest diameters of all lesions; stable disease was defined for bidimensionally measurable disease as a decrease of less than 50% or an increase of less than 25% in the sum of the products of the largest perpendicular diameters of all measurable lesions, and for unidimensionally measurable disease as a decrease of less than 50% or an increase of less than 25% in the sum of the diameters of all lesions. Each response defined was valid only in the absence of new CNS lesions.

The alternative hypothesis was selected as the minimum increase in the OIRR that would be clinically relevant.

The study is designed to have 81.44% statistical power to detect an OIRR of at least 0.25 in subjects who receive GSK2118436 in each of the two cohorts. These hypotheses will be tested in each cohort using a one-sided test for superiority with $\alpha=0.041$. The study does not require that the null hypothesis is rejected in both cohorts to be successful. Therefore, there will be no adjustment of the Type I error for multiple testing."

Major Protocol Revisions and Rationale For BREAK-MB

The original protocol for Study BREAK-MB was approved on November 4, 2010 and was amended 3 times. The first subject was dosed on February 2, 2011. The data cut-off date was November 28, 2011, and the Clinical Study Report was dated July 2012.

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Major revisions to the clinical protocol were incorporated in the second amendment to the protocol (effective March 22, 2011). These were:

- Primary efficacy population was revised to limit the primary analyses of efficacy to patients with BRAF V600E mutation positive melanoma
- Secondary efficacy analyses identified as those conducted in patients with BRAF V600K mutation positive melanoma
- the two-stage design was changed to a one-stage design and the alternative hypothesis was changed from OIRR≥0.25 to OIRR≥0.30
- the Type I error rate was decreased to 0.025 (one-sided);
- addition of IDMC to review data periodically throughout the study;
- changes to inclusion/exclusion criteria to clarify eligibility with regard to anti-epileptic drug use and clarify eligibility regarding prior treatment for Cohort B

The statistical analysis plan was revised as follows

"This single stage study is designed to provide evidence to support the null hypothesis H0: OIRR ≤ 0.10 or to reject it in favour of the alternative hypothesis HA: OIRR ≥ 0.30 for BRAF V600E mutation positive subjects in each of the cohorts.

This study, or a single cohort thereof, may be stopped at any time if excessive toxicities with the study treatment are observed.

Evidence from the BRF112680 study suggests that 15% of subjects will be V600K mutation positive, therefore the projected number of subjects in each cohort is 71- 60 V600E mutation positive and approximately 11 V600K mutation positive subjects."

Rationale: The changes for Study BREAK-MB regarding the BRAF V600 populations were implemented based on the FTIH study (BRF112680) in which (1) the response rate was lower in subjects with BRAF V600K mutated tumors than in those with the more common BRAF V600E mutation and (2) the BRAF V600D mutation was so rare (<0.001%) [COSMIC Database, 2012] it was unlikely that sufficient subjects could be enrolled to validate the relevance of this mutation.

Clinical Trial results

The first patient was enrolled February 2, 2011, the study was "completed" with a data cut-off date of November 28, 2011, and the clinical study report was completed July 2012. This trial was conducted at 24 clinical study sites across Australia, Canada, France, Germany, Italy, and the US; the majority were enrolled in the US (28%), Germany (28%) and Australia (16%). A total of 172 patients were registered on protocol; all 172 received at least one dose of study treatment. As anticipated, the majority of patients (81%) had V600E mutation-positive melanoma. There were 89 patients enrolled in Cohort A and 83 patients enrolled in Cohort B. The primary efficacy population in both cohorts was patients with BRAF V600E mutation-positive melanoma, which consisted of 74 patients in Cohort A and 65 patients in Cohort B.

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	Cohort A (n=74)	Cohort B (n=65)
Investigator-assessed		
Overall responses (rate %) (95% confidence interval)	29 (39%) (28%, 51%)	20 (31%) (20%, 43%)
Complete responses (rate %)	2 (4%)	0
Partial responses (rate %)	27 (36%)	20 (31%)
Duration of response (weeks)	20.1	28.1
Independent Review Committee		
Overall responses (rate %) (95% confidence interval)	15 (20%) (12%, 31%)	12 (18%) (9.9%, 30%)
Complete responses (rate %)	1(1%)	0
Partial responses (rate %)	14 (19%)	12 (18%)
Duration of response (weeks)	20.3	20.1

A post hoc adjudication was conducted based on the finding that the investigator and independent review assessments of OIRR were discordant for approximately half of the response determinations in Cohort A and 60% of patients in Cohort B. For Cohort A, the IRC identified CR for one of the 2 patients and PR for 13 of the 27 patients identified as CR or PR, respectively, by the investigators. In Cohort B, the IRC identified 11 patients with PR among the 20 identified as having PR by the investigators. In each cohort, the IRC identified one patient as a PR that was identified as stable disease by the investigator assessment. Concordance is reproduced from Table 7.0006 of the clinical study report

IRC Best Response	Investigator-Assessed Best Response					
	CR	PR	SD	PD	NE	Total
Cohort A						
Complete Reponse (CR)	1	0	0	0	0	1
Partial Response (PR)	0	13	1	0	0	14
Stable Disease (SD)	0	9	19	0	0	28
Progressive Disease (PD)	0	4	5	8	0	17
Not Evaluable	1	0	2	1	0	9
Not Applicable	0	1	4	0	5	5
Total	2	27	31	9	0	74
Cohort B						
Complete Reponse (CR)	0	0	0	0	0	0
Partial Response (PR)	0	11	1	0	0	12
Stable Disease (SD)	0	6	24	2	0	35
Progressive Disease (PD)	0	1	11	3	0	15
Not Evaluable	0	0	0	0	2	2
Not Applicable	0	2	2	0	0	4
Total	0	20	38	5	2	65

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In the clinical study report, GSK states "In order to better understand the discordance, a blinded, third-party adjudication was performed on discordant cases." In this evaluation, the adjudicator agreed with the investigator-determined response assessment for 68% of the patients with BRAF V600E mutation-positive melanoma with discordant OIRR response determinations and with the independent review-determined response assessment for the remaining 32% of the patients with BRAF V600E mutation-positive melanoma with discordant OIRR response determinations.

A partial summary of the reasons for discordance between investigator and IRC response determinations were listed in the clinical summary report as follows:

- Multiple target lesions were present in some cases and investigator and the independent review selected different lesions as targets. With a degree of heterogeneity among individual target lesions, there was a discordance based upon target lesion selection.
- Furthermore, some of the lesions became necrotic or hemorrhagic following treatment, limiting reproducibility of lesion measurements.
- The identification of new lesions due to variability in the image acquisition technique and the large number of MRI series led to discordance in some cases.
- Discordances also were present due to borderline response and progression.

Conclusions

Based on the Office of Hematology and Oncology's usual practice of citing independently verified response data when obtained in open-label trials for clinical claims, the product labeling will cite only the IRRC-determined response rates. (b) (4)

BREAK-2 (Protocol BRF113710) was a single-arm, open-label, activity-estimating trial of the anti-tumor activity dabrafenib in patients with BRAF V600E or V600K mutation-positive metastatic melanoma who had received prior chemotherapy or prior biologic therapy (but not prior BRAF inhibitor therapy). Ninety-two patients were enrolled in this trial, of whom 16 (17%) had BRAF V600K mutation-positive melanoma.

The results, by mutation-type (V600E vs. V600K), as determined by an independent radiologic review committee (IRC) for overall response rates in the BREAK-2 and BREAK-MB trials are summarized in the table below.

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Efficacy outcome	BREAK-MB				BREAK-2	
	Cohort A		Cohort B			
	V600E (n=74)	(b) (4)	V600E (n=65)	(b) (4)	V600E (n=76)	(b) (4)
IRC-assessed ORR						
Patients with Responses (%)	21 (28%)		15 (23%)		31 (41%)	
(95% confidence intervals)	(18%,40%)		(14%, 25%)		(30%,52%)	
Complete Response rate	0		0		3%	
Partial Responses Rate	28%		23%		38%	
Median DOR[1] (mos)	4.7		4.7		6.2	

[1] DOR=Duration of Response
[2] NC=Not calculable

Consistent with usual practices in the Office of Hematology and Oncology Products, the IRC-determined response rates and duration of responses have been used to assess the strength of the findings in support of labeling claims for open-label, tumor-based endpoints. The results reported by the IRC were lower than that reported by investigators, and were also lower than the response rates reported for BRAF V600E mutation-positive melanoma in the BREAK-3 trial, which suggests that response rates may vary by extent of prior treatment. However, the most significant findings were of the large and clinically relevant difference in response rates between patients with V600E and V600K mutation-positive disease. Across all subgroups (BRAF V600K mutation-positive patients in BREAK-MB Cohort A, BREAK-MB Cohort B, and BREAK-2) the lower limit of the response rate was below 10%. This suggests that anti-tumor activity is no better than available therapy, such as the 17% ORR for the dacarbazine arm in the BREAK-3 trial. (b) (4)

8. Safety

Size of the database

The safety database for dabrafenib is sufficient to identify serious adverse reactions occurring at an incidence of 0.5% or greater. The safety of TAFINLAR was evaluated in 586 patients with BRAF V600E or V600K mutation-positive, unresectable or metastatic melanoma, previously treated or untreated, who received TAFINLAR 150 mg orally twice daily as monotherapy until disease progression or unacceptable toxicity, including 181 patients treated for at least 6 months and 86 additional patients treated for more than 12 months.

Major safety concerns

The most clinically important risks of dabrafenib are an increased risk of developing new cutaneous squamous cell carcinomas (cuSCC) (nine patients (5%) developing new cuSCC in the dabrafenib arm of the BREAK-3 trial as compared to none in the dacarbazine arm), new

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keratoacanthomas (five patients (3%) in the dabrafenib arm compared to none in the dacarbazine arm), basal cell carcinomas (five patients (3%) in the dabrafenib arm compared to none in the dacarbazine arm), and new primary melanomas (three patients (2%) in the dabrafenib arm compared with one in the dacarbazine arm). The one case of melanoma in the dacarbazine arm was identified 16 days after initiation of treatment and thus unlikely to have been drug-related. . Across the 586 patient safety database, the incidence of new cuSCC was 11% (64/586) and the incidence of new primary melanomas was 1% (6/586).

An additional clinically significant risk in indication patient population, which is suggested by non-clinical studies but has not been confirmed in human subjects, is the risk of cardiac valvular disease. However, as detected through serial LVEF monitoring in the BREAK-3 trial, there was an increased incidence in left ventricular dysfunction with clinically significant decreases in LVEF (≥10% below the institutional lower limit of normal) in four dabrafenib-treated patients compared to none in the dacarbazine arm; of the four dabrafenib-treated patients, only one had a history of cardiac disease.

In the BREAK-3 trial, the most common serious adverse reactions of dabrafenib are drug-induced febrile reactions, particularly when complicated by dehydration and pre-renal azotemia, and embryofetal teratogenicity.

In the BREAK-3 trial, 3% of dabrafenib-treated patients discontinued treatment due to adverse reactions and 18% required dabrafenib dose reductions for adverse reactions. The most frequent adverse reactions leading to dose reduction of dabrafenib were pyrexia (9%), PPES (3%), chills (3%), fatigue (2%), and headache (2%). It is noted that patients did not discontinue dabrafenib upon the development of a second primary cancer. The most common adverse reactions of dabrafenib, based on an increased incidence in the dabrafenib-treated group compared to dacarbazine, are listed in the table below.

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TABLE 2: Selected Common (≥ 20%) Adverse Reactions Occurring More Frequently (≥5%) or with Greater Severity (≥2% Higher Rate for Grade 3-4 Adverse Reactions) in Dabrafenib-Treated Patients

ADVERSE REACTION	Dabrafenib n=187		Dacarbazine n=59	
Primary System Organ Class Preferred Term	**All Grades (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Skin and subcutaneous tissue disorders				
Hyperkeratosis	37	2	0	0
Alopecia	22	0	2	0
Palmar-plantar erythrodysesthesia syndrome	20	2	2	0
Rash	17	0	0	0
Nervous system disorders				
Headache	32	0	8	0
General disorders and administration site conditions				
Pyrexia	28	3	10	0
Musculoskeletal and connective tissue disorders				
Arthralgia	27	1	2	0
Back pain	12	3	7	0
Myalgia	11	0	-	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)				
Papilloma[2]	27	0	2	0
cuSCC[3]	7	4	0	0
Gastrointestinal disorders				
Vomiting	12	2	25	0
Constipation	11	2	14	0
Respiratory, thoracic and mediastinal disorders				
Cough	12	0	5	0
Infections and infestations				
Nasopharyngitis	10	0	3	0
Metabolism and nutrition disorders				
Hyperglycemia[4]	50	6	42	2
Hypophosphatemia[4]	35	5	14	2
Hyponatremia[4]	8	2	3	-
Investigations				
Increased alanine aminotransferase[4]	11	1	22	-

[1] NCI CTCAE version 4.
[2] skin papilloma and papilloma
[3] squamous cell carcinoma of the skin and keratoacanthoma
[4] based on laboratory tests

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REMS
I concur with the clinical reviewer and the DRISK consultant that a REMS is not required to ensure safe use of dabrafenib. GSK submitted a risk management plan consisting of professional and patient labeling and did not submit a REMS. This is similar to the approach taken by the manufacturer of the other product in this class, vemurafenib. Both products carry the serious risk of an increased incidence of second primary cancers, specifically primary squamous cell cancers of the skin and keratoacanthomas, as well as a possible increased risk of new primary melanomas. These risks cannot be mitigated by patient selection as there have been no factors identified which predict these increased risks. Additional training is not required as the health professionals prescribing this product (oncologists) are trained to identify these lesions, and professional labeling accurately describes these risks and steps for patient monitoring.

PMRs and PMCs
In Dr. Theoret's review, multiple post-marketing requirements (PMRs) were identified to further characterize the risks of dabrafenib, including PMRs for

- Long-term follow-up to assess for serious, late adverse reactions including secondary cutaneous and non-cutaneous malignancies, based on the observation of the increased risk of cuSCC and new melanomas in the BREAK-3 trial and of the following treatment-emergent non-cutaneous malignancies in dabrafenib-treated patients, consistent of acute myeloid leukemia, myelodysplastic syndrome (n=2), adenocarcinoma of the breast (n=2), adenocarcinoma of the cervix, mycosis fungoides, gastric cancer, renal cell carcinoma, squamous cell cancer of the head and neck, glioblastoma, pancreatic cancer, and one case of recurrence in a patient with BRAF wild-type, KRAS mutation-positive colon cancer.

- 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.

9. Advisory Committee Meeting

This NDA was not referred for review to the Oncologic Drugs Advisory Committee because this is not the first drug (BRAF inhibitor) in its class, there were no issues related to the clinical trial design or primary endpoint used, and there were no novel issues identified that would benefit from the Advisory Committee's expertise.

10. Pediatrics

Orphan drug designation was granted for dabrafenib on January 12, 2011 for treatment of BRAF V600 mutation positive Stage IIb through IV melanoma. Therefore, this application is exempt from the requirements for the Pediatric Research Equity Act (PREA).

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11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: The proprietary name of TAFLINAR has been determined to be acceptable from a promotional and safety (potential for drug error) perspective by the DMEPA and DOP2 reviewers.

- Physician labeling:
  Agreement has not been reached on product labeling for the following: description of the recommended dose modifications for adverse reactions; inclusion in the Warnings and Precautions section of a subsection on risks of hyperglycemia, risks of tumor progression in BRAF wild type melanoma, and potential risks of hemolysis in patients with G6PD; inclusion of description of the adverse reactions from uncontrolled, Phase 2 trials and a listing of uncommon adverse reactions from the ISS already included in the Warnings and Precautions section or which are not clinically significant; and the inclusion of the description and results of supportive Phase 2 trials in Section 14; as well as editorial changes and minor wording changes.

  Proposed labeling comments for the following sections are provided
  - Indications and Usage: Indication will be limited to patients with BRAF V600E mutation-positive melanoma (GSK agrees)
  - Dosage and Administration: in accordance with current FDA policy on labeling of products for which a combination diagnostic is required to identify the indicated population, a subsection 2.1 titled "Patient Selection" has been added. In addition, the subsection on dose modification for adverse reactions should be edited for clarity. Information describing febrile adverse reactions should not be included in this section but can be covered with a cross-reference to the appropriate subsection in Warnings and Precautions
  - Warnings and Precautions
    - The subsections have been re-ordered to place information on secondary malignancies first as the most clinically important warnings (in place of febrile reactions)
    - Subsection on hyperglycemia added by FDA. Inclusion of this information seems warranted given that, of the 12 dabrafenib-treated patients with a medical history of diabetes at study entry, five (42%) required an increase in therapy within 8 weeks of initiation of dabrafenib treatment while no diabetic patient in the dacarbazine arm required such changes in medical management. In addition, one dabrafenib-treated patient without a reported history of diabetes required initiation of oral hypoglycemic therapy while on treatment with dabrafenib.
    - Subsection on pancreatitis added by GSK in May 17, 2013, based on a single case report with positive rechallenge and Dr. Theoret's request for additional information on cases of pancreatitis. This information is under review however

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Dr. Theoret's review would support inclusion of this information, which identified three cases of pancreatitis in the ISS, of which one had a negative rechallenge.

- FDA added the subsection on G6PD and possible hemolysis, noting that such patients were excluded from clinical trials based on the drug class (sulfonamide); (b) (4)
- (b) (4)

- Adverse Reactions: as noted above, information from the uncontrolled Phase 2 trials should not be included, given the availability of controlled trial data. Information in the tabular description of adverse reactions from the BREAK-3 trial should be edited to remove adverse reactions which do not occur at a higher overall rate or with greater severity than in the control arm (b) (4) as this is potentially promotional. In addition, uncommon adverse reactions identified in the overall safety database only if causally-related (based on controlled comparisons, rarity of the event or positive rechallenge), clinically significant (e.g., likely to alter the decision to initiation treatment or to continue to take dabrafenib), and not described elsewhere. (b) (4) .
- Drug Interactions: Subsections retitled and information on the potential effects of pH-altering drugs on absorption included.
- Use in Specific Populations: Modifications to subsections 8.1 and 8.3 and inclusion of new subsection 8.6 regarding Females of Reproductive Potential for consistency with current labeling recommendations by the Maternal Health Team; subsection on 8.5 to be modified to exclude description of specific risks which are not based on small patient numbers and not supported by biologic plausibility.
- Overdosage: Inclusion of available data on overdosage requested by FDA; information is under review
- Description: Edited for brevity. Information on mechanism of action moved to section 12.1
- Clinical Pharmacology: Subsection 12.2 (Pharmacodynamics) deleted and relevant information moved to subsection 12.1. Subsection 12.3 edited for brevity.
- Nonclinical Pharmacology/Toxicology: Information on clinical adverse reactions (b) (4) removed; information on hematologic adverse reactions observed only in animals deleted.
- Clinical Studies:
  - (b) (4)
  - (b) (4)

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- [redacted] (b) (4)
- Information on exploratory analyses of progression-free survival using the to-be-marketed companion diagnostic and based on an independent review committee added and summarized briefly
- Additional description of study design added.

  - How Supplied: no recommended changes
  - Patient Counseling Information: edited for brevity

- Carton and immediate container labels: All FDA-recommended revisions to carton and immediate container have been incorporated and there are no outstanding issues.

- Medication guide: GSK submitted a non-REMS Medication Guide. All patient labeling issues have been addressed.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: I concur with the recommendations of the review team that this NDA be approved for the indication in the agreed-upon product labeling

- Risk Benefit Assessment: I concur with the recommendations of all review disciplines that this application should be approved. Dabrafenib would be indicated to treat a serious and life-threatening disease for which there are effective but not curative therapies. The clinical benefits of dabrafenib which include a clinically meaningful improvement in progression-free survival [HR 0.32 (95% CI: 0.19, 0.53), $p<0.001$] with an increase in median PFS from 2.7 months with dacarbazine to 5.1 months with dabrafenib, and an substantial increase in overall response rate (52% vs. 17%) compared to dacarbazine are similar to that seen with the other drug in this class, vemurafenib. It is noted that there is insufficient data to determine the effect, if any, of dabrafenib on overall survival and thus there is no evidence that dabrafenib represents an advance over vemurafenib or ipilimumab, both of which have been shown to prolong survival in patients with melanoma. The side effect profile of dabrafenib includes increased risks of second cutaneous malignancies and of uveitis, embryofetal toxicity, and possible tumor promotion for BRAF wild type melanoma which have also been seen with vemurafenib. These adverse reactions are considered acceptable in light of the seriousness of the disease (metastatic melanoma) and observed benefits in terms of reduction in tumor/delay in tumor growth. Both drugs in this class have additional serious adverse reactions which include the risks of febrile drug reactions, pancreatitis, and hyperglycemia with dabrafenib and the risks of QT prolongation, serious dermatologic reactions (TEN, Stevens Johnson syndrome) and photosensitivity with vemurafenib. Therefore, although the effects of dabrafenib on survival have not been established, it may be a reasonable alternative particularly patients who develop QT prolongation or severe skin reactions. Considering all of the above information, dabrafenib treatment provides a favorable risk:benefit assessment for the treatment of patients with BRAF V600E metastatic melanoma.

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- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  I concur with the recommendations of the clinical reviewer and the DRISK consultant that a REMS is not required to ensure safe use and the physician and patient labeling will convey information necessary to mitigate the serious risk of secondary cutaneous malignancies.

- Recommendation for other Postmarketing Requirements and Commitments
  The following post-marketing trials have been required for the reasons outlined below. Additional PMRs based on clinical concerns have not been finalized at the time of this review.

  - 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*". This PMR has been required because the NDA lacked adequate data to rule out the QT prolongation potential of dabrafenib, which may require specific monitoring or preclude use of dabrafenib in patients with QT prolongation and dose modifications to ensure safe use.

  - 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*". This PMR has been required because the mass balance study suggests that dabrafenib is mainly (71%) eliminated through the liver and the NDA lacked adequate data to characterize the pharmacokinetics of dabrafenib in patients with moderate to severe hepatic impairment, which may require dose modification to avoid unacceptable toxicity.

  - 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*". This PMR has been required because mass balance study suggests that a 23% of dabrafenib dose is excreted in urine and the NDA lacked adequate data to characterize the pharmacokinetics of dabrafenib in patients with severe renal impairment, which may require dose modification to avoid unacceptable toxicity.

  - 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. This post-marketing trial has been required because i*n vitro* studies showed that dabrafenib metabolism is mediated by CYP2C8 and CYP3A4 while the two active metabolites, hydroxy- and desmethyl-dabrafenib, are CYP3A4 substrates; dose modifications of dabrafenib may be recommended in patients taking strong CYP3A4 and CYP2C8 inducers to ensure safe and effective levels of dabrafenib are achieved.

  - 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

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dose dabrafenib with regard to concomitant strong CYP3A4 inhibitors. This post-marketing trial has been required because *in vitro* studies showed that dabrafenib metabolism is mediated by CYP2C8 and CYP3A4 while the two active metabolites, hydroxy- and desmethyl-dabrafenib, are CYP3A4 substrates; dose modifications of dabrafenib may be recommended in patients taking strong CYP3A4 and CYP2C8 inhibitors to avoid unnecessary toxicity.

- 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. This post-marketing trial has been required because *in vitro* studies showed that dabrafenib metabolism is mediated by CYP2C8 and CYP3A4; dose modifications of dabrafenib may be recommended in patients taking CYP2C9 inducers to avoid unnecessary toxicity.

- 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. This post-marketing trial has been required because *in vitro* studies showed that dabrafenib is an inducer of CYP2C9; dose modifications of CYP2C9 substrates may be recommended in patients taking dabrafenib to ensure reasonably safe and effective levels of CYP2C9 substrates are achieved.

- Conduct a clinical trial to evaluate if proton pump inhibitors, H_2 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. This post-marketing trial has been required because dabrafenib is a low solubility drug and its solubility is pH-sensitive, which may alter dabrafenib bioavailability.

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/s/

PATRICIA KEEGAN
05/28/2013

Division Director Summary Review

Date	May 19, 2013
From	Patricia Keegan
Subject	Division Director Summary Review
NDA #	NDA 202806
Applicant Name	GlaxoSmithKline
Date of Submission	July 30, 2012
PDUFA Goal Date	May 30, 2013
Proprietary Name / Established (USAN) Name	Taflinar/ dabrafenib capsules
Dosage Forms / Strength	oral capsules / 50 mg and 75 mg
Proposed Indication(s)	"[redacted] (b) (4) is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF [redacted] (b) (4) mutation as detected by an FDA approved test. **Limitation of use:** [redacted] (b) (4) is not recommended for use in patients with wild-type BRAF melanoma."
Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager Review	Norma Griffin
Medical Officer Review	Marc Theoret
Statistical Review	Weishi (Vivian) Yuan
Non-clinical Pharmacology/Toxicology Review	Alexander Putman
CMC Review	Gaetan Ladouceur (DS), Amit Mitra (DP)
Biopharmaceutics Review	Akm Khairuzzaman
Microbiology Review	Bryan S Riley
Clinical Pharmacology Review	Jian Wang
Pharmacometrics Review	Justin Earp
Pharmacogenomics Review	Christian Grimstein
CDRH/OIVD	Donna Roscoe
OSI	Jean Mulinde
OC	Mahesh Ramandan
CDTL	Suzanne Demko
OPDP	Quynh-Van Tran
OSE/DMEPA	James H. Schlick
OSE/DRISK	Amarilys Vega
Maternal Health Team Consult	Tammie Brent Howard
Office of Medical Policy/Patient Labeling Review	Latonia Ford

CDRH=Center for Devices and Radiologic Health
OIVD= Office of In Vitro Diagnostics
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

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Division Director Summary Review

1. Introduction

GlaxoSmithKline submitted NDA 202806 seeking approval of dabrafenib (Taflinar capsules) for the proposed indication of "the treatment of patients with unresectable or metastatic melanoma with BRAF (b) (4) mutation as detected by an FDA approved test." Dabrafenib would be the second drug approved for this patient population; Zelboraf (vemurafenib), another RAF kinase inhibitor, was approved for this indication in August 2011.

Dabrafenib mesylate is a small molecule, RAF kinase inhibitor; based on *in vitro* data, dabrafenib inhibits wild type BRAF, BRAF V600E, BRAF V600K, and BRAF V600D protein kinase activity at clinically relevant concentrations.

The application was supported by a single randomized, open-label, multicenter trial (Protocol PRF113683, also known as the BREAK-3 trial) which compared the safety and efficacy of dabrafenib to dacarbazine in patients with previously untreated, unresectable locally advanced or metastatic cutaneous melanoma with BRAF V600E mutations as detected by a clinical trials assay. The NDA was also included supportive data, i.e., evidence of clinical activity (objective tumor responses) in two non-comparative trials of single agent dabrafenib in patients with previously untreated or previously treated, BRAF V600E or V600K mutation-positive, metastatic melanoma (BREAK –2 and BREAK-MB trials), (b) (4) for patients with unresectable locally advanced or metastatic cutaneous melanoma with BRAF V600K mutations and for treatment of CNS metastases from BRAF V600E primary melanomas.

The results of the BREAK-3 trial demonstrated a statistically robust and clinically important improvement in progression-free survival (HR 0.33 $p<0.001$; median PFS of 5.4 months vs. 2.7 months) and a higher response rate (52% vs. 17%) for patients with previously untreated, metastatic or unresectable, BRAF V600E, cutaneous melanoma who were randomized to dabrafenib as compared to those randomized to dacarbazine. In an immature analysis of overall survival (30 deaths), there was no difference in overall survival and no suggestion of a detrimental effect on overall survival. The most common serious adverse reactions were an increased risk of new cutaneous squamous cell cancers of the skin (7% vs. none in controls), serious non-infectious, febrile drug reactions (3% grade 3 pyrexia vs. none in controls), and severe hyperglycemia (>250-500 mg/dL) resulting in the need for medical management in non-diabetics or change in medical management of diabetic patients. The most common (incidence ≥ 20%) adverse reactions of dabrafenib were hyperglycemia (50%), hyperkeratosis (37%), hypophosphatemia (35%), headache (32%), arthralgia and papilloma (27% each), alopecia (22%), and palmar plantar erythrodysesthesias (20%).

The results of the BREAK-2 and BREAK-MB trials were reviewed and, as discussed in Section 7 of the review, these data did not constitute substantial evidence of effectiveness (b) (4) for BRAF V600K mutation-positive cutaneous melanoma or for treatment of CNS metastases from BRAF V600E or K mutation-positive cutaneous melanoma primaries.

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The major issues identified with this NDA were the lack of executable analysis programs and data quality issues which precluded an efficient review. As noted in the New Drug Guidance Document: Refusal to File (July 12, 1993), "the practice of submitting an incomplete or inadequate application and then 'repairing' it in the course of an extended review period is inherently inefficient and wasteful of agency resources." The Guidance also notes that "An application that has required major repair during review will also usually provide to be one with a prolonged review time, even if the actually agency review was efficient and swift." Based on GSK's submission of 'corrected' datasets in order to address data quality issues during the filing review period, data quality issues persisted and the lack of analysis programs based on GSK's determination that FDA systems could not support their proprietary software programs, resulted in increased burdens on the statistical and clinical reviewers to generate analysis datasets in order to verify the reported results.

Additional issues included resolution of process validation issues, lack of complete pharmacokinetic characterization resulting in the need for multiple post-marketing requirements, (b) (4)

As of the date of this review, agreement on post-marketing required trials and the physician package insert have not been reached.

2. Background

Indicated Population

Cutaneous melanoma, arising from malignant transformation of melanocytes in the skin, is the most aggressive malignancy arising from the skin; based on trend analyses, the incidence of melanoma has been increasing over the past several decades. The National Cancer Institute estimates that in 2013 there will be 76, 690 new cases of melanoma and 9,480 deaths due to melanoma in the United States. [1] While 84% of melanoma presents with localized disease which may be cured with surgical excision alone or with adjuvant interferon or investigational agents and has a 5-year survival rate of 98%, for the 4% who present with metastatic disease and receive systemic treatment, the 5-year survival rates is only 15%. Of patients presenting with cutaneous melanoma, approximately 50% will have melanoma bearing BRAF V600 mutations.

There are five drugs that have been approved by the US FDA for the treatment of metastatic melanoma: vemurafenib, ipilimumab, aldesleukin, dacarbazine, and hydroxurea. Hydroxurea which was FDA-approved in the 1970's, is no longer used or recommended by clinical practice guidelines. Dacarbazine and aldesleukin (interleukin-2) were approved by FDA for the treatment of metastatic melanoma in May 1975 and January 1998, respectively, based on evidence of durable objective tumor responses. Their use for the initial treatment of metastatic melanoma has declined following approval of ipilimumab and vemurafenib.

[1] http://www.cancer.gov/cancertopics/types/melanoma

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Commonly used off-label treatments, whose use has also declined following approval of vemurafenib and ipilimumab, include temozolomide alone or in combination with other drugs, dacarbazine-based combination chemotherapy regimens, and interferon alone or in combination with chemotherapy, as well as investigational immunotherapy treatments. All currently used treatment approaches are characterized by low objective tumor response rates (<20%) and no evidence of improved survival.

On March 25, 2011, FDA approved ipilimumab (Yervoy, Bristol Myers Squibb) for the treatment of unresectable or metastatic melanoma. Ipilimumab is a fully human IgG1 kappa monoclonal antibody that is directed against the human cytotoxic lymphocyte antigen-4 (CTLA-4) present on activated T-cells. The approval of ipilimumab was based on the results of a single, randomized trial which demonstrated a statistically significant improvement in overall survival for patients receiving ipilimumab in combination with a peptide vaccine (gp100 peptides) compared to those receiving peptide vaccine alone [HR 0.66 (95% CI: 0.55, 0.85), p=0.0004] with median survival times of 9.95 months and 6.44 months in the combination and gp100 monotherapy arms, respectively. The application was also supported by the high level results of Protocol CA 184024, a randomized trial of dacarbazine with or without ipilimumab, in which the high level results also demonstrated an improvement in overall survival [HR 0.85 (95% CI: 0.76, 0.93)] with a nominal p-value of 0.001, stratified log-rank test.

On August 17, 2011 vemurafenib (ZELBORAF, Genentech Inc.) an inhibitor of some mutated forms of BRAF serine-threonine kinase, including BRAF V600E, was approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test[2]. At the time of approval, labeling for vemurafenib also carried the following limitation of use: "ZELBORAF is not recommended for use in patients with wild-type BRAF melanoma." The approval was based on the results of a single, multicenter, randomized (1:1), open-label, active-controlled (dacarbazine) trial conducted in 675 patients with treatment naive, BRAF V600E mutation-positive unresectable or metastatic melanoma as detected by the cobas 4800 BRAF V600 Mutation Test. The trial demonstrated a statistically significant improvement in overall survival [HR 0.44 (95% CI: 0.33, 0.59); p < 0.0001] and progression-free survival [HR 0.26 (95% CI: 0.20, 0.33); p <0.0001] for patients in the vemurafenib arm. The median survival time not reached in the vemurafenib arm as compared to 7.9 months in the dacarbazine arm. The median PFS was 5.3 months in the vemurafenib arm compared with 1.6 months in the dacarbazine arm. The confirmed, investigator-assessed best overall response rate was 48.4% (95% CI: 41.6%, 55.2%) in the vemurafenib arm compared to 5.5% (95% CI: 2.8%, 9.3%) in the dacarbazine arm. These data were supported by the results of a single arm trial in 132 patients with previously treated, BRAF V600E mutation-positive, metastatic melanoma. In this trial, the confirmed best overall response rate as assessed by an independent review committee (IRC) was 52% (95% CI: 43%, 61%), with three complete responses. The median duration of response was 6.5 months.

[2]http://www.accessdata fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#labelinfo

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Pre-Submission Regulatory History

IND 105032: Original IND submission for GSK2118436, a small molecule designed to inhibit BRAF V600 muations. The IND was submitted June 26, 2009 and active as of July 26, 2009.

May 5, 2010: teleconference held and agreement reached on the clinical pharmacology program supporting a planned NDA for dabrafenib monotherapy. GSK confirmed that the dosage form of dabrafenib to be used in dabrafenib monotherapy trials would be the HPMC capsules and agreed to conduct enhanced pharmacovigilance of HPMC capsules due to concerns of increased myelosuppression with this dosage form.

May 5, 2010: The draft Protocol BRF113683 (BREAK-3 trial) was submitted to IND 105032

July 6, 2010: End-of-Phase 1/pre-Phase 3 meeting held to discuss the proposed development program for dabrafenib for treatment of BRAF V600 mutation-positive advanced melanoma, supported by Protocol BRF113710, a single-arm, open-label study of dabrafenib in patients with BRAF mutation-positive, metastatic melanoma who have received prior systemic therapy and Protocol BRF113683, a randomized, open-label, multicenter, Phase 3 trial comparing dabrafenib to dacarbazine in previously untreated patients with BRAF mutation-positive metastatic melanoma. Key agreements reached and comments provided during the meeting are as follows

- Regarding Protocol BRF113683, the proposed co-primary endpoints of PFS and OS were acceptable, with hierarchical testing to preserve Type I error for the co-primary endpoints, however the effect size for the PFS endpoint (difference in median PFS of 2 months) may not be sufficient to demonstrate clinical benefit. FDA and GSK agreed that the final analysis of PFS should occur after 60% of the planned number of OS events had occurred. A preNDA meeting should be requested to discuss the top-line results for PFS when available.
- The primary analysis of PFS based on investigator-determined assessment was acceptable, however the acceptability of a supporting analysis based on a random audit of PFS by an independent review committee could not be determined due to lack of details. GSK confirmed that all patient scans will be obtained to allow IRC review of additional patients. FDA stated that the proposed plan would be assessed when the final protocol/SAP were submitted.
- The proposed control (dacarbazine) and patient population were acceptable for Protocol BRF113683.
- GSK agreed to increase monitoring for secondary malignancies, biopsy of all suspicious lesions, and to provide analysis of second malignancies in BRF113683.
- Regarding Protocol BRF113710, FDA strongly recommended that the design be modified to be a dose-ranging comparison against a low-dose arm (e.g., 35 mg BID). GSK raised concerns regarding suboptimal dosing but agreed to consider this request.
- Regarding Protocol BRF113710, FDA stated that evidence of an overall response rate of sufficient magnitude and duration in patients who have received prior systemic therapy for melanoma may support a request for accelerated approval.

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October 7, 2010:

- FDA advised that if another agent receives approval for the treatment of first-line treatment of BRAF mutation-positive metastatic melanoma based on demonstration of improved survival, an accelerated approval could not be granted for this population.
- GSK noted that following the July 6, 2010 meeting, Protocol BRF113683 was revised such that PFS was the sole primary endpoint. GSK further noted that based on agreements with (b) (4), all patients in the control arm would be allowed to cross-over to dabrafenib at the time of progression. FDA stated that an improvement in PFS of sufficient magnitude may be an appropriate endpoint provided that an improvement in OS is not demonstrated in a prior approval of another drug in GSK's proposed population.
- FDA questioned whether dacarbazine remains an appropriate control and recommended that GSK conduct a 3-arm trial of GSK1120212 alone, dabrafenib alone, and the combination of GSK1120212 and dabrafenib. FDA advised that two pairwise comparisons of monotherapy to combination therapy would allow isolation of the treatment effects (b) (4) .
- FDA noted that in the modification of Protocol BRF113710 to a two-arm trial, the low dose arm selected was 50 mg BID (as compared to 150 mg BID). FDA did not object to the low dose selected. FDA noted that the alternative hypothesis (overall response rate of 40%) was lower than that observed in the Phase 1 trials (overall response rate of 60%) and stated that acceptability of the final response rate from the Phase 2 study will be a review issue.
- FDA and GSK agreed on monitoring of special adverse events of interest, which include second malignancies, cutaneous malignancies,
- (b) (4) .

October 22, 2010: BREAK-3 protocol (b) (4) . Trial design issues that prevented acceptance were the primary endpoint of progression-free survival and concerns regarding the acceptability of the control, dacarbazine. FDA also noted that the trial be designed to assess whether the proportion of BRAF V600 mutation-positive tumor was a determinant of disease progression, in light of the rapid disease progression noted in a subset of patients with BRAF wild-type tumors treated with GSK2118436.

December 30, 2010: Meeting held to discuss the possible submission of an NDA seeking accelerated approval in patients who had received and progressed following prior treatment for BRAF mutation-positive, metastatic melanoma based on evidence of a clinically meaningful response rate, duration of response, and acceptable risk:benefit profile, which would be evaluated in the context of available therapy. FDA stated that a submission containing data on 45 patients, supplemented by additional clinical trial data during the NDA review would be acceptable. FDA also advised that a companion diagnostic test would need to be approved concurrently with the approval of dabrafenib.

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February 11, 2011: FDA designated as a Fast Track program the investigation of GSK2118436 (dabrafenib) for the treatment of patients with BRAF mutation positive (V600E [redacted] (b) (4)) advanced melanoma.

January 12, 2011: FDA granted Orphan Drug designation for dabrafenib for the treatment of BRAF V600 mutation positive Stage IIb through IV melanoma.

January 31, 2012: CMC pre-NDA meeting held.

May 9, 2012: preNDA meeting held. Key agreements reached were

- The design and the reported results of Study BREAK-3 together with the proposed supportive data appear sufficient to support the filing of an NDA from a clinical perspective. The wording of the final indication statement will be determined based on the NDA review.
- Including information from the prespecified, IRC-assessed PFS endpoint in the absence of a pre-specified plan for controlling type I error is not likely to provide additional information useful to prescribing physicians. After review of the data in the NDA, FDA and GSK may discuss the appropriateness of inclusion of IRC determined PFS results.
- FDA agreed to consider labeling [redacted] (b) (4) if safety and efficacy in this subgroup is adequately supported by clinical study results and mechanism of action of dabrafenib.
- GSK agreed to provide interim data for cohort B and complete data for cohort D from Study BRF113771 in the NDA to address drug-drug interactions and also agreed to provide the final study report for Study BRF113771 as a post-marketing requirement addressing potential drug interactions.
- GSK agreed to conduct post-marketing trials for dedicated organ dysfunction studies and evaluation of effects on QTc in Protocol BRF113773.
- GSK agreed to provide the results of the exploratory analysis of efficacy based on the population identified as V600E mutation-positive according to the to-be-marketed diagnostic test in the clinical study report for the BREAK-3 trial. GSK agreed to include information on the mutation status based on the to-be-marketed test in the clinical study datasets to allow FDA to confirm the exploratory analysis.

June 20, 2012: FDA granted approval for submission of the NDA under an agreed-upon schedule for rolling review.

NDA Submission History

June 21, 2012: First module submitted
July 30, 2012: The final components of the NDA were received.
October 12, 2012: The 74-day letter issued, notifying GSK that the NDA had been filed and had been designated as a "standard" review.
October 27, 2012: FDA issued a letter notifying GSK that the proprietary name of [redacted] (b) (4) was denied

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The application was amended 66 times as of the date of this review; the bulk of these amendments were submitted in response to information requests from FDA.

3. CMC/Biopharmaceutics/Device

Chemistry, Manufacturing, and Controls
I concur with the conclusions reached by the chemistry and biopharmaceutics reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 24 months when stored at 25° C with excursions between 15° C and 30 °C. There are no outstanding issues..

Dabrafenib is a new molecular entity that is manufactured as a mesylate salt. Dabrafenib mesylate (b) (4). The drug product is an immediate release capsule, which will be marketed in two strengths, 50 mg and 75 mg. Each 50 mg capsule contains 59.25 mg dabrafenib mesylate equivalent to 50 mg dabrafenib free base. The major efficacy trial was conducted with the hypromellose (HPMC) capsule shells, which will be marketed.

The CMC and biopharmaceutics reviewers recommended approval and did not request postmarketing commitments.

Device (companion diagnostic)
The NDA contained a letter authorizing CDER to refer to bioMerieux's IDE G120011 for the THxID™ BRAF assay in support of NDA 202806. Concurrent with the review of this NDA, a pre-market application (PMA) was submitted for the companion diagnostic for identification of patients with BRAF V600 mutation-positive melanoma, manufactured by bioMerieux.

I concur with the conclusions reached by the device reviewer regarding the acceptability of the companion diagnostic test kit, manufactured by bioMerieux, for the identification of patients for whom dabrafenib is indicated. Manufacturing site inspections for this test kit were acceptable. There are no outstanding issues.

4. Nonclinical Pharmacology/Toxicology

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

As noted in Dr. Putman's review, nonclinical pharmacology studies demonstrated that dabrafenib is an inhibitor of wild-type BRAF (IC_{50} = 3.2 nM), wild-type CRAF (IC_{50} = 5 nM), and BRAFV600E (IC_{50} =0.65nM), BRAFV600K (IC_{50} =0.5nM), and BRAFV600D (IC_{50} =1.48 nM) kinases. Dabrafenib-induced inhibition of BRAF kinases appeared to be time-dependent, reversible, and ATP-competitive. In vitro incubation with dabrafenib decreased phosphorylation of extracellular signal regulated kinase (ERK) in cell lines. In contrast, in a

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panel of tumor cell lines, the effects on tumor cell growth (gIC_{50}) was limited to cell lines from some primary cancers containing BRAFV600E mutations but was ineffective in cell growth inhibition for cell lines derived from colon cancer (3 of 4 cell lines), sarcomas, ovarian cancers, and lung cancers bearing BRAF V600E mutations. Dabrafenib was also ineffective in suppression of tumor growth in cell lines with wild-type BRAF or cell lines with KRAS, NRAS, or HRAS mutations.

Repeat dose (13-week) toxicology studies in rats and dogs supported the safety of the proposed recommended human dose (animal exposures 4-fold higher than humans) and the major metabolites of dabrafenib in humans (30-50% of human exposures). The rat and dog are acceptable species for assessment of toxicology based on similar inhibition of dog and rat wild-type BRAF in *in vitro* studies. The main target organs of toxicity were the skin manifesting as proliferative skin lesions and papules at exposures achievable with the recommended human dose, male reproductive organs consisting of aspermia and degeneration of the testes at exposures achievable with the recommended human dose, heart with development of marked atrophy and hemorrhage in the right atrioventricular at exposures 5-fold greater than that achieved with the recommended human dose, and stomach manifesting as hyperplasia and infiltration. Specifications for impurities and degradants were qualified by 4-week toxicology studies.

Dabrafenib was not mutagenic in the AmesTest or the mouse lymphoma assay, and was not clastogenic in an *in vivo* rat bone marrow micronucleus test. Carcinogenicity studies were not conducted since the indicated population has advanced cancer and clinical trials demonstrated that dabrafenib is carcinogenic (increased incidence of cutaneous squamous cell cancers). Dabrefenib was shown to impair fertility and to be embryotoxic in a combined fertility and embryofetal study in rats.

The non-clinical reviewer recommended approval and did not request post-marketing commitments or require post-marketing required studies for safety.

5. Clinical Pharmacology

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

The clinical pharmacology program of the NDA included single and multiple-dose pharmacokinetic, food effect, mass balance, absolute bioavailability, and drug-drug interactions studies and the results of population pharmacokinetic (PK) analysis. Formal QT studies, dedicated DDI studies, and evaluation of PK in patients with severe renal or hepatic impairment were not provided in the NDA. The clinical pharmacology reviewer did not identify any exposure-response (progression-free survival) relationships or exposure-toxicity (evaluated for ≥ grade 3 adverse reactions, and for ≥ grade 3 hyperglycemia, hyponatremia, hypophosphatemia, palmar-plantar erythrodysesthesia and ≥ grade 2 fever). There were no intrinsic factors (age, gender, weight, race) identified that resulted in clinically important effects on the pharmacokinetics of dabrafenib.

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Following oral administration of dabrafenib, the median time to achieve peak plasma concentration was 2 hours. Mean absolute bioavailability of oral dabrafenib was 95% in the fasted state however administration of a single 150 mg dose of dabrafenib with a high-fat meal resulted in a 51% reduction in Cmax and 31% reduction in AUC as compared to the fasted state. Dabrafenib is 99.7% bound to human plasma proteins.

The metabolism of dabrafenib is primarily mediated by CYP2C8 and CYP3A4; its active metabolites are hydroxy-dabrafenib and desmethyl-dabrafenib, which are also metabolized by CYP3A4, carboxy-dabrafenib which is excreted in bile and urine or decarboxylated. The terminal half-lives of dabrafenib is approximately 8 hours, that of hydroxy-dabrafenib is approximately 10 hours, while those of the carboxy- and desmethyl-metabolites are longer, (21 to 22 hours). 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. Fecal excretion is the major route of dabrafenib elimination (71%) and urinary excretion accounts for 23%.

Dabrafenib induces cytochrome P450 isoenzyme (CYP) 3A4-mediated metabolism and may induce other enzymes.

The pharmacogenomics reviewer evaluated the treatment effects of dabrafenib by mutation type (BRAF V600E vs. BRAF V600K). His analysis summarized published literature noting that, as compared to patients with BRAF wild-type melanoma, those with BRAF V600 mutation-positive melanoma were younger at diagnosis, are more likely to have primary melanoma at skin sites without chronic sun damage, and had a poorer outcome (shorter progression-free survival). Literature reports assessing characteristics of patients with melanoma bearing BRAF V600E as compared with those bearing BRAF V600K mutations noted that those with BRAF V600K mutations were older and a higher proportion were male. These findings were confirmed in FDA's analysis of the two supportive trials (BREAK-2 and BREAK-MB) which enrolled patients with both BRAF V600 E and BRAF V600K mutation –positive melanoma. In FDA's analysis, the Patients with V600K mutation were more likely to be men compared to patients with V600E mutation [82% vs. 60%, p=0.0048], and patients with BRAF V600K mutation were significantly older at screening [median (min, max): 63 (31, 87)] compared to patients with V600E mutation [median (min, max): 51 (19-79), p<0.0001]. In addition, the pharmacogenomics reviewer noted that although pre- clinical data show similar IC50 values for the V600E and V600K mutations, limited clinical data from Phase 2 studies BREAK-MB and BREAK-2 suggest marginal dabrafenib activity in patients with the BRAF V600K mutation compared to patients harboring the V600E mutation.

Based on the information provided (or not provided) in the application, the following post-marketing requirements have been imposed to address important unresolved potential safety issues

- Assesssment of dabrafenib effects on the QTc interval
- Assessment of pharmacokinetics in patients with severe renal impairment
- Assessment of pharmacokinetics in patients with moderate to severe hepatic impairment

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- Assessment of drug interactions based on metabolism of dabrafenib and on dabrafenib's effects on the cytochrome P450 system.

6. Clinical Microbiology

I concur with the conclusions reached by the clinical microbiology reviewer that there are no sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

Protocol History

August 17, 2010: The original version of Protocol 113683 (BREAK-3) trial was submitted to IND 105032, following the July 6, 2010 End-of-Phase 1/pre-Phase 3 meeting with GSK. On October 7, 2010, FDA met to discuss trial design issues and on October 22, 2010 issued an SPA Non-Agreement letter for Protocol 113683.

November 3, 2010: Amendment 1
- Modification to contraception section based upon nonclinical tox;
- Addition of CT for respiratory symptoms to dose modification table;
- Change to slide requirements for tumor tissue testing (20 to 15);
- addition of secondary malignancies as secondary objective;

March 23, 2011 Amendment 3
- Inclusion of serial PK sampling on a subset of patients to further characterize final formulation;
- clarification of crossover eligibility criteria;
- modification to tumor tissue requirements to allow primary tissue for screening,
- addition of statistical objective to analyze at best overall response rate.

June 3, 2011 Amendment 4
- Dose monitoring and management guidelines for neutropenia and fever updated based on grade 4 neutropenia and complicated pyrexia in dabrafenib trial using HPMC capsule dosage form.
- Full body skin photos at baseline have been changed from required to recommended.

November 14, 2011 Amendment 5
- Revised to permit patients with investigator reported disease progression on the dabrafenib arm to continue dabrafenib if investigator determines that the patient is still benefitting from dabrafenib treatment after consultation with the Medical Monitor.
- A guideline for renal insufficiency was added for the management of renal toxicities.
- Added the collection of serum creatinine and BUN laboratory values in febrile patients

April 20, 2012 Amendment 6

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- Based on IDMC determination that the primary endpoint was met, patients randomized to dacarbazine were allowed the option to receive dabrafenib prior to investigator-determined disease progression and requirement for independent review confirmation of disease progression prior to crossover was discontinued.
- Statistics section updated to reflect the current plans for analyses and address multiple testing issues.
- Modified to clarify intent in the collection of events of pyrexia and basal cell carcinoma.

Trial Design
The NDA is supported primarily by the results of a single trial, Protocol 113683 (BREAK-3), which is a randomized (3:1), two-arm, open-label, active-controlled trial conducted in patients with previously untreated, unresectable or metastatic, BRAF V600E mutation-positive melanoma, as determined by an investigational-use only test at a CLIA-certified centralized testing facility. Randomization was stratified for stage (unresectable stage III, stage IV M1a, and stage IV M1b vs. stage IV M1c).

The primary endpoint of the BREAK-3 trial was investigator-assessed progression-free survival (PFS). Key secondary efficacy objectives were comparison of overall survival, investigator-assessed overall response rates and durations of response between the two treatment arm, and validation of a BRAF V600E mutation assay as a companion diagnostic test. Additional endpoints were determination of the response rate and duration in patients randomized to dacarbazine who received dabrafenib as second-line therapy, comparison of changes in patient-reported outcomes between the treatment arms, characterization of the toxicity, notably rate of non-melanoma skin lesions in both arms, and of the pharmacokinetic profile of dabrafenib and several exploratory analyses.

Key eligibility criteria were histologically confirmed, unresectable stage III or metastatic melanoma, BRAF V600E mutation-positive tumor by central testing, no prior systemic treatment for metastatic or unresectable disease <u>except</u> aldesleukin (interleukin-2), measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, ECOG performance status of 0 or 1, and HIV sero-negative. Key exclusion criteria were ocular or primary mucosal melanoma; history or evidence of cardiac metastases or active central nervous system disease; history of other malignancy within the past 5 years; major surgery within 4 weeks prior to entry; history of cardiovascular disease (e.g., acute coronary syndrome, coronary angioplasty, cardiac arrhythmia, or coronary stenting within the past 24 weeks, abnormal cardiac valve morphology, QTc≥480 msec, or New York Heart Association (NYHA) Class II-IV heart failure).

Patients were randomized to receive
- dacarbazine 1000mg/m^2 intravenously on day 1 of each 21-day cycle (control)
- dabrafenib 150 mg orally, one hour before or two hours after eating, twice daily (experimental)

Treatment on both arms was to continue until disease progression, death or an unacceptable adverse event. Patients allocated to dacarbazine were permitted to receive open-label dabrafenib following investigator-assessed disease progression and completion of a 21-day washout period from last dose of dacarbazine.

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The sample size of 200 patients, with a 3:1 randomization, was based on the ability to detect, with more than 95% power at a one-sided alpha level of 2%, a 67% decrease in the immediate risk of progression or death (HR of 0.33) in patients with BRAF V600E mutation-positive melanoma at 102 PFS events, 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 conducted in the intent-to-treat (all randomized) population and compared using a log-rank test stratified on disease stage (unresectable stage III, stage IV M1a, or stage IV M1b vs. stage IV M1c). For the reasons discussed in the statistical review, the stratification variables were based on those used for randomization assignment rather than those recorded on the case report form for the primary analysis. The hazard ratio (HR) was to be calculated using the Pike estimator and one-sided 98% confidence intervals determined for the HR. The timing of the analysis of OS was not specified in the original protocol and no power calculations were provided. Analyses of secondary efficacy endpoints were to be conducted using a two-sided α of 0.05; no adjustment for multiplicity was specified in the original protocol.

Results

A total of 250 patients were enrolled across 70 investigative sites, with the first patient enrolled on February 2, 2011, and 187 patients assigned to dabrafenib and 63 patients assigned to dacarbazine. The majority, 74%, were enrolled in European study sites, 20% in North America study sites, and 6% in Australian study sites. At the data cut-off date for the key efficacy analyses, 57% of patients in the dabrafenib arm and 22% of patients in the dacarbazine arm remained on assigned therapy. Twenty-eight (44%) of the 63 patients assigned to dacarbazine identified as having disease progression by study investigators had received post-progression dabrafenib treatment.

Baseline demographics were similar in the two treatment arms. Nearly all patients (99%) were White, 60% were male, and 79% were less than 65 years of age. With regard to baseline disease characteristics, 67% had an ECOG PS of 0, 31% had an ECOG PS of 1, and 2% had an ECOG PS of 2; 66% had Stage IV M1c disease, 33% had an LDH value above the upper limit of normal, 60% had both visceral and non-visceral sites of disease while 12% had visceral disease only, and 48% of patients had 3 or more sites of disease. Most (88%) had primary cutaneous melanoma and 3% had non-cutaneous primary sites (a protocol violation), however data were missing on primary site of origin for 7%. Prior surgery was reported for 96% of the population and data on prior surgery were missing for 4%. Information on prior chemotherapy treatment was missing for 70% of the population, while 30% were reported to have had prior chemotherapy. Similarly, information on prior radiotherapy was missing for 81% of the population, while 19% were reported to have had prior radiotherapy.

The trial demonstrated a statistically significant and clinically meaningful improvement in PFS for the dabrafenib arm compared to the dacarbazine arm as well as a higher overall response rate for dabrafenib compared to dacarbazine. The key efficacy endpoints are summarized in the following table and figures.

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TABLE 1: Key Efficacy Outcomes in the BREAK-3 Trial

Efficacy Outcome	Dabrafenib (n=187)	Dacarbazine (n=63)
Progression-free survival[1]		
Number of PFS events	78 (42%)	41 (65%)
Number of disease progression events	76	41
Number of deaths	2	0
Hazard ratio[2] (95% confidence interval) p-value[3]	0.32 (0.19, 0.53) P<0.001	
Median PFS in months	5.1	2.7
Overall survival		
Number of deaths (%)	21 (11%)	9 (14%)
Hazard ratio[2] (95% confidence interval) p-value	0.67 (0.28, 1.58) 0.31	
Overall Response Rate[1] (95% confidence interval)	52% (44%, 59%)	17% (9%, 29%)
Complete responses (rate)	6 (3%)	0
Partial Responses (rate)	91 (49%)	11 (17%)

[1] Investigator-assessed
[2] Pike estimator, unstratified
[3] Unstratified log-rank test

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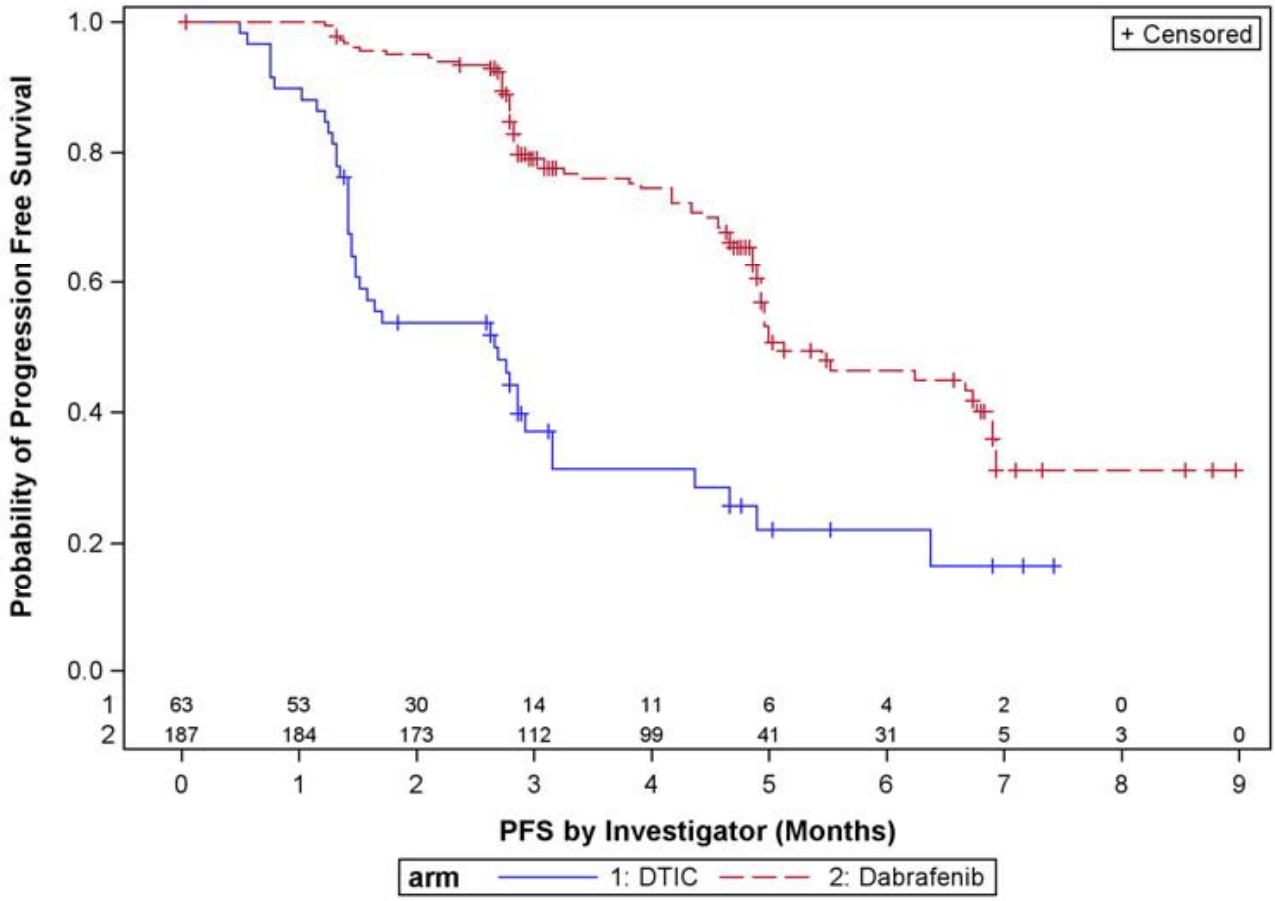
Figure 3. K-M Curves of PFS by investigator (from statistical review)



The results for independent review committee (IRC)-determined PFS using radiologic imaging review alone (IRC IR) or radiologic review combined with an independent oncologist's review of photographic images (IRC IR IO) based on FDA's analysis program were similar to those obtained with investigator-determined PFS. However, FDA did not agree that the point estimates obtained for IRC review be included in product labeling because the "primary" IRC analysis (with or without the oncologist's input) was not specified and because FDA was unable to replicate the GSK's reported results, likely due to differences in programming to generate the analysis dataset.

The analysis of overall survival, provided in the NDA at FDA's request, was not mature. At the time of the analysis, there were 30 deaths, constituting 12% of the study population. There was no evidence of a detrimental effect of dabrafenib treatment of survival in this assessment.

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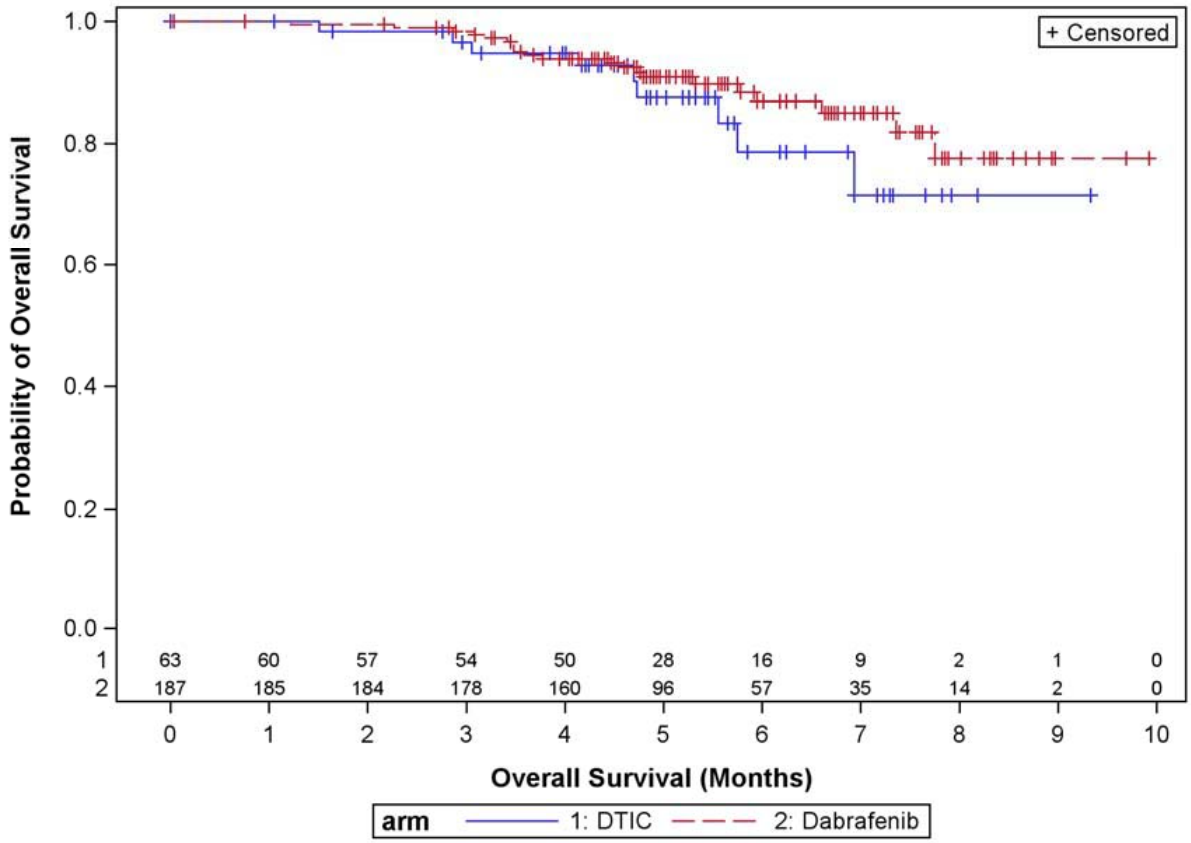
Figure 6. K-M Curves of OS



The overall response rate (ORR) was also higher in the dabrafenib arm as compared to dacarbazine by all assessors (investigator, IRC IR and IRC IR IO), however for those did respond, response durations were similar for patients in both treatment arms. Given the absence of a prespecified plan for multiplicity adjustment and the absence of a statistically significant effect on survival at this time, formal statistical comparisons are not appropriate for secondary outcomes including ORR.

Supportive trials

The NDA contained two supportive trials, intended to provide supportive evidence of anti-tumor activity (objective response rate) for BRAF V600E mutation-positive melanoma (BREAK-2), to provide data supporting anti-tumor activity directly and by relying on the results of BREAK-3 for extrapolation of anti-tumor activity to efficacy to support approval for patients with BRAF V600K mutation-positive melanoma (BREAK-2 and BREAK-MB), (b) (4) . The design and key results of these trials are summarized below:

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BREAK-MB (Protocol BRF113929) was a single-arm, open-label, two-cohort, multicenter, activity-estimating trial of dabrafenib in treatment-naïve (Cohort A) and previously-treated (Cohort B) patients with BRAF V600E or V600K mutation-positive melanoma with central nervous system (CNS) metastases. Cohort A enrolled 89 patients with CNS metastases who had received no prior local (CNS) therapy, of whom 15 (17%) were BRAF V600K mutation-positive. Cohort B enrolled 83 patients with prior local therapy for CNS metastases, of whom 18 (22%) were BRAF V600K mutation-positive.

The primary endpoint of this trial was determination of objective response for intracranial lesions (OIRR). The results, by mutation-type (V600E vs. V600K), as determined by an independent radiologic review committee (IRC) are summarized in the table below.

Efficacy Outcome	BREAK-MB Cohort A		BREAK-MB Cohort B	
	BRAF V600E (n=74)	(b) (4)	BRAF V600E (n=65)	(b) (4)
IRC-assessed OIRR				
No. of Patients with Responses (%)	15 (20%)		12 (18%)	
(95% confidence intervals)	(11.8%, 31.2%)		(9.9%, 30.0%)	
Complete Response rate	1%		0	
Partial Responses Rate	14%		18%	

Consistent with usual practices in the Office of Hematology and Oncology Products, the IRC-determined response rates and duration of responses have been used to assess the strength of the findings in support of labeling claims for open-label, tumor-based endpoints. The results reported by the IRC were lower than that reported by investigators, which may reflect the difficulty in accurately measuring CNS lesions. The response rates reported for CNS metastases (18%-20% for BRAF V600E mutation-positive CNS metastases) are less than half that of the 52% reported ORR for extra-cranial metastases in the BREAK-3 trial. (b) (4)

BREAK-2 (Protocol BRF113710) was a single-arm, open-label, activity-estimating trial of the anti-tumor activity dabrafenib in patients with BRAF V600E or V600K mutation-positive metastatic melanoma who had received prior chemotherapy or prior biologic therapy (but not prior BRAF inhibitor therapy). Ninety-two patients were enrolled in this trial, of whom 16 (17%) had BRAF V600K mutation-positive melanoma.

The results, by mutation-type (V600E vs. V600K), as determined by an independent radiologic review committee (IRC) for overall response rates in the BREAK-2 and BREAK-MB trials are summarized in the table below.

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Efficacy outcome	BREAK-MB				BREAK-2	
	Cohort A		Cohort B			
	V600E (n=74)	(b) (4)	V600E (n=65)	(b) (4)	V600E (n=76)	(b) (4)
IRC-assessed ORR						
Patients with Responses (%)	21 (28%)		15 (23%)		31 (41%)	
(95% confidence intervals)	(18%,40%)		(14%, 25%)		(30%,52%)	
Complete Response rate	0		0		3%	
Partial Responses Rate	28%		23%		38%	
Median DOR[1] (mos)	4.7		4.7		6.2	

[1] DOR=Duration of Response
[2] NC=Not calculable

Consistent with usual practices in the Office of Hematology and Oncology Products, the IRC-determined response rates and duration of responses have been used to assess the strength of the findings in support of labeling claims for open-label, tumor-based endpoints. The results reported by the IRC were lower than that reported by investigators, and were also lower than the response rates reported for BRAF V600E mutation-positive melanoma in the BREAK-3 trial, which suggests that response rates may vary by extent of prior treatment. However, the most significant findings were of the large and clinically relevant difference in response rates between patients with V600E and V600K mutation-positive disease. Across all subgroups (BRAF V600K mutation-positive patients in BREAK-MB Cohort A, BREAK-MB Cohort B, and BREAK-2) the lower limit of the response rate was below 10%. This suggests that anti-tumor activity is no better than available therapy, such as the 17% ORR for the dacarbazine arm in the BREAK-3 trial. (b) (4)

8. Safety

Size of the database

The safety database for dabrafenib is sufficient to identify serious adverse reactions occurring at an incidence of 0.5% or greater. The safety of TAFINLAR was evaluated in 586 patients with BRAF V600E or V600K mutation-positive, unresectable or metastatic melanoma, previously treated or untreated, who received TAFINLAR 150 mg orally twice daily as monotherapy until disease progression or unacceptable toxicity, including 181 patients treated for at least 6 months and 86 additional patients treated for more than 12 months.

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Major safety concerns
The most clinically important risks of dabrafenib are an increased risk of developing new cutaneous squamous cell carcinomas (cuSCC) (nine patients (5%) developing new cuSCC in the dabrafenib arm of the BREAK-3 trial as compared to none in the dacarbazine arm), new keratoacanthomas (five patients (3%) in the dabrafenib arm compared to none in the dacarbazine arm), basal cell carcinomas (five patients (3%) in the dabrafenib arm compared to none in the dacarbazine arm), and new primary melanomas (three patients (2%) in the dabrafenib arm compared with one in the dacarbazine arm). The one case of melanoma in the dacarbazine arm was identified 16 days after initiation of treatment and thus unlikely to have been drug-related. . Across the 586 patient safety database, the incidence of new cuSCC was 11% (64/586) and the incidence of new primary melanomas was 1% (6/586).

An additional clinically significant risk in indication patient population, which is suggested by non-clinical studies but has not been confirmed in human subjects, is the risk of cardiac valvular disease. However, as detected through serial LVEF monitoring in the BREAK-3 trial, there was an increased incidence in left ventricular dysfunction with clinically significant decreases in LVEF (≥10% below the institutional lower limit of normal) in four dabrafenib-treated patients compared to none in the dacarbazine arm; of the four dabrafenib-treated patients, only one had a history of cardiac disease.

In the BREAK-3 trial, the most common serious adverse reactions of dabrafenib are drug-induced febrile reactions, particularly when complicated by dehydration and pre-renal azotemia, and embryofetal teratogenicity.

In the BREAK-3 trial, 3% of dabrafenib-treated patients discontinued treatment due to adverse reactions and 18% required dabrafenib dose reductions for adverse reactions. The most frequent adverse reactions leading to dose reduction of dabrafenib were pyrexia (9%), PPES (3%), chills (3%), fatigue (2%), and headache (2%). It is noted that patients did not discontinue dabrafenib upon the development of a second primary cancer. The most common adverse reactions of dabrafenib, based on an increased incidence in the dabrafenib-treated group compared to dacarbazine, are listed in the table below.

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TABLE 2: Selected Common (≥ 20%) Adverse Reactions Occurring More Frequently (≥5%) or with Greater Severity (≥2% Higher Rate for Grade 3-4 Adverse Reactions) in Dabrafenib-Treated Patients

ADVERSE REACTION	Dabrafenib n=187		Dacarbazine n=59	
Primary System Organ Class Preferred Term	**All Grades (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Skin and subcutaneous tissue disorders				
Hyperkeratosis	37	2	0	0
Alopecia	22	0	2	0
Palmar-plantar erythrodysesthesia syndrome	20	2	2	0
Rash	17	0	0	0
Nervous system disorders				
Headache	32	0	8	0
General disorders and administration site conditions				
Pyrexia	28	3	10	0
Musculoskeletal and connective tissue disorders				
Arthralgia	27	1	2	0
Back pain	12	3	7	0
Myalgia	11	0	-	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)				
Papilloma[2]	27	0	2	0
cuSCC[3]	7	4	0	0
Gastrointestinal disorders				
Vomiting	12	2	25	0
Constipation	11	2	14	0
Respiratory, thoracic and mediastinal disorders				
Cough	12	0	5	0
Infections and infestations				
Nasopharyngitis	10	0	3	0
Metabolism and nutrition disorders				
Hyperglycemia[4]	50	6	42	2
Hypophosphatemia[4]	35	5	14	2
Hyponatremia[4]	8	2	3	-
Investigations				
Increased alanine aminotransferase[4]	11	1	22	-

[1] NCI CTCAE version 4.
[2] skin papilloma and papilloma
[3] squamous cell carcinoma of the skin and keratoacanthoma
[4] based on laboratory tests

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REMS
I concur with the clinical reviewer and the DRISK consultant that a REMS is not required to ensure safe use of dabrafenib. GSK submitted a risk management plan consisting of professional and patient labeling and did not submit a REMS. This is similar to the approach taken by the manufacturer of the other product in this class, vemurafenib. Both products carry the serious risk of an increased incidence of second primary cancers, specifically primary squamous cell cancers of the skin and keratoacanthomas, as well as a possible increased risk of new primary melanomas. These risks cannot be mitigated by patient selection as there have been no factors identified which predict these increased risks. Additional training is not required as the health professionals prescribing this product (oncologists) are trained to identify these lesions, and professional labeling accurately describes these risks and steps for patient monitoring.

PMRs and PMCs
In Dr. Theoret's review, multiple post-marketing requirements (PMRs) were identified to further characterize the risks of dabrafenib, including PMRs for

- Long-term follow-up to assess for serious, late adverse reactions including secondary cutaneous and non-cutaneous malignancies, based on the observation of the increased risk of cuSCC and new melanomas in the BREAK-3 trial and of the following treatment-emergent non-cutaneous malignancies in dabrafenib-treated patients, consistent of acute myeloid leukemia, myelodysplastic syndrome (n=2), adenocarcinoma of the breast (n=2), adenocarcinoma of the cervix, mycosis fungoides, gastric cancer, renal cell carcinoma, squamous cell cancer of the head and neck, glioblastoma, pancreatic cancer, and one case of recurrence in a patient with BRAF wild-type, KRAS mutation-positive colon cancer.

- 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.

9. Advisory Committee Meeting

This NDA was not referred for review to the Oncologic Drugs Advisory Committee because this is not the first drug (BRAF inhibitor) in its class, there were no issues related to the clinical trial design or primary endpoint used, and there were no novel issues identified that would benefit from the Advisory Committee's expertise.

10. Pediatrics

Orphan drug designation was granted for dabrafenib on January 12, 2011 for treatment of BRAF V600 mutation positive Stage IIb through IV melanoma. Therefore, this application is exempt from the requirements for the Pediatric Research Equity Act (PREA).

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11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: The proprietary name of TAFLINAR has been determined to be acceptable from a promotional and safety (potential for drug error) perspective by the DMEPA and DOP2 reviewers.

- Physician labeling:
  Agreement has not been reached on product labeling for the following: description of the recommended dose modifications for adverse reactions; inclusion in the Warnings and Precautions section of a subsection on risks of hyperglycemia, risks of tumor progression in BRAF wild type melanoma, and potential risks of hemolysis in patients with G6PD; inclusion of description of the adverse reactions from uncontrolled, Phase 2 trials and a listing of uncommon adverse reactions from the ISS already included in the Warnings and Precautions section or which are not clinically significant; and the inclusion of the description and results of supportive Phase 2 trials in Section 14; as well as editorial changes and minor wording changes.

  Proposed labeling comments for the following sections are provided
  - Indications and Usage: Indication will be limited to patients with BRAF V600E mutation-positive melanoma (GSK agrees)
  - Dosage and Administration: in accordance with current FDA policy on labeling of products for which a combination diagnostic is required to identify the indicated population, a subsection 2.1 titled "Patient Selection" has been added. In addition, the subsection on dose modification for adverse reactions should be edited for clarity. Information describing febrile adverse reactions should not be included in this section but can be covered with a cross-reference to the appropriate subsection in Warnings and Precautions
  - Warnings and Precautions
    - The subsections have been re-ordered to place information on secondary malignancies first as the most clinically important warnings (in place of febrile reactions)
    - Subsection on hyperglycemia added by FDA. Inclusion of this information seems warranted given that, of the 12 dabrafenib-treated patients with a medical history of diabetes at study entry, five (42%) required an increase in therapy within 8 weeks of initiation of dabrafenib treatment while no diabetic patient in the dacarbazine arm required such changes in medical management. In addition, one dabrafenib-treated patient without a reported history of diabetes required initiation of oral hypoglycemic therapy while on treatment with dabrafenib.
    - Subsection on pancreatitis added by GSK in May 17, 2013, based on a single case report with positive rechallenge and Dr. Theoret's request for additional information on cases of pancreatitis. This information is under review however

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Dr. Theoret's review would support inclusion of this information, which identified three cases of pancreatitis in the ISS, of which one had a negative rechallenge.

- FDA added the subsection on G6PD and possible hemolysis, noting that such patients were excluded from clinical trials based on the drug class (sulfonamide);
- [redacted] (b) (4) (b) (4) .

- Adverse Reactions: as noted above, information from the uncontrolled Phase 2 trials should not be included, given the availability of controlled trial data. Information in the tabular description of adverse reactions from the BREAK-3 trial should be edited to remove adverse reactions which do not occur at a higher overall rate or with greater severity than in the control arm [redacted] (b) (4) as this is potentially promotional. In addition, uncommon adverse reactions identified in the overall safety database only if causally-related (based on controlled comparisons, rarity of the event or positive rechallenge), clinically significant (e.g., likely to alter the decision to initiation treatment or to continue to take dabrafenib), and not described elsewhere. [redacted] (b) (4) .
- Drug Interactions: Subsections retitled and information on the potential effects of pH-altering drugs on absorption included.
- Use in Specific Populations: Modifications to subsections 8.1 and 8.3 and inclusion of new subsection 8.6 regarding Females of Reproductive Potential for consistency with current labeling recommendations by the Maternal Health Team; subsection on 8.5 to be modified to exclude description of specific risks which are not based on small patient numbers and not supported by biologic plausibility.
- Overdosage: Inclusion of available data on overdosage requested by FDA; information is under review
- Description: Edited for brevity. Information on mechanism of action moved to section 12.1
- Clinical Pharmacology: Subsection 12.2 (Pharmacodynamics) deleted and relevant information moved to subsection 12.1. Subsection 12.3 edited for brevity.
- Nonclinical Pharmacology/Toxicology: Information on clinical adverse reactions [redacted] (b) (4) removed; information on hematologic adverse reactions observed only in animals deleted.
- Clinical Studies:
  - [redacted] (b) (4)
  - [redacted] (b) (4)

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- [redacted] (b) (4)
- Information on exploratory analyses of progression-free survival using the to-be-marketed companion diagnostic and based on an independent review committee added and summarized briefly
- Additional description of study design added.

  - How Supplied: no recommended changes
  - Patient Counseling Information: edited for brevity

- Carton and immediate container labels: All FDA-recommended revisions to carton and immediate container have been incorporated and there are no outstanding issues.

- Medication guide: GSK submitted a non-REMS Medication Guide. All patient labeling issues have been addressed.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: I concur with the recommendations of the review team that this NDA be approved for the indication in the agreed-upon product labeling

- Risk Benefit Assessment: I concur with the recommendations of all review disciplines that this application should be approved. Dabrafenib would be indicated to treat a serious and life-threatening disease for which there are effective but not curative therapies. The clinical benefits of dabrafenib which include a clinically meaningful improvement in progression-free survival [HR 0.32 (95% CI: 0.19, 0.53), $p<0.001$] with an increase in median PFS from 2.7 months with dacarbazine to 5.1 months with dabrafenib, and an substantial increase in overall response rate (52% vs. 17%) compared to dacarbazine are similar to that seen with the other drug in this class, vemurafenib. It is noted that there is insufficient data to determine the effect, if any, of dabrafenib on overall survival and thus there is no evidence that dabrafenib represents an advance over vemurafenib or ipilimumab, both of which have been shown to prolong survival in patients with melanoma. The side effect profile of dabrafenib includes increased risks of second cutaneous malignancies and of uveitis, embryofetal toxicity, and possible tumor promotion for BRAF wild type melanoma which have also been seen with vemurafenib. These adverse reactions are considered acceptable in light of the seriousness of the disease (metastatic melanoma) and observed benefits in terms of reduction in tumor/delay in tumor growth. Both drugs in this class have additional serious adverse reactions which include the risks of febrile drug reactions, pancreatitis, and hyperglycemia with dabrafenib and the risks of QT prolongation, serious dermatologic reactions (TEN, Stevens Johnson syndrome) and photosensitivity with vemurafenib. Therefore, although the effects of dabrafenib on survival have not been established, it may be a reasonable alternative particularly patients who develop QT prolongation or severe skin reactions. Considering all of the above information, dabrafenib treatment provides a favorable risk:benefit assessment for the treatment of patients with BRAF V600E metastatic melanoma.

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- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  I concur with the recommendations of the clinical reviewer and the DRISK consultant that a REMS is not required to ensure safe use and the physician and patient labeling will convey information necessary to mitigate the serious risk of secondary cutaneous malignancies.

- Recommendation for other Postmarketing Requirements and Commitments
  The following post-marketing trials have been required for the reasons outlined below. Additional PMRs based on clinical concerns have not been finalized at the time of this review.

  - 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*". This PMR has been required because the NDA lacked adequate data to rule out the QT prolongation potential of dabrafenib, which may require specific monitoring or preclude use of dabrafenib in patients with QT prolongation and dose modifications to ensure safe use.

  - 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*". This PMR has been required because the mass balance study suggests that dabrafenib is mainly (71%) eliminated through the liver and the NDA lacked adequate data to characterize the pharmacokinetics of dabrafenib in patients with moderate to severe hepatic impairment, which may require dose modification to avoid unacceptable toxicity.

  - 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*". This PMR has been required because mass balance study suggests that a 23% of dabrafenib dose is excreted in urine and the NDA lacked adequate data to characterize the pharmacokinetics of dabrafenib in patients with severe renal impairment, which may require dose modification to avoid unacceptable toxicity.

  - 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. This post-marketing trial has been required because i*n vitro* studies showed that dabrafenib metabolism is mediated by CYP2C8 and CYP3A4 while the two active metabolites, hydroxy- and desmethyl-dabrafenib, are CYP3A4 substrates; dose modifications of dabrafenib may be recommended in patients taking strong CYP3A4 and CYP2C8 inducers to ensure safe and effective levels of dabrafenib are achieved.

  - 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

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dose dabrafenib with regard to concomitant strong CYP3A4 inhibitors. This post-marketing trial has been required because *in vitro* studies showed that dabrafenib metabolism is mediated by CYP2C8 and CYP3A4 while the two active metabolites, hydroxy- and desmethyl-dabrafenib, are CYP3A4 substrates; dose modifications of dabrafenib may be recommended in patients taking strong CYP3A4 and CYP2C8 inhibitors to avoid unnecessary toxicity.

- 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. This post-marketing trial has been required because *in vitro* studies showed that dabrafenib metabolism is mediated by CYP2C8 and CYP3A4; dose modifications of dabrafenib may be recommended in patients taking CYP2C9 inducers to avoid unnecessary toxicity.

- 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. This post-marketing trial has been required because *in vitro* studies showed that dabrafenib is an inducer of CYP2C9; dose modifications of CYP2C9 substrates may be recommended in patients taking dabrafenib to ensure reasonably safe and effective levels of CYP2C9 substrates are achieved.

- Conduct a clinical trial to evaluate if proton pump inhibitors, H_2 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. This post-marketing trial has been required because dabrafenib is a low solubility drug and its solubility is pH-sensitive, which may alter dabrafenib bioavailability.

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/s/

PATRICIA KEEGAN
05/20/2013