CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202806Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Efficacy
Application Number(s)	202,806
Priority or Standard	Standard
Submit Date(s)	July 30, 2012
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Division / Office	DOP2 / OHOP
Reviewer Name(s)	Marc Theoret Suzanne Demko, Team Leader
Review Completion Date	May 15, 2013
Statistical Team	Weishi Yuan Ke Hun, Team Leader
Established Name	Dabrafenib (GSK 2118436)
(Proposed) Trade Name	Tafinlar
Therapeutic Class	Kinase Inhibitor
Applicant	GlaxoSmithKline
Formulation(s)	Capsules: 50 mg, 75 mg
Dosing Regimen	150 mg orally twice daily
Indication(s)	Unresectable or metastatic melanoma with BRAF V600E mutation by an FDA-approved test

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

According to the review of the clinical data, the reviewer recommends regular approval of dabrafenib for the following indication:

TAFINLAR is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.

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

1.2 Risk Benefit Assessment

Melanoma develops at a relatively early age which results in a substantial number of years of life lost per person (Ekwueme, Guy, et al. 2011), and once metastatic carries a grim prognosis—the five year survival rate is historically less than 10% for patients. There are few FDA-approved treatments for metastatic melanoma—vemurafenib, ipilimumab, aldesleukin, and dacarbazine (DTIC)—and only vemurafenib, an inhibitor of the mutant BRAF V600E kinase, was specifically studied in patients with BRAF V600E mutation-positive unresectable or metastatic melanoma. In this molecularly defined subgroup of melanoma patients, vemurafenib demonstrated a prolongation of investigator-assessed progression-free survival (PFS) from a median of 1.6 months [95% confidence interval (CI): 1.5, 1.7] with DTIC to 5.3 months (95% CI: 4.8, 6.6) with vemurafenib with a hazard ratio (HR) of 0.26 (95% CI: 0.20, 0.33; p-value <0.0001). Vemurafenib also demonstrated improved overall survival (OS) compared to DTIC with a HR of 0.44 (95% CI: 0.33, 0.59; p <0.0001).

The recommendation for approval of NDA 202806 (dabrafenib) is primarily based on the results of the BRF113683 trial which demonstrated a statistically persuasive and robust, clinically meaningful prolongation in PFS. The BRF113683 trial was a multicenter, international, open-label, randomized (3:1), active-controlled trial comparing single agent dabrafenib to DTIC in 250 patients with previously untreated, histologically confirmed, advanced (unresectable Stage III) or metastatic (Stage IV) melanoma determined to be BRAF V600E mutation-positive based upon centralized testing. Patients were allocated to receive dabrafenib 150 mg orally twice daily (n=187) or DTIC 1000 mg/m^2 IV every 3 weeks (n=63) until disease progression or intolerable toxicity. The BRF113683 trial met its primary endpoint of investigator-assessed PFS demonstrating a statistically significant 67% reduction in the hazard rate of progression of disease or death [HR 0.33 (95% CI: 0.20, 0.55); 2-sided p-value <0.001 (stratified log-rank test)] on the dabrafenib arm compared to the DTIC arm. The median PFS on the dabrafenib arm was 5.1 months (95% CI: 4.9, 6.9) compared to 2.7 months (95% CI: 1.5, 3.2) on the DTIC arm. Analyses based on a blinded, independent central review assessment of PFS supported the

primary efficacy analysis using investigator assessments. The results of the OS analysis are not mature but do not suggest a detriment in overall survival with dabrafenib compared to DTIC [HR of 0.67 (95% CI: 0.28, 1.58)]. The investigator-assessed, confirmed objective response rates (ORR) were 52% (95% CI: 45%, 59%) on the dabrafenib arm, including 6 (3%) complete responders, and 17% (95% CI: 9%, 29%) on the DTIC arm, all partial responders. The Applicant did not evaluate the efficacy of dabrafenib in patients with BRAF V600K mutation-positive melanoma, a subgroup with apparent clinicopathologic differences from those with the BRAF V600E mutation subtype, as this important subgroup was not eligible for the primary trial; in activity-estimating trials, however, ORRs in patients with BRAF V600K mutation-positive metastatic melanoma do not suggest the same high level of anti-tumor activity with dabrafenib as that observed in patients with BRAF V600E mutation-positive metastatic melanoma.

A premarket approval application for the Biomerieux THxID BRAF Kit (PMA P120014), which is intended for use as an in vitro companion diagnostic assay to detect BRAF V600 (E or K) mutations in melanoma to aid in the selection of patients for treatment with dabrafenib, is currently under review in the Center for Devices and Radiological Health.

The primary safety risks of dabrafenib are new primary malignancies, including cutaneous squamous cell carcinoma/keratoacanthoma (cuSCC) and new primary melanomas, as well as serious febrile drug reactions, defined as fever complicated by hypotension, dehydration, severe rigors/chills, or renal failure in the absence of another identifiable etiology (e.g., infection). The rate of cuSCC was 11% across clinical trials of dabrafenib and, in the BRF113683 trial, was 7.5% in dabrafenib-treated patients and nil in DTIC-treated patients. In addition, new primary melanoma lesions occurred in three (1.6%) dabrafenib-treated patients and in none of the DTIC-treated patients. Cutaneous malignancies appear to be manageable with excision and do not require dose modification of dabrafenib.

The most frequent (≥ 20%) adverse reactions of dabrafenib were hyperkeratosis, headache, pyrexia, arthralgia, skin papilloma, alopecia, and palmar-plantar erythrodysesthesia syndrome. Approximately 3% of dabrafenib-treated patients experienced adverse events (AE) leading to treatment withdrawal. Dose reductions for AEs occurred in 18% of dabrafenib-treated patients, most frequently for pyrexia (9% in the dabrafenib treatment group vs. 0 in the DTIC treatment group), palmar-plantar erythrodysesthesia syndrome (3% vs. 0), chills (3% vs. 0), fatigue (2% vs. 0), and headache (2% vs. 0). Adverse events led to withholding treatment without dose reduction in 16% of dabrafenib-treated patients, most commonly for pyrexia (6% vs. 0). Grade 3 or 4 AEs occurred in 33% of dabrafenib-treated patients—the most frequent were cutaneous squamous cell carcinoma (4%), pyrexia (3%), and back pain (3%).

Dabrafenib has a favorable benefit-risk profile for treatment of patients with BRAF V600E mutation-positive unresectable or metastatic melanoma when compared to available treatment. Dabrafenib represents another therapeutic option from the same pharmacologic class as vemurafenib for treatment of this patient population. Dabrafenib demonstrated superiority to DTIC—a clinically relevant comparator at the time of initiation of the BRF113683 trial—with a prolongation of PFS of sufficient magnitude, when compared to treatment effects of available

therapy, to be considered clinical benefit. Whether the prolongation in PFS will also result in an improvement in OS, similar to the treatment effects observed with vemurafenib, is uncertain. One of the major safety risks of dabrafenib, new primary cutaneous malignancies, appears to be mitigated with appropriate monitoring and early intervention by clinicians. As with vemurafenib, the increased risk of cuSCC requires a non-REMS Medication Guide to inform patients about this risk as well as the requirement for frequent skin examinations to diagnose these lesions in early stages. This reviewer recommends that, as postmarketing requirements, the Applicant define the risk of new primary malignancies, including non-cutaneous new primary malignancies, as well as the potential risk of cardiac valvular abnormalities.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

The reviewer recommends the following post-marketing requirements:

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

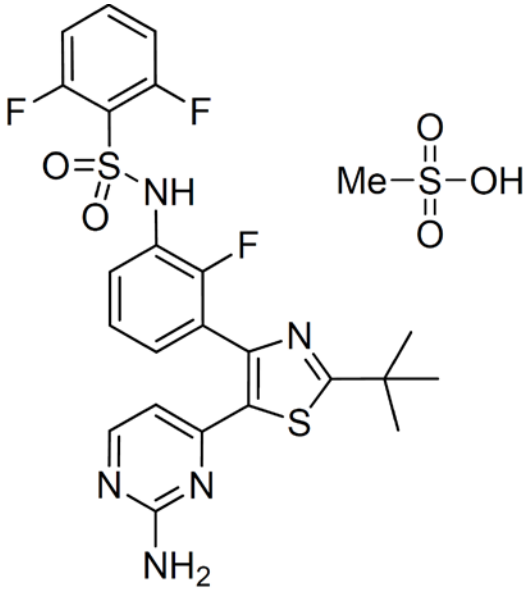
Submit the first interim report within six months of the date of FDA-approval of NDA 202806 and every two years thereafter until FDA determines that the final report submission fulfills this postmarketing requirement.

2 Introduction and Regulatory Background

2.1 Product Information

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

Figure 1: Structural Formula of Dabrafenib



2.2 Tables of Currently Available Treatments for Proposed Indications

Melanoma is the fifth most common cancer in men and seventh most common cancer in women in the United States. In 2013, it is estimated that there will be 76,690 new melanoma cases and 9,480 deaths from melanoma in the U.S. (Siegel, Naishadham, et al. 2013). Metastatic melanoma accounts for approximately 4% of all newly diagnosed melanoma cases (Howlader and Noone, et al. 2012). Melanoma, once metastatic, carries a grim prognosis— the five year survival rate is historically less than 10%—and develops at a relatively early age which results in a substantial number of years of life lost per person (Ekwueme, Guy, et al. 2011).

BRAF mutations are commonly found in human cancers; melanoma harbors BRAF mutations in approximately 40-60% of patients (Davies, Bignell, et al. 2002; Jakob, Bassett, et al. 2012; Long, Menzies, et al. 2011). The most common mutation accounting for 70-95% of BRAF V600 mutations in melanoma results in replacement of valine with glutamic acid at position 600 (V600E) of the BRAF protein and constitutive extracellular signal-regulated kinase (ERK) signaling (Rubinstein, Sznol, et al. 2010). Suppression of an activating BRAF mutation in human melanoma cell lines inhibits the mitogen-activated protein kinase (MAPK) signaling pathway, leading to cell growth arrest and apoptosis, and abrogates the transformed phenotype (Hingorani, Jacobetz, et al. 2003).

Until 2011, FDA-approved treatment options for metastatic melanoma were limited to DTIC and interleukin-2 (aldesleukin). In clinical trials, DTIC consistently demonstrated ORRs in the 5 to 20% range, mostly partial objective responses (Huncharek, Caubet, et al. 2001). In 270 patients treated in eight trials, administration of high-dose interleukin-2 demonstrated a 16% ORR, including a 6% complete response rate (Proleukin USPI). Importantly, the median duration of response in patients who experienced a complete response had not been reached, but was 5 years (range 1 to >112 months) at a minimum.

In 2011, FDA approved two products, ipilimumab and vemurafenib, based on demonstration of an improvement in OS in patients with unresectable or metastatic melanoma.

On March 25, 2011, FDA approved ipilimumab (BLA 125377), a recombinant human IgG1 immunoglobulin monoclonal antibody which binds to the cytotoxic T-lymphocyte associated antigen 4 (CTLA-4), a negative regulator of T-cell activation, for the treatment of unresectable or metastatic melanoma based primarily on the results of the MDX010-20 trial. This was a multicenter, placebo-controlled, double-blind clinical trial that randomized (3:1:1) 676 HLA-A2*0201 positive patients with previously treated unresectable Stage III or IV malignant melanoma to receive (a) ipilimumab 3 mg/kg intravenously (IV) every 3 weeks up to 4 doses in combination with gp100 peptide subcutaneously every 3 weeks up to 4 doses, (b) ipilimumab 3 mg/kg IV every 3 weeks up to 4 doses plus gp100 placebo every 3 weeks for 4 doses, or (c) ipilimumab placebo IV every 3 weeks up to 4 doses plus gp100 peptide subcutaneously every 3 weeks up to 4 doses. Patients randomized to the ipilimumab containing arms had a significantly longer median overall survival (mOS) than the gp100 vaccine arm:

- mOS of 10.2 months in the ipilimumab monotherapy arm compared to mOS of 6.4 months in the gp100 arm, HR of 0.66 (95% CI: 0.51, 0.87; p-value=0.0026, stratified log-rank test)
- mOS of 10 months in the ipilimumab monotherapy plus gp100 arm compared to mOS of 6.4 months in the gp100 arm, HR of 0.68 (95% CI: 0.55, 0.85; p-value=0.0004, stratified log-rank test)

The ipilimumab prescribing information (Yervoy USPI) includes a boxed warning based on the risk of severe and fatal immune-mediated reactions due to T-cell activation and proliferation including enterocolitis, hepatitis, dermatitis, neuropathies, endocrinopathies, and ocular manifestations, among others. The most common adverse reactions (≥5%) at a dose of 3 mg/kg were fatigue, diarrhea, pruritis, rash, and colitis.

On August 17, 2011, FDA approved vemurafenib (NDA 202429), an inhibitor of some mutant forms of BRAF serine-threonine kinase, including BRAF V600E, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. FDA approval was based primarily on the results of the NO25026 trial, a Phase 3, open-label, active-controlled trial that randomized (1:1) 675 patients with previously untreated for unresectable or metastatic melanoma to receive vemurafenib 960 mg orally twice daily (n=337) or DTIC 1000 mg/m^2 IV on Day 1 every 3 weeks (n=338). PFS and OS were co-primary endpoints of this trial. Vemurafenib demonstrated a clinically meaningful prolongation of PFS from a median of 1.6 months [95% CI: 1.5, 1.7] with DTIC to 5.3 months (95% CI: 4.8, 6.6) with vemurafenib with a HR of 0.26 (95% CI: 0.20, 0.33; p-value <0.0001). The NO25026 trial also demonstrated a statistically significant increase in OS of the vemurafenib arm compared to the DTIC arm with a HR of death of 0.44 (95% CI: 0.33-0.59; p<0.0001). At the time of the final OS analysis, the median OS for the vemurafenib arm had not been reached (95% CI: 9.6, NR), while the median OS for the DTIC arm—censoring those patients on DTIC who crossed over to vemurafenib—was 7.9 months (95% CI: 7.2, 9.6). The primary safety risks of vemurafenib include new primary malignancies, hypersensitivity reactions, dermatologic reactions, QT prolongation, liver laboratory abnormalities, photosensitivity, and ophthalmologic reactions (see Section 2.4). The most common Grade 1-4 treatment-emergent AEs in vemurafenib-treated patients were: arthralgia (49%), rash (36%), alopecia (33%), fatigue (32%), nausea (30%), photosensitivity reaction (30%), diarrhea (25%), pruritus (21%), headache (21%), hyperkeratosis (19%), pyrexia (18%), skin papilloma (18%), and decreased appetite (16%).

Table 1 lists the FDA-approved therapies for metastatic melanoma with details on clinical benefit/activity outcomes for each drug.

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

FDA Approved Drug[1]	Approval Year	Trial Design	Endpoint(s)	Clinical Benefit/Effect
DTIC (dacarbazine)[2]	1975	Single-arm	ORR	ORR of 5-20%
Proleukin[2] (interleukin-2)	1998	Multicenter, single-arm	ORR	ORR 16% (CR 6%); DOR CR: 59+ (range 3 to 122+ months) PR or CR: 59 months+ (range 1-122+ months)
Yervoy[2] (ipilimumab)	2011	Multicenter, randomized, blinded, active-controlled, three-arm	OS ORR	**Ipi vs. gp100:** OS: HR 0.66 (95% CI: 0.51, 0.87) median 10 vs. 6 months BORR: 10.9% vs. 1.5% mDOR: not reached in either arm **Ipi+gp100 vs. gp100:** OS: HR 0.68 (95% CI: 0.55, 0.85) median 10 vs. 6 months Best ORR: 5.7% vs. 1.5% mDOR: 11.5 months vs. NR
Zelboraf[3] (vemurafenib)	2011	Randomized, open-label active-controlled, two-arm	OS PFS ORR	**Vemurafenib vs. DTIC** mOS: NR vs. 7.9 months HR: 0.44 (95% CI: 0.33, 0.59) mPFS: 5.3 vs. 1.6 months HR: 0.26 (95% CI: 0.20, 0.33) BORR: Vemurafenib: 48.4% (95% CI: 41.6%, 55.2%) CR 0.9% PR 47.4% DTIC: 5.5% (95% CI: 2.8%, 9.3%) PR: 5.5%

Source: Proleukin (USPI), Yervoy (USPI), Zelboraf (USPI); Dacarbazine (USPI; Huncharek, Caubet, et al. 2001)
Abbreviations in Table: BORR, best overall response rate; CR, complete response; DOR, duration of response; HR, hazard ratio; Ipi, ipilimumab; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; NR, not reached; ORR, objective response rate; OS, overall survival; PR, partial response; +, response is ongoing.
[1] Hydroxyurea is also FDA-approved for treatment of melanoma but is of historical interest.
[2] BRAF V600 mutation status unknown.
[3] Patient selection based on BRAF V600E mutation-positive tumors.

2.3 Availability of Proposed Active Ingredient in the United States

Dabrafenib is not available in the U.S.

2.4 Important Safety Issues With Consideration to Related Drugs

Vemurafenib, an inhibitor of some mutant forms of BRAF serine-threonine kinase, including BRAF V600E, is FDA-approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. Important safety issues with vemurafenib include the following:

- New primary malignancies, including cutaneous squamous cell carcinomas (cuSCC), melanomas and basal cell carcinoma
- Hypersensitivity reactions
- Dermatologic toxicities, including serious reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis
- QT prolongation
- Hepatotoxicity
- Photosensitivity
- Uveitis

REVIEWER COMMENT:

(b) (4)

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following summarizes the presubmission regulatory activity for dabrafenib:

- The Applicant submitted IND 105032 on June 26, 2009, and received notification from FDA that the first-in-human study (BRF112680) was allowed to proceed on July 24, 2009.
- On July 6, 2010, FDA held a Type B, EOP1/Pre-Phase 3 meeting with the Applicant to discuss the development program for dabrafenib in the proposed indication: treatment of patients with BRAF V600E (b) (4) mutation-positive advanced and/or metastatic melanoma. The Applicant proposed to conduct two clinical studies to support the proposed indication: (1) BRF113710, a Phase 2 single-arm, open label, trial of GSK2118436 in 100 patients with BRAF mutant metastatic melanoma (Stage IV) who received prior systemic therapy to evaluate an overall response rate primary endpoint and (2) study BRF113683, a two-arm, open-label Phase 3 trial of 600 patients randomized to receive DTIC or GSK2118436. The Applicant proposed use of co-primary endpoints of PFS and OS for the BRF113683 trial. The key agreements and issues communicated to the Applicant were:

  - recommendation that the Applicant perform a dose-response study
  - recommendation that the Applicant monitor for development of squamous cell carcinoma
  - agreement with the proposed co-primary endpoints of PFS and OS
  - recommendation that that the final PFS analysis should be performed after enrollment has been completed and 60% events for survival have occurred
  - acknowledgement that approval based on PFS would be a review issue dependent upon the risk/benefit assessment

- FDA held a Type A Meeting with the Applicant on October 7, 2010, to discuss the Applicant's revised clinical development plan. At this meeting, the Applicant stated that the in vitro companion diagnostic to identify the BRAF V600 mutation subtype (V600E or V600K) in melanoma was on track to be ready at the time of registration of dabrafenib. Key agreements and issues communicated to the Applicant were:
  - ORR would not be considered an acceptable endpoint for FDA approval in the proposed population if an approval in BRAF mutant melanoma is granted based on an improvement in OS
  - improvement in PFS of sufficient magnitude may be an appropriate endpoint for the proposed Phase 3 study (BRF113683) provided that an improvement in OS is not demonstrated in a prior approval of another drug in the proposed population
  - DTIC may not be an appropriate comparator for the BRF113683 trial and the Agency suggested that a possible trial design may include a three-arm randomized study of GSK1120212 [inhibitor of MEK1/2] vs. GSK2118436 vs. the combination
- (b) (4)
- FDA held a Type A meeting on December 6, 2010, to discuss the potential for an accelerated approval for GSK2118436. Key agreements and issues communicated to the Applicant were:
  - submission of a single-arm study to support an accelerated approval of GSK2118436 would be acceptable if based on a clinically meaningful response rate, duration of response and an acceptable benefit-risk profile
  - clearance of the companion diagnostic test by the Center for Devices and Radiological Health (CDRH) should occur by the time of action on an NDA for GSK2118436
- GSK2118436 received orphan designation on January 12, 2011, for the treatment of BRAFV600 mutation-positive Stage IIb through IV melanoma.

- FDA granted Fast Track designation of GSK2118436 on February 11, 2011, for the investigation of GSK2118436 for the treatment of patients with BRAF mutation-positive (V600E or (b) (4) advanced melanoma.
- FDA granted the Applicant's request, submitted April 25, 2011, for a Type B meeting to discuss with the Agency revisions to the ongoing Phase 2 study BRF113929 (amendment submitted April 4, 2011, serial 0171) to potentially allow study results to provide robust evidence of clinical activity in patients with BRAF V600 mutation-positive metastatic melanoma with brain metastases to support an accelerated approval. FDA granted the meeting request on May 6, 2011, and tentatively scheduled the meeting on August 8, 2011. The Applicant sent a request by email on July 6, 2011, to cancel the scheduled meeting. On August 15, 2012, the Applicant submitted to IND 105032 a request to withdraw the meeting request.
- FDA held a Type B, Chemistry Manufacturing, and Controls Pre-NDA meeting on January 31, 2012, in regard to the proposed content for the CMC section of the planned NDA. FDA communicated the following agreements and concerns to the Applicant:
  - quality by design concept to drug substance process development was reasonable
  - control of genotoxic substances as proposed by the Applicant appeared reasonable but FDA would make its determination during the NDA review
  - testing intervals for post-approval stability testing as proposed by the Applicant did not conform with ICH Q1A and FDA stated that the testing interval should be the same as that used for the primary batches, i.e., every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf-life
  - (b) (4) not acceptable
  - inclusion of 12 months of stability data from 3 primary batches of each strength and packaging configuration as proposed by the Applicant was acceptable
- FDA held a Type B, Pre-NDA meeting on May 9, 2012, to reach agreement on the content and format of two planned NDA submissions [GSK2118436 (dabrafenib) and GSK1120212 (trametinib)] and to acquaint the review teams with the information and strategic intent of the information to be included in each application. FDA communicated the following key agreements and issues to the Applicant:
  - inclusion in labeling of (b) (4) mutation subtype or brain metastases must be supported by substantial evidence of effectiveness based on adequate and well-controlled trials under 21 CFR 201.57
  - integration of safety data from clinical trials that used different versions of the National Cancer Institute (NCI)-common toxicity criteria for AEs (CTCAE) for

severity grading of AEs is not acceptable and the Applicant agreed to provide a pooled data set of clinical trials conducted using CTCAE version 4.0

- inclusion of the text portion of the integrated summary of efficacy and integrated summary of safety in the electronic common technical document (eCTD) Modules 2.7.3 and 2.7.4, respectively, would be acceptable if sufficiently detailed to serve as the narrative portions of the integrated summary of safety and integrated summary of efficacy as per 21 CFR 314.50
- agreement that studies the BRF113683, BRF113929, BRF113710, and BRF112680 are covered studies under 21 CFR Part 54.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The quality of the submission did not permit an efficient and timely review. The key determinants of this assessment included the following:

- Missing components of the eCTD in the original NDA submission
- Data discrepancies resulting from, at least in part, inconsistent data cutoff dates used to generate the datasets and to create the patient case report forms (CRF) in the NDA submission. As a result, all safety findings based on the ISS database required reanalysis using the ISS database that was submitted in the 120-Day safety update.
- Data discrepancies resulting from errors in the eCTD submission documents
- Dataset definition files which did not contain definitions of multiple variables
- Dataset definition files which contained an inadequate level of detail in the variable definitions to facilitate efficient review
- Inadequate and/or incorrect annotations within the annotated CRFs
- Key variables in datasets were absent, inconsistent in name or definition across datasets, and/or incomplete
- Non-functioning SAS programs for statistical analyses

21st Century Review timelines were not met for the primary clinical and statistical reviews as a result of the data quality and integrity. Please see Dr. Yuan's Statistical review for additional details in regard to data quality and integrity.

3.2 Compliance with Good Clinical Practices

The Applicant stated the following:

- All studies were undertaken in accordance with standard operating procedures of the GlaxoSmithKline Group of Companies, which comply with the principles of Good Clinical Practice (GCP)
- All studies were conducted with the approval of Ethics Committees or Institutional Review Boards
- Informed consent was obtained for all patients
- Studies were performed in accordance with the version of the Declaration of Helsinki that applied at the time the studies were conducted
- Regulatory approval was obtained from the relevant health authority where required to conduct the trials

The Division of Oncology Products 2 (DOP2) consulted the Office of Scientific Investigation (OSI) on September 6, 2012, to perform an audit of two clinical study sites to identify any data quality issues and to document that the study was performed according to GCP. The Division, in consultation with OSI, selected clinical sites for inspection based on enrollment characteristics, patterns of protocol violations reported for the sites, and patterns of serious adverse event (SAE) reporting.

OSI inspected two clinical sites as well as the Applicant. The following is excerpted from the OSI review:

> Lev Demidov, M.D.
> Site #86717
> Assessment of data integrity:
> Notwithstanding the observations above, the data provided by Dr. Demidov's site for Study BRF113683 that were submitted to the Agency in support of NDA 202806 appear to be reliable and acceptable for use in support of the pending application.
>
> Jean-Jacques Grob, M.D.
> Site #87119
> Assessment of data integrity:
> The data provided by Dr. Grob's site for Study BRF113683 that were submitted to the Agency in support of NDA 202806 appear to be reliable and acceptable for use in support of the pending application.
>
> GlaxoSmithKline
> Assessment of data integrity:
> The data generated, as it pertains to Study BRF113683 were inspected in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. Study BRF113683 appears to have been conducted adequately by GlaxoSmithKline and the

data submitted by the Applicant for this study may be used in support of the pending Application.

OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS
Based on the review of inspectional findings for the inspections of GlaxoSmithKline, Dr. Demidov, and Dr. Grob, the data submitted by the Applicant for Study BRF113683 appear reliable in support of NDA 202806.

The final classifications for the inspections of Dr. Grob and the Sponsor, GlaxoSmithKline, are No Action Indicated (NAI).

The preliminary classification for the inspection of Dr. Demidov is Voluntary Action Indicated (VAI). The Form FDA 483 observations noted for Dr. Demidov's site are considered minor and unlikely to significantly impact the results of efficacy and safety analyses reported by the Applicant.

REVIEWER COMMENTS:

1. *OSI issued to Dr. Demidov an FDA Form 483 for two observations:*
   - *Treatment of a patient past unequivocal progression of disease (PD) prior to date that the Ethics Committee approved BRF113683 Protocol amendment 5, the amendment which permitted patients with PD, whom the investigator considered still benefitting from therapy, to remain on study drug*
   - *Pharmacokinetic samples were either not collected or collected out of the protocol specified time frame for one patient*
2. *This reviewer agrees with the OSI reviewer's assessment that the observations are minor and unlikely to significantly impact the results of efficacy and safety analyses reported by the Applicant.*
3. *The protocol deviations observed in the BRF113683 trial should not impact the overall integrity of the data used in the analyses of efficacy and safety.*

3.3 Financial Disclosures

In accordance with 21 CFR 54.2, the Applicant submitted a list of the BRF113683, BRF113710, BRF113929, and BRF1126890 trial investigators attached to FDA form 3454 certifying that the investigators had no financial arrangements as defined in 21 CFR 54.2(a, b, and f) that could affect the outcome of the study. Randal Batenhorst, Pharm.D, Vice President, Global Regulatory Affairs certified this disclosure for the Applicant. According to review of the submitted information, financial arrangements with the investigators do not raise questions about the integrity of the BRF113683 trial data.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Refer to the CMC review.

4.2 Clinical Microbiology

The drug product is a non-sterile capsule for oral administration. Refer to the FDA Product Quality Microbiology review for details.

4.3 Preclinical Pharmacology/Toxicology

The Applicant conducted 4- and 13-week toxicity studies in rats and dogs. The main target organs of toxicity were skin, male reproductive organs, heart (dog only), and stomach (rats only). The following target organ toxicity information is excerpted from the FDA Pharmacology/Toxicology NDA review:

> Dose-responsive increases in skin lesions and papules were considered clinically relevant since these toxicities occurred in rats and dogs at plasma levels (AUC_{0-24}) equivalent to human exposure at the recommended human dose of dabrafenib. Male reproductive toxicity (degeneration/depletion in the testis and aspermia in the epididymis) is also expected to manifest itself in humans at the recommended dose of dabrafenib and was therefore noted in the Tafinlar™ label. Heart toxicity in dogs consisted of marked hypertrophy and hemorrhage of the right atrioventricular valve at plasma levels (AUC_{0-24}) $\geq$ 5 times human exposure following the recommended dose of dabrafenib. Stomach toxicity consisted of histopathological findings of hyperplasia, epithelial down-growth, and infiltration at all doses tested in rats. Epithelial hyperplasia in the forestomach of mice and rats and in other tissues, including the esophagus, urinary bladder, and renal pelvis, has been reported with other RAF inhibitors. Development of proliferative skin and epithelial forestomach lesions in animals is considered to be pharmacologically-mediated as RAF inhibition has been shown to enhance cell growth in BRAF wild-type cells with subsequent paradoxical activation of RAS/RAF/MEK/ERK pathway signaling.

Dabrafenib was not mutagenic or clastogenic based on in vitro studies. The Applicant did not conduct carcinogenicity studies of dabrafenib based on the intended use in patients with advanced cancer. In humans, administration of dabrafenib 150 mg orally twice daily increased the risk of developing cutaneous squamous cell carcinomas (see Section 7.3.2).

In safety pharmacology studies, dabrafenib demonstrated weak in vitro hERG blocking activity.

The following summary of the findings from the combined fertility and embryo-fetal study is excerpted from the FDA Pharmacology/Toxicology NDA review:

> Dabrafenib was evaluated in a combined fertility and embryo-fetal study in Sprague-Dawley rats. Plasma exposure levels (AUC_{0-24}) were up to 3 times the exposure level in humans receiving the recommended dose of dabrafenib. Dabrafenib-induced toxicity included cardiac malformations in developing fetuses (cardiac ventricular septal defects), and a number of visceral and skeletal malformations, including misshapen or split thymuses and decreased skeletal ossification. Dabrafenib also caused a decrease in the number of corpora lutea, implantations, and live fetuses, an increase in pre- and post-implantation loss, and a reduction in fetal body weights.

Please refer to the FDA Pharmacology/Toxicology NDA review for additional details of the evaluation of pharmacology/toxicology.

4.4 Clinical Pharmacology

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

4.4.1 Mechanism of Action

Dabrafenib is an inhibitor of some mutated and wild-type forms of BRAF kinases with in vitro IC50 values of 0.65 nM for BRAF V600E , 0.5 nM for BRAF V600K, 1.84 nM for BRAF V600D, 3.2 nM for wild-type BRAF, and 5.0 nM for CRAF kinases. Dabrafenib also inhibits other kinases such as SIK1, NEK11, and LIMK1 at clinically relevant concentrations. BRAF V600E mutations can result in constitutively activated BRAF kinases that may stimulate tumor cell growth. BRAF mutations have been identified at a high frequency in specific cancers, including approximately 40-60% of melanomas.

4.4.2 Pharmacodynamics

Analyses of tumor biopsies from trial BRF112680, collected at baseline and 1 to 2 weeks of dabrafenib dosing in eight patients (receiving between 70 to 200 mg orally twice daily), demonstrated a median decrease from baseline of 83.9% (range 38.0 to 93.3%) in phosphorylated ERK (pERK), a downstream biomarker of the RAS/RAF/MEK/ERK pathway. Six of eight patients experienced a $\geq$ 80% inhibition of pERK compared to baseline.

4.4.3 Pharmacokinetics

The following pharmacokinetic information on absorption, food effect, distribution, and elimination is excerpted from the FDA Clinical Pharmacology NDA review:

> *Absorption:* After oral administration of dabrafenib, the median time to achieve peak plasma concentration is 2 hours. Mean absolute bioavailability of oral dabrafenib is 95%.

Dabrafenib exposure (Cmax and AUC) increased in a dose proportional manner between 12 and 300 mg following single-dose administrations, but the increase was less than dose-proportional after repeat twice daily dosing. This observed decrease in exposure with repeat dosing is likely due to induction of its own metabolism. Mean accumulation ($AUC_{Day18/Day1}$) ratios averaged 0.73. Following administration of 150 mg dabrafenib twice daily, geometric mean (CV%) Cmax, AUC(0-τ), and predose concentration values were 1,478 ng/mL (37%), 4,341 ng*hr/mL (38%), and 26 ng/mL (119%), respectively.

Food effect: Administration of a single 150 mg dose of dabrafenib capsules with a high-fat meal decreased its Cmax and AUC by 51% and 31%, respectively, when compared to the fasted state.

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

Metabolism: The metabolism of dabrafenib is primarily mediated by CYP2C8 and CYP3A4 to form hydroxy-dabrafenib, which is further oxidized via CYP3A4 to form carboxy-dabrafenib and is excreted in bile and urine. Carboxy-dabrafenib can be decarboxylated via a non-enzymatic process in the gut to form desmethyl-dabrafenib and reabsorbed. Desmethyl-dabrafenib is metabolized by CYP3A4 to oxidative metabolites. Hydroxy-dabrafenib terminal half-life parallels that of the parent drug with a half-life of 10 hours while the carboxy- and desmethyl-metabolites exhibited longer half-lives (21 to 22 hours). Mean metabolite to parent AUC ratios following repeat-dose administration were 0.9, 11, and 0.7 for hydroxy-, carboxy-, and desmethyl-dabrafenib, respectively. Based on exposure, relative potency and pharmacokinetic properties, both hydroxy- and desmethyl-dabrafenib are likely to contribute to the clinical activity of dabrafenib; the activity of carboxy-dabrafenib is not likely to be clinically meaningful.

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

Patients with mild and moderate renal impairment or with mild hepatic impairment should not require dose adjustments of dabrafenib based on the FDA Clinical Pharmacology NDA Review. The following is excerpted from the FDA Clinical Pharmacology NDA review:

No formal PK study in patients with renal impairment has been conducted. The PK of dabrafenib is evaluated using a population analysis in 233 patients with mild renal impairment (GFR 60-89 mL/min/1.73 m2) and in 30 patients with moderate renal impairment (GFR 30-59 mL/min/1.73 m2) enrolled in clinical trials. Mild or moderate renal impairment has no effect on systemic exposures to dabrafenib and its metabolites. No data are available in patients with severe renal impairment.

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

Additionally, dabrafenib is likely to interact with other drugs. Dabrafenib is primarily metabolized by CYP2C8 and CYP3A4. Strong inhibitors (e.g., grapefruit juice) or inducers (e.g., phenytoin, St. John's wort) of CYP3A4 or CYP2C8 may increase or decrease, respectively, concentrations of dabrafenib. Dabrafenib also induces CYP3A4 and possibly other enzymes including CYP2B6, CYP2C8, CYP2C9, and CYP2C19. If co-administered, dabrafenib can result in decreased concentrations of other substrates of these enzymes (e.g., warfarin, dexamethasone, or hormonal contraceptives) and may cause loss of efficacy.

The FDA Clinical Pharmacology NDA review did not identify an exposure-response relationship for efficacy or safety of dabrafenib at the 150 mg orally twice daily dose regimen.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2 lists the clinical studies in the NDA submission as well as the purpose of each trial. The Applicant states that the principal evidence of safety and effectiveness is provided by three clinical trials: BRF113683, BRF113929, and BRF113710. The Applicant also states that two additional trials, BRF112680 and BRF113220 (Part C), provide information to further characterize the safety profile of dabrafenib monotherapy administered at 150 mg orally twice daily.

Table 2: Tabular Listing of Clinical Trials of GSK2118436 (dabrafenib) in NDA submission.

Trial ID	Purpose	Population[a]	Formulation[b]	Sites, N	Countries	Subjects N
BRF113683[c]	Efficacy/ Safety	Melanoma	HPMC	70	United States, Canada, Australia, Germany, France, Italy, Spain, Poland, Russia, Netherlands, Ireland, Hungary	250

Trial ID	Purpose	Population[a]	Formulation[b]	Sites, N	Countries	Subjects N
BRF113710[c]	Efficacy/ Safety	Melanoma	Gelatin	21	United States, Australia, France, Germany, Italy	92
BRF113929[c]	Efficacy/ Safety	Melanoma	HPMC	24	United States, Canada, Australia, France, Germany, Italy	172
BRF113220, Part C[c]	Clinical activity/ Safety/ PK/ PD	Melanoma	Gelatin	16	United States, Australia	53[d]
BRF112680[c]	Safety/ PD	BRAF mutant tumors	Gelatin	8	United States, Australia	184
BRF113468	BP[e]	BRAF mutant tumors	Gelatin / HPMC	4	United States	28
BRF113479	BP[f]	BRAF mutant tumors	HPMC	1	United States	4
BRF113463	PK[g]	BRAF mutant tumors	14-C labeled GSK2118436	1	United States	4
BRF113771	PK[h]	BRAF mutant tumors	HPMC	6	United States	22
BRF113928	Clinical activity/ Safety/ PK	NSCLC	HPMC	NR	United States, France, United Kingdom	6
BRF114144	Rollover Trial	BRAF mutant tumors	HPMC		United States, United Kingdom, Australia	98
BRF115252	CU	Melanoma	NR	NR	NR	166
BRF115015	SPI	Melanoma	NR	1	NR	1
BRF115262	CU	Melanoma	NR	1	NR	1

Abbreviations in Table: BP, biopharmaceutic trial; CU, Compassionate use; HPMC, hydroxypropyl methylcellulose; ID, identifier; NR, not reported; NSCLC, non-small cell lung cancer; PD, Pharmacodynamic trial, PK, pharmacokinetic trial, SPI, single-patient investigational new drug application.

[a] All patients with BRAF mutation-positive malignancies.
[b] HPMC or gelatin capsule formulation.
[c] Trial reviewed in the clinical review of efficacy and/or safety.
[d] Number of patients enrolled in the dabrafenib monotherapy arm of Part C of BRF113220.
[e] Single dose PK food effect and particle size.
[f] Single dose PK, absolute bioavailability.
[g] Single dose radiolabeled ADME trial.
[h] Repeat dose drug-drug interaction trial, PK.

5.2 Review Strategy

The clinical review of safety and efficacy focused on data from five trials to support the proposed indication (see Table 2); the NDA contains a single randomized, active-controlled trial which serves as the primary evidence of efficacy. The primary clinical review includes a joint clinical-statistical review of efficacy. The FDA statistician was the primary reviewer of the BRF113683 trial. The clinical review of efficacy presents the findings of the primary statistical review of the BRF113683 trial in applicable subsections within Section 6 of the clinical review. In addition, the FDA statistician generated a separate, primary review of the NDA. One medical officer performed the primary clinical review of safety as well as completed the remaining sections of the NDA review template. Please note that Section 5.3 contains the review of the individual clinical trial methods and Sections 6 and 7 present the reviews of efficacy and safety, respectively.

The clinical review of efficacy focused on detailed review and analyses of data from the BRF113683 trial including the clinical study reports, CRFs, and SAS datasets. The clinical review also included review and analyses of the trial designs, statistical and analytic plans (SAP), and results of the activity-estimating trials, BRF113710 and BRF113929, mainly to evaluate whether these trials support the results of the BRF113683 trial.

The clinical review of safety focused on safety data from the BRF113683 trial with additional analyses focused on clinically important AEs with dabrafenib (e.g., deaths, non-fatal SAEs, AEs leading to treatment modifications, significant AEs) from the BRF113710, BRF113929, BRF112680, and BRF113220 (Part C) trials.
The clinical review included the following:

- Evaluation of the current literature on melanoma epidemiology, genetics, diagnosis, prognostic features, and treatment
- Review of the trials listed in Table 2 including clinical study reports, protocols, protocol amendments, and SAPs
- Assessment of the Module 2 summaries including the Clinic Module, Summary of Clinical Effectiveness, and Summary of Clinical Safety, Integrated Summary of Efficacy, Integrated Summary of Safety, Risk Management Plan, and proposed labeling
- Analyses using the Applicant's data sets, with a focus on the data sets derived directly from the original CRFs (listings data sets), to evaluate the safety and efficacy of dabrafenib
- Consultations with FDA statisticians
- Formulation of the benefit-risk analysis and recommendations

5.3 Discussion of Individual Studies/Clinical Trials

PROTOCOL ID: BRF113683

REVIEWER COMMENT: Section 5.3 of the review summarizes the BRF113683 protocol (Amendment 5). The Applicant submitted amendment 6 following the data-cutoff date. At the end of the protocol (Amendment 5) summary, this section provides a summary of the key revisions contained within each amendment.

Clinical Trial Title

A Phase III randomized, open-label study comparing GSK2118436 to DTIC in previously untreated subjects with BRAF mutation positive advanced (Stage III) or metastatic (Stage IV) melanoma.

Study Sites

The Applicant conducted this study in 70 centers in 12 countries in North America, Europe, and Australia.

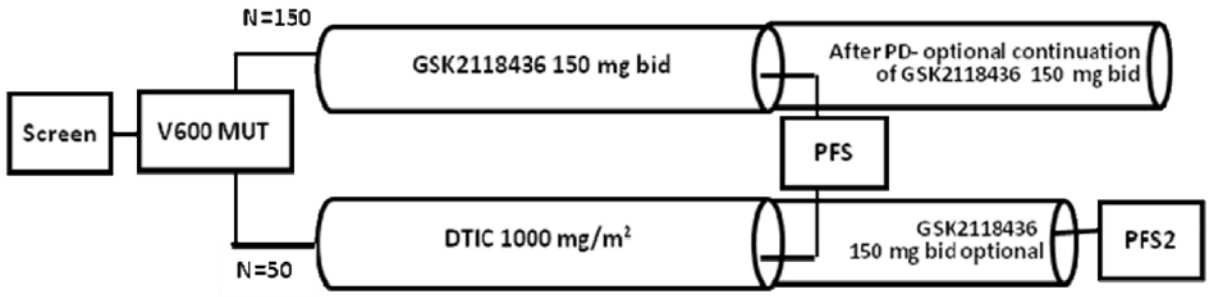
Objectives

- **Primary**: to establish the superiority of GSK2118436 over DTIC with respect to PFS for patients BRAF mutation-positive metastatic melanoma
- **Secondary**:
    - to compare OS between treatment groups
    - to assess the best overall response rate and PFS of patients in the DTIC treatment group after initial progression and subsequent crossover to GSK2118436
    - to compare best overall response rate between treatment groups
    - to assess duration of response in patients receiving GSK2118436
    - to further validate a BRAF mutation assay for regulatory approval and registration

Study Design

The BRF113683 trial was a two-arm, open-label, randomized (3:1), active-controlled trial in patients with histologically confirmed advanced (unresectable Stage III) or metastatic (Stage IV) BRAF V600E mutation-positive cutaneous melanoma who have received no prior systemic treatment for advanced (unresectable) or metastatic disease (with the exception that the eligibility criteria permitted prior interleukin-2 therapy). The single randomization stratification factor was stage of disease [Stage III (unresectable), M1a, M1b vs. M1c]. In addition, the trial used a central interactive voice response system (IVRS) to randomize patients to receive GSK2118436 or DTIC. As shown in Figure 2, at the time of progression of disease (PD), patients on the DTIC arm were permitted to receive GSK2118436 at the same dose and schedule as that administered to patients randomized to the GSK2118436 arm:

Figure 2: BRF113683 Trial Design.



Reproduced from BRF113683 Clinical Study Report (CSR), Page 20

Study Population

Inclusion criteria:

- Men or women ≥ 18 years of age
- Histologically confirmed advanced (unresectable Stage III) or metastatic (Stage IV) melanoma and BRAF V600E mutation-positive as determined by central testing with a BRAF mutation assay
- Treatment naïve for advanced (unresectable) or metastatic melanoma, with the exception of IL-2, surgery, and radiotherapy which were allowed
- Measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Able to swallow and retain oral medication
- Women of childbearing potential (WOCBP) and men with reproductive potential must be willing to practice acceptable methods of birth control during the study. WOCBP must have a negative serum pregnancy test prior to the first dose of study treatment
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 1

- Organ Function criteria: ANC ≥1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L, Hb ≥ 9g/dL, PT/INR and PTT ≤ 1.3 x upper limit of normal (ULN), serum bilirubin ≤ 1.5 x ULN, AST and ALT ≤ 2.5 x ULN, serum creatinine ≤ 1.5 mg/dL or creatinine clearance using Cockcroft and Gault method > 50 mL/min, and left ventricular ejection fraction (LVEF) ≥ lower limit of normal (LLN)
- French patients: In France, a patient will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category

Exclusion criteria:

- Previous treatment for metastatic melanoma, including treatment with BRAF or MEK inhibitor
- Known ocular or primary mucosal melanoma
- Current use of cancer therapy (chemotherapy, radiation therapy, immunotherapy, biologic therapy, or surgery)
- Use of any investigational anti-cancer or other drug within 28 days or 5 half-lives, whichever was longer, prior to the first dose of GSK2118436
- Current or expected use of any prohibited medication during treatment with GSK2118436
- Any major surgery, radiotherapy, or immunotherapy within 4 weeks prior to enrollment
- Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption of drugs
- History of human immunodeficiency virus (HIV) infection or glucose-6-phosphate dehydrogenase (G6PD) deficiency
- History of other malignancy. Subjects who have been disease-free for 5 years, or patients with a history of completely resected non-melanoma skin cancer or successfully treated in situ carcinoma are eligible
- Evidence of active CNS disease (radiographically unstable, symptomatic lesions). Patients with newly diagnosed, untreated brain metastases were not eligible. However, prior treatment with stereotactic radiosurgery (SRS) or surgical resection was allowed if the patient remained without evidence of disease progression in the brain ≥ 3 months, and had been off corticosteroids for ≥ 3 weeks. Whole brain radiotherapy was not allowed except in those patients who had definitive resection or SRS of all radiographically detectable parenchymal lesions
- History of alcohol or drug abuse within 6 months prior to screening
- Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol, or unwillingness or inability to follow the procedures required in the protocol
- The following cardiac abnormalities:
  - corrected QT (QTc) interval ≥480 msec

  - history of acute coronary syndromes (including unstable angina) within the past 24 weeks
  - coronary angioplasty, or stenting within the past 24 weeks
  - Class II, III, or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system
  - abnormal cardiac valve morphology (≥ Grade 2) documented by echocardiogram (patients with Grade 1 abnormalities [i.e., mild regurgitation/stenosis] can be entered on study). Subjects with moderate valvular thickening should not be entered on study
  - history of known cardiac arrhythmias (except sinus arrhythmia) within the past 24 weeks
  - known cardiac metastases
- Pregnant or lactating female

Treatment Plan

The protocol specified stratified randomization (3:1) using the randomization factor stage of disease [Stage III (unresectable), M1a, M1b vs. M1c] to the following treatment arms:

- Arm A
  - GSK2118436 150 mg administered orally with approximately 200 mL of water twice daily under fasting conditions
- Arm B
  - DTIC 1000mg/m^2 administered IV once every three weeks

Treatment continued until PD, death, or unacceptable toxicity.

The protocol allowed crossover of patients randomized to the DTIC arm who experienced documented PD–confirmed by the blinded independent central review (BICR) based on RECIST 1.1—to receive GSK2118436 if the patient met the following criteria:

- Washout period of at least 21 days but no longer than 35 days between the last dose of DTIC and the first dose of GSK2118436
- Toxicities due to chemotherapy were CTCAE (Version 4.0) ≤ Grade 1 with the exception of alopecia and anemia (minimum hemoglobin of 9g/dl)
- No known brain metastases or neurologic symptoms indicating brain metastases
- ECOG PS of 0-1
- Echocardiogram results were within normal limits at the time of the last evaluation and there were no evidence of cardiac valve abnormalities > Grade 1.
- QTc ≤ 480 msec

Dose Modification and Supportive Care Guidelines

The protocol specified the following GSK2118436 dose levels (Table 3):

Table 3: Dose Levels of Dabrafenib. BRF113683 Protocol.

Dose Level	Dose/Schedule
0	150 mg twice daily day
-1	100 mg twice daily
-2	75 mg twice daily
-3	50 mg twice daily

Protocol BRF113683 provided general dose modification guidelines for GSK2118436 (Table 4) as well as specific treatment modification guidelines for rash, hand-foot skin reaction, left-ventricular ejection fraction decrease, renal insufficiency, fever, neutropenia, and liver function testing abnormalities (*see Appendix 9.5 Treatment Modification Plan for Toxicity, BRF113683*).

Table 4: General Guidelines for Dose Modification of Dabrafenib for Non-Hematological and Hematological Toxicity. BRF113683 Protocol.

Non-hematologic and Hematologic Toxicity (Except Neutropenia)	Dose Modification of GSK2118436[1,2,3,4]
Grade 1	Continue at current dose level, monitor as clinically indicated.
Grade 2	Diarrhea with accompanying risk factors[3]: Hold GSK2118436 until return to ≤ Grade 1, provide supportive care. All other toxicities: consider holding GSK2118436 until resolution to Grade 1 or baseline, provide supportive care as clinically indicated, and monitoring of laboratory values should occur as clinically indicated. Respiratory symptoms: Evaluation by a CT scan is recommended
Grade 3	Temporarily interrupt dose until toxicity resolves to Grade 1 or baseline, reduce by one dose level (may continue at same dose if toxicity deemed by the investigator to be unrelated to GSK2118436). If any Grade 3 toxicity recurs, interrupt dosing until toxicity resolves to Grade 1 or baseline, then reduce current dose of GSK2118436 by one dose level.
Grade 4	Discontinue GSK2118436. Provide supportive care as needed. If toxicity unlikely to recur in the opinion of the investigator, hold until toxicity is Grade 1 or baseline, then reduce GSK2118436 by 1 dose level.

[1] The minimum dose was 50mg BID. Discontinuation from study medication was required if the patient required a dose reduction below 50mg BID.
[2] Collection of amylase and lipase samples was recommended for abdominal pain or suspected pancreatitis.
[3] Protocol defined risk factors for cancer treatment-induced diarrhea included: fever, orthostatic symptoms (i.e. dizziness), abdominal pain/cramping, or weakness.
[4] Dose modification was not required if the patient has a Grade 3 or 4 laboratory abnormality that, in the judgment of the investigator, was not considered clinically significant.

The protocol permitted a maximum of two dose reductions of DTIC for clinically significant non-hematological (Table 5) or hematological (Table 6) toxicities, respectively.

Table 5: Guidelines for Dose Modification of DTIC for Non-Hematological Toxicity. BRF113683 Protocol.

Toxicity Grade	Dose Modification[1]
1 or 2	Continue DTIC therapy except: Grade 2 diarrhea with accompanying risk factors [3]: hold DTIC until return to ≥ Grade 1, then decrease DTIC dose by 20%.
3 or 4	Hold DTIC therapy until recovery to Grade ≤1, decrease DTIC dose by 20%.
Grade 3 or 4 and AEs not resolved to Grade ≤2 within a maximum of 4 weeks from last planned administration[2]	Discontinue DTIC therapy

[1] Up to two dose reductions will be allowed per protocol. If a third dose reduction is required the patient should be removed from study treatment and enter follow-up.
[2] May hold DTIC for a maximum of 6 weeks, if toxicity persists, then patient must be discontinued from DTIC and begin follow up portion of the study.
[3] Risk factors for cancer treatment-induced diarrhea include: fever, orthostatic symptoms (i.e. dizziness), abdominal pain/cramping, or weakness.

Table 6: Guidelines for Dose Modification of DTIC for Hematological Toxicity. BRF113683 Protocol.

Toxicity Grade	Dose Modification[1]
1 or 2	Continue DTIC therapy, monitor hematology laboratory values weekly until return to baseline. Consider supportive care per local institutional practice.
3	Hold DTIC therapy until recovery to Grade ≤1, decrease DTIC dose by 20%[2] Consider supportive care per local institutional practice.
4	Hold DTIC therapy until recovery to Grade ≤1, decrease DTIC dose by 20%[2] Consider supportive care. If Grade 4 toxicity recurs after dose reduction then discontinue DTIC

[1] Up to two dose reductions will be allowed per protocol. If a third dose reduction is required the patient should be removed from study treatment and enter follow-up.
[2] May hold DTIC for a maximum of 6 weeks, if toxicity persists, then patient must be discontinued from DTIC and begin follow up portion of the study.

Monitoring Plan

The monitoring plan and study scheduled tests and evaluations are summarized in Table 7.

Table 7: Schedule of Assessments. BRF113683 Protocol.

Study Assessments	Screen[1]	Day 1	Day 8	Wk 3	Wk 6	Wk 9	Wk 12	Wk 15	Wk 18	Wk 21	Wk 24	Wk 27	Wk 30	Wk 33	Wk 36	Wk 39	Wk 42	Wk 45	Wk 48	Wk 51[25]	Unsch	Disc	Fwp	Conc
Informed consent	X																							
PGx research consent[2]	X																							
Inclusion / exclusion criteria[3]	X																							
Demographic data	X																							
Serum pregnancy test[4]	X																							
Register / randomize subject	X	X																						
Disease characteristics[5]	X																							
Prior anti-cancer therapy	X																							
Prior radiotherapy	X																							
Past and current medical conditions	X																							
Prior surgical procedures	X																							
Family history	X																							
Dispense oral study medication and assess compliance[6]		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
DTIC administration		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Target and non-target lesion assessment, including melanoma lesion skin photography [7]	X				X		X			X			X			X			X			X[25]		
Response					X		X			X			X			X			X			X[25]		
Brain MRI or CT with contrast (if MRI contraindicated)	X																							
Non-melanoma Skin lesion photography[8]	X			X	X			X			X			X			X			X		X		
Height/Weight[9]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Blood pressure	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Other vital signs[10]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Performance status (ECOG)	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Physical examination[11]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		
Dermatologic skin assessment[12]	X			X	X			X			X			X			X			X		X		
ECG[13]	X			X	X		X			X			X			X			X			X		
Echocardiogram (ECHO)[14]	X				X		X			X			X			X			X			X		

Study Assessments	Screen[1]	Day 1	Day 8	Wk 3	Wk 6	Wk 9	Wk 12	Wk 15	Wk 18	Wk 21	Wk 24	Wk 27	Wk 30	Wk 33	Wk 36	Wk 39	Wk 42	Wk 45	Wk 48	Wk 51[25]	Unsch	Disc	Fwp	Conc
Concomitant medications	X	X		Cpntinously																	X	X		
Blood products and blood supportive care products		X		Continuously																	X	X		
Adverse events[15]	X	X		Continuously																	X	X	X	X
Chemistry[16]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		
Hematology[17]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		
Coagulation	X																							
Cardiac Troponin[18] I	X																							
Blood sample for PGx[19]		X																						
Blood sample for circulating cell free DNA[20]	X																					X		
Tumor tissue sample for V600 E testing and biomarker research[21]	X																					X		
QoL Assessment [22]	X				X		X	X														X	X	
PK sampling(all subjects)[23]				X	X	X	X		X		X													
PK sampling (subset) [24]					X																			
Study medication discontinuation																						X		
Follow-up contact[25]																							X	
Follow-up anti-cancer therapy																							X	
Follow-up radiotherapy[25]																							X	
Follow-up surgery																							X	
Subject completion																								X
Death record																								X

PGx = pharmacogenetics; MRI = magnetic resonance imaging; ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; ECHO = echocardiogram; PK = pharmacokinetic; Unshc = unscheduled; Disc = discontinued; Fwp = follow-up; Conc = conclusion

1. Screening procedures may be performed 14 days prior to first dose of study drug, except for tumor assessments which may be performed 28 days prior to first dose of study drug, ECGs and echocardiograms may be performed 35 days prior to the first dose of study drug. Testing for BRAF mutation V600 E via central testing with a BRAF mutation assay, must be conducted.
2. Informed consent for PGx research is to be obtained before any PGx-related procedures. Only subjects consented for the main clinical study are eligible for consent for PGx.
3. Only subjects who meet all inclusion and exclusion criteria will be eligible to enter into the study.
4. Serum pregnancy test will be required within 14 days prior to the first dose of study drug. Subsequent tests may be urine tests, and should be performed as clinically indicated.
5. Disease characteristics: Record date of diagnosis, primary tumor type, histology, stage, etc.
6. Dispense study medication with instructions. Record dose reductions, dose interruptions/delays, and/or dose escalations.
7. Target and non-target lesions must be identified at time of screening scan and the same lesions must be re-assessed at each restaging scan, using the same modality throughout the course of the study. A MRI/CT of the Chest, Abdomen and Pelvis should be done at each timepoint regardless of disease status. These disease assessments should also include skin photography of melanoma skin lesions if applicable, at the same interval as radiologic imaging, as target and non-target lesions. . At Week 48 scans and photographs may occur every 12 weeks. If the last radiographic or photographic assessment was more than 12 weeks prior to subject discontinuation from study and progressive disease has not been documented, a disease assessment should be obtained at the time of study discontinuation.
8. At baseline a full set of body photos for non-melanoma skin lesions photography should be obtained. Thereafter skin photography of any changing or new non-melanoma skin lesions should be obtained according to the time and events table, and electronically forwarded to the vendor.
9. Measurements should be in Metric scale. Height needs to be measured only at screening.
10. Record body temperature, pulse rate, respirations.
11. Physical examination should be done at all visits. At screening and discontinuation it should include a thorough genitourinary (pelvic) and rectal exam. In females, genitourinary exam should include a visual inspection of the cervix. If the subject has had a genitourinary and rectal exam within 6 months of screening the genitourinary and rectal exam do not need to be repeated.
12. Dermatologic exams should be performed by the Investigator at screening and according to table. This may be referred to a dermatologist, at the discretion of the investigator. If possible, the same physician should perform each exam for the duration of the study (i.e. if the subject is referred to a dermatologist for the screening exam, the dermatologist should do all follow up dermatologic assessments) to ensure consistency between evaluations.
13. ECG assessments must be performed within 35 days prior to first dose. Two copies of the ECG tracing should be obtained at the time of the ECG, one to be kept in the source documentation and one should be submitted to GSK. At each assessment a 12-lead ECG will be performed by qualified personnel at the site after at least a five-minute rest with the subject in a semi-recumbent or supine position. ECGs should be done in triplicate when the initial test is abnormal.
14. Echocardiogram assessments must be performed within 35 days prior to First Dose, . An echocardiogram does not need to be performed at study discontinuation unless one has not been performed within the last 9 weeks.
15. Adverse event assessment should be continuous.
16. Chemistry: Evaluations performed by the central laboratory. Screening laboratory assessments performed within 14 days of first dose of study drug do not need to be repeated at Day 1. Recent lab results should be reviewed prior to each dosing period.
17. Hematology: Evaluations performed by the central laboratory assessments. Screening laboratory assessments performed within 14 days of first dose of study drug do not need to be repeated at Day 1. Recent lab results should be reviewed prior to each dosing period. Day 8 hematology (CBC with differential to obtain ANC) may be performed at the central or with a local lab. A visit to the clinical site is not required unless the investigator considers it necessary. This visit should be recorded in an "unscheduled visit" tab and local lab ranges should be entered into "local lab" tab within the "unscheduled" visit tab. Please follow section 4.8 for Hematologic Dose Toxicity Guidelines if necessary.
18. A cTnI blood sample will be drawn at screening and stored at the central laboratory. Subsequent blood samples will be drawn and analyzed with screening sample if clinically indicated.
19. Blood sample for PGx: To be obtained only if the informed consent for PGx research has been obtained. Sample can be collected at any timepoint during the study, however collection at the first opportunity following randomization on Day 1 is preferred.
20. A mandatory circulating cell free DNA sample will be assessed at screening and at the time of disease progression.
21. Mandatory tumor tissue sample to be obtained per requirements in Section 6.6.1 at screening to assess for V600E DNA mutation and to further validate a BRAF mutation assay for regulatory approval and registration. Also, a growing lesion in the setting of overall clinical benefit should be biopsied to confirm melanoma and for further genetic testing. An additional optional tumor tissue sample from a lesion not required for disease assessment may be obtained via core biopsy at baseline and at the time of disease progression for biomarker analyses.
22. QoL will be measured at screening prior to any study related assessments, during study participation as indicated, at progression and 30 days (± 7 days) after progression.
23. For ALL subjects randomized to GSK2118436 arm (not DTIC arm), one PK sample for each study visit noted above is to be obtained. Subjects with morning clinic visits will be instructed to withhold their morning dose, and a PK sample will be collected prior to GSK2118436 administration; for subjects with afternoon clinic visits, subjects will take their morning dose as usual, and a sample will be collected 4 to 8 hours following GSK 2118436 administration. Date and exact time of PK sample and of most recent dose must be recorded.
24. In addition to the sparse sampling, the following samples will be obtained at Week 6 in a subset of subjects randomized to GSK2118436: predose (0 hrs) , and at 0.5, 1, 2, 3, 4, 6, and 8 hrs post-dose. Subjects will be instructed to withhold their morning dose and the morning dose will be administered at the site following predose sample collection. The time of GSK2118436 administration and the actual time and date of PK samples must be recorded
25. Safety Assessments will continue every 3 weeks while the subject remains on study drug, with the exception of, ECHOand ,ECG which will be every 9 weeks after week 21 unless clinically indicated, and dermatologic skin examinations (with photography as appropriate) which will be every 9 weeks after week 6.. Efficacy assessments will occur every 12 weeks after week 48 until progression or death.
26. Follow-up contact: All subjects who permanently discontinue study treatment will be followed for survival and additional anti-cancer therapies [including radiotherapy] every 12 weeks until death or study completion. Record the date of last contact in follow-up. Record first anti-cancer therapy and radiotherapy after discontinuation from study drug. Contact includes clinic visits, telephone contacts, and e-mail. Follow up disease assessment results and will be collected for subjects who discontinue study medication due to any other reason than progression or death

Source: Reproduced from Protocol BRF113683 (Amendment 5), Table 12

The protocol specified testing of standard clinical and laboratory parameters at baseline, during therapy, and at treatment discontinuation. Patients underwent tumor response evaluations at Week 6, Week 12, Week 21, Week 30, every 12 weeks thereafter until determination of PD, at PD, and six weeks following PD.

Statistical and Analytical Plan

The primary endpoint of the trial was PFS, defined as the time from randomization until the earliest date of radiological disease progression as documented by the investigator per RECIST 1.1 guidelines, or death from any cause, in the intent-to-treat population (ITT). Secondary endpoints were OS, time to progression or death of patients in the DTIC treatment group who crossed over to GSK2118436 after initial PD, ORR, duration of response, duration of response in patients who crossed over to GSK2118436 after initial progression on DTIC, and BRAF mutation validation for regulatory approval and registration.

The sample size determination was based on the following assumptions:

- Exponential survival distribution
- HR of 0.33 (median PFS of 2 months in the control arm and 6 months in the experimental arm)
- A 3:1 randomization scheme
- One-sided significance level α=0.02
- Log-rank test
- Power of $\geq$ 99%
- Accrual of 1.2 patients in Month 1; 6 in Month 2; 12.2 in Month 3; 22.2 in Month 4, and uniform accrual of 30 patients thereafter
- A 2% and 10% dropout rate on the GSK2118436 and DTIC arms, respectively

Under these assumptions, the statistical plan estimated that with enrollment of 200 patients to observe 102 PFS events, the trial was powered to detect with statistical significance a HR of 0.6251.

The SAP specified the following analysis populations:

- ITT population, defined as all randomized subjects regardless of whether treatment was administered
- Safety population, defined as all randomized subjects who received at least one dose of study medication and allocated to a treatment group based on the actual treatment received (in the randomized phase)
- GSK2118436 crossover population, defined as the subset of subjects who were randomized to the DTIC arm and who elected at the time of disease progression to receive GSK2118436 and subsequently received at least one dose of GSK2118436

The primary analysis specified in the SAP was PFS, based on investigator-assessment of tumor response measurements (RECIST 1.1) in the ITT, summarized using Kaplan-Meier estimates and compared between treatment arms using the stratified log-rank test [stratifying for disease stage [Stage III (unresectable), M1a, or M1b vs. M1c] with a significance level of 0.02 and two-sided

96% confidence interval. The SAP specified use of the Pike estimator of the treatment HR, together with a one-sided 98% confidence interval.

The SAP specified use of a two-sided α of 0.05 for analyses of secondary endpoints. The Applicant did not adjust the significance level for multiplicity because it considered secondary endpoints and subgroup analyses as supportive. The SAP also specified use of the ITT population in all efficacy analyses of secondary endpoints.

OS, a key secondary endpoint for the study, was defined as the time from randomization to death due to any cause—including deaths that occurred following crossover. The SAP specified use of Kaplan-Meier estimates to summarize OS and the stratified log-rank test to compare OS between treatment arms. The SAP also specified use of the Pike estimator of the treatment HR based on the log-rank test along with 95% confidence intervals (CI). Patients who had not died were censored for OS at the date the patient was last known to be alive.

Analyses of secondary endpoints in addition to OS which were specified in the SAP were:

- ORR, defined as the percentage of patients achieving either a CR or PR per RECIST (v 1.1), calculations using either the investigator's and the independent reviewer's assessment of response as well using either confirmed responses or unconfirmed responses. A comparison of ORRs between treatment arms used the Fischer's exact test. The SAP also planned analyses of ORR in the crossover population
- Duration of Response (DOR), defined as time from first documented evidence of PR or CR until the first documented sign of disease progression or death due to any cause, was summarized using based on responses as evaluated by the investigator. The SAP also planned analyses of DOR in the crossover population
- PFS analyses (unstratified) in the Stage III (unresectable), M1a, or M1b subgroup and in the M1c subgroup
- PFS2, defined as the time from first dose of GSK2118436 in patients randomized to DTIC who crossover to GSK2118436 after initial progression to the earliest date of radiographic or photographical disease progression or death due to any cause, was estimated using the Kaplan-Meier method for patients in the crossover population

Following the final PFS analysis, the SAP specified that the study would remain open for further follow-up to collect additional survival and safety data. Specifically, follow-up is planned until 70% of the total number of randomized patients have died or been otherwise lost to follow-up. Patients with continued response and still receiving GSK2118436 at that time may continue treatment in a rollover protocol.

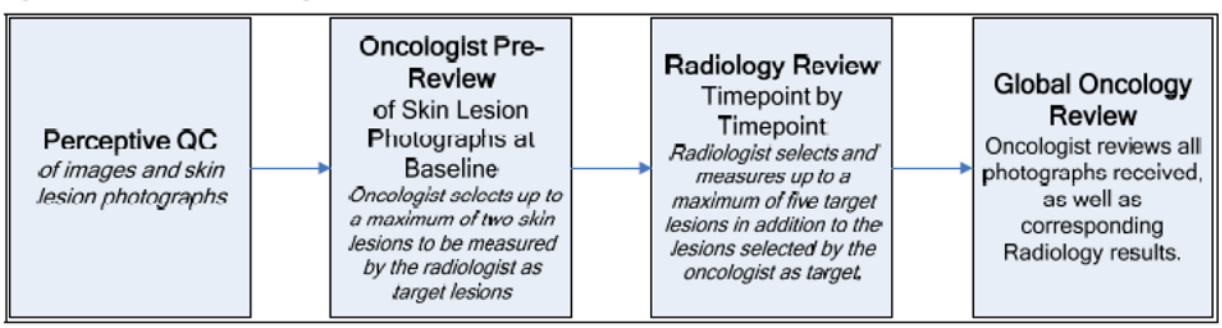
The Applicant performed the analysis of safety based on the Safety Population. The Applicant used Medical Dictionary for Regulatory Activities (MedDRA) version 14.1 to code AEs. The Applicant summarized the incidence of AEs by worst severity according to NCI- CTCAE version 4.

Blinded Independent Central Review

The Applicant planned to evaluate tumor-assessment endpoints using BICR. According to the BICR charter, independent review consisted of two sequential stages of review: (1) independent radiology (IR) review, a central blinded assessment of medical imaging data by one qualified radiologist and (2) the independent oncology (IO) review in which one independent oncologist assessed the skin lesion photographs in addition to the IR review findings to make a final efficacy endpoint determination (i.e., PFS, objective response assessment) for the case, if applicable.

In the process of IR review, the primary radiologist assessed study imaging –measurements of radiographic and, if applicable, photographic images of target lesions in the skin selected by the independent oncologist—to determine an overall imaging tumor response as per modified RECIST 1.1 at each timepoint. Following the imaging evaluation by the primary radiologist, the independent oncologist assessed any additional clinically assessed lesions, such as skin lesions from photographs as well as reports with site measurements of any clinically assessed subcutaneous target lesions, and determined relevant endpoints based on a combined assessment of radiologic and clinically assessed lesions. Figure 3 summarizes the BICR review procedure.

Figure 3: Blinded Independent Central Review Process. BRF113683 Independent Review Charter.



Reproduced from Section 7.1 of IRC charter

REVIEWER COMMENT:
The Applicant requested that the BICR amend the review charter (version 2.0, September 14, 2011) to allow the presentation to the independent oncologist of clinical measurements of subcutaneous lesions, as assessed by the site if there was no CT or MRI of the lesion(s). This amendment also removed the requirement in the charter for the independent oncologist to document an overall tumor response assessment for each timepoint. The independent oncologist-assessed PFS was captured as a PFS event date without corroborating raw data such as tumor measurements (site or IO), identification of new lesions, or overall tumor response assessment. Thus, FDA was unable to verify, based on raw data, any PFS analysis which included an assessment by the independent oncologist. Please see Dr. Yuan's Statistical Review for further details.

Protocol Amendments

The Applicant submitted six amendments to Protocol BRF113683. Key revisions in each amendment were:

- Amendment 1 (November 3, 2010)—added assessment of secondary malignancies to the secondary safety objectives
- Amendment 2 (March 4, 2011)— amended the QTc stopping criteria for subjects enrolled at sites in France
- Amendment 3 (March 23, 2011)—clarified eligibility criteria for crossover. In addition, the Applicant added best overall response rate as a secondary efficacy objective.
- Amendment 4 (June 3, 2011)—added dose monitoring and management guidelines for neutropenia as well as fever based on emerging safety data from other ongoing GSK2118436 studies
- Amendment 5 (November 14, 2011)—amended the study design to allow patients with investigator-reported disease progression who were still benefitting from study treatment with GSK2118436 to continue study drug. In addition, the amended protocol added new guidelines for the management of renal insufficiency as well as new criteria for dose modifications related to Grade 3 toxicities
- Amendment 6 (April 27, 2012; amendment submitted after the data cutoff date)—amended the protocol to allow patients randomized to the DTIC arm, based on the judgment of the investigator, to crossover to receive GSK2118436 prior to documented disease progression

Primary and Supportive Trials of GSK2118436 in Patients with BRAFV600 Mutation-positive Advanced (unresectable Stage III) or Metastatic (Stage IV) Melanoma

Table 8 summarizes the trial designs and key features of the five trials submitted by the Applicant to support the efficacy and safety of dabrafenib for the treatment of patients with BRAFV600 Mutation-positive advanced (unresectable Stage III) or Metastatic (Stage IV) Melanoma.

Table 8: Summary of Trial Designs of Key GSK2118436 Monotherapy Trials for Melanoma.

Trial ID (CT ID[a])	Design	Population[b]	N	Treatment Regimen	Key Endpoints
BRF113683 (NCT01227889)	OL, MC, RCT (3:1)	Stage III (unresectable) or IV, PS 0-1; BRAF V600E by centralized testing; No prior systemic therapy;	187	GSK21128436 150mg PO BID	**Primary: PFS** Secondary: OS,PFS2, ORR, DOR
			63	DTIC 1000 mg/m^2 D1 q 21d	
BRF113929 (NCT01266967)	OL, MC, two-arm	Metastatic melanoma to the brain; PS 0-1; BRAF V600E or V600K by centralized testing; Up to 2 prior systemic treatment regimens for melanoma; Local treatment for brain metastases: no prior treatment (Cohort A) or previously treated (Cohort B)	89	Cohort A (No prior local treatment to brain metastases): GSK2118436 150 mg PO BID	**Primary: OIRR in BRAF V600E patients** Secondary: ORR; OIRR in V600K; DOR; PFS, OS
			83	Cohort B (Prior local treatment(s) to brain metastases): GSK2118436 150 mg PO BID	
BRF113710 (NCT01153763)	OL, MC, single-arm	Metastatic melanoma, PS 0-1; BRAF V600E or V600K by central testing; Treatment-naïve or received prior systemic therapy in the metastatic setting	92	GSK2118436 150mg PO BID	**Primary: ORR in BRAF V600E patients** Secondary: ORR in BRAF V600K; PFS, DOR, OS
BRF113220, Part C (NCT01072175)	OL, MC, RCT (1:1:1), three-arm	Metastatic melanoma, PS 0-1; BRAF V600E, V600K, or V600D by local testing; Up to one prior systemic therapy for metastatic disease	162[c]	Arm A: GSK2118436 150mg PO BID	**Primary: safety and tolerability of GSK2118436 and GSK1120212 dosed in combination**
				Arm B: GSK2118436 150mg PO BID + GSK1120212 1mg PO QD	
				Arm C: GSK2118436 150mg PO BID + GSK1120212 2mg PO QD	
BRF112680 (NCT00880321)	FTIH, OL, MC, DE	BRAF mutation-positive (*by local testing)* solid tumors; PS 0-1	184[d]	GSK2118436 150mg PO BID	**Primary: safety and tolerability of GSK2118436**

Abbreviations in Table: BRAFi, BRAF inhibitor; DE, dose-escalation; DOR, duration of response; FTIH, first time in human; MC, multicenter; MEKi, MEK inhibitor; OL, open label; ORR, overall response rate; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; PS, Eastern Cooperative Oncology Group performance status; RCT, randomized controlled trial; RP2D, recommended Phase 2 dose;
[a]ClinicalTrials.gov Identifier
[b] No prior use of BRAF inhibitors or MEK inhibitors

[c] Analyses of safety included the available safety data from the 53 patients enrolled in Arm A patients who received GSK2118436 150mg PO BID as monotherapy as well as selected SAEs experienced by the 109 patients enrolled in the two GSK2118436 + GSK1120212 combination arms.
[d] Of the 184 enrolled patients, 47 melanoma patients received GSK2118436 150 mg PO BID in dose-escalation or expansion cohorts.

6 Review of Efficacy

Efficacy Summary

The NDA submission contained a single randomized controlled trial, BRF113683, in support of the proposed indication:

> Tafinlar is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation as detected by an FDA approved test.

BRF113683 was a multicenter, international, open-label, randomized (3:1), active-controlled trial comparing single agent dabrafenib to DTIC in 250 patients with previously untreated, histologically confirmed, advanced (unresectable Stage III) or metastatic (Stage IV) melanoma determined to be BRAF V600E mutation-positive based upon centralized testing of formalin fixed paraffin embedded tumor tissue using an investigational use only (IUO) assay. There was one randomization stratification factor: stage of disease [unresectable Stage III melanoma (regional nodal or in-transit metastases), M1a melanoma (distant skin, subcutaneous, or nodal metastases), or M1b melanoma (lung metastases) vs. M1c melanoma (all other visceral metastases or any distant metastasis with an elevated serum LDH)].

The BRF113683 trial met its primary endpoint of investigator-assessed PFS demonstrating a statistically significant 67% reduction in the hazard rate of progression of disease or death [HR 0.33 (95% CI: 0.20, 0.55)] on the dabrafenib arm compared to the DTIC arm based on the stratified log-rank test with a p-value <0.001. The median PFS on the dabrafenib arm was 5.1 months (95% CI: 4.9, 6.9) compared to 2.7 months (95% CI: 1.5, 3.2) in the DTIC arm. Nearly all of the 119 PFS events observed during the trial were disease progression events (98%) whereas few were deaths (2%). Analyses of PFS based on blinded, independent central review assessment, sensitivity analyses, and demographic and prognostic baseline disease characteristic subgroups confirmed a statistically persuasive and robust, clinically meaningful prolongation of PFS in the dabrafenib arm. The investigator-assessed, confirmed ORR was 52% (95% CI: 45%, 59%) with 6 (3%) complete responders on the dabrafenib arm and was 17% (95% CI: 9%, 29%) on the DTIC arm, all partial responders. The median duration of response was 5.6 months (95% CI: 5.4, not estimable) for the objective responders to dabrafenib and was not estimable for the objective responders to DTIC. The interim OS analysis performed at the time of the final PFS analysis demonstrated an estimated HR of 0.67 (95% CI: 0.28, 1.58) and median OS was not estimable because the OS data were not mature. Currently under review by CDRH is a premarket approval application for the Biomerieux THxID BRAF Kit (PMA P120014) which is

intended for use as an in vitro companion diagnostic assay to detect BRAF V600 (E or K) mutations in melanoma.

Of note, patients with BRAF V600K mutations, a subgroup consisting of approximately 5 to 30% of patients with BRAF V600 mutation-positive melanoma, were not eligible for the BRF113683 trial (Rubinstein, Sznol, et al. 2010). However, the Applicant assessed the anti-tumor activity of dabrafenib in the subgroup of patients with previously treated or untreated, BRAF V600K mutation-positive metastatic melanoma as secondary endpoints in two activity-estimating trials (BRF113710 and BRF113929). In the BRF113710 trial, which was conducted in patients without active brain metastases, the investigator-assessed, confirmed ORR in patients with previously treated or untreated, BRAF V600K mutation-positive melanoma was 2/13 (13%; 95% CI: 0, 29). In the BRF113929 trial, which was conducted in patients with asymptomatic brain metastases, the investigator-assessed, confirmed ORR in the subgroup of patients with BRAF V600K mutation-positive metastatic was 0/15 (0; 95% CI: 0, 21.8) in the cohort that received no prior local therapy for brain metastases and was 5/18 (28%; 95% CI: 9.7, 53.5) in the cohort that received prior local therapy for brain metastases.

6.1 Indication

The Applicant proposes the following indication:

> Tafinlar is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation as detected by an FDA approved test.

6.1.1 Methods

The Applicant submitted data from one adequate and well-controlled trial (BRF113683) which is described in detail in Section 5.3. In addition to data from the BRF113683 trial, the Applicant provided the results from two open-label, multicenter, non-comparative, activity-estimating trials, BRF113710 and BRF113929 (see Table 8). The review of efficacy did not include an analysis of pooled clinical efficacy data.

6.1.2 Demographics

Overall, the treatment arms were balanced for demographics and baseline characteristics.

Patients were predominantly men (60% on the dabrafenib arm vs. 59% on the DTIC arm), younger than 65 years of age (78% vs. 81%), Caucasian (98% vs. 100%), and enrolled in Europe (75% vs. 70%). At enrollment, the majority of patients had an ECOG PS of 0 (66% on dabrafenib arm vs. 70% on DTIC arm), M1c disease (66% vs. 63-67%), visceral involvement with metastases (73% vs. 68%), and normal LDH (62% vs. 63%).

Table 9 and Table 10 summarize the demographics and baseline characteristics of patients randomized on the BRF113683 trial.

Table 9: Demographics by Treatment Arm. Intent-to-Treat Population. BRF113683 Trial.

	Dabrafenib N= 187	**DTIC N=63**
Gender		
Male, n (%)	112 (60)	37 (59)
Female, n (%)	75 (40)	26 (41)
Race		
Caucasian, n (%)	184 (98)	63 (100)
Other, n (%)	3 (2)	0
Age, years		
Median	53	50
Range, min-max	22-93	21-82
< 65, n (%)	146 (78)	51 (81)
≥ 65, n (%)	41 (22)	12 (19)
Region		
Europe, n (%)	140 (75)	44 (70)
North American, n (%)	36 (19)	14 (22)
Australia, n (%)	11 (6)	5 (8)

Source: FDA Statistical review; Pop.xpt

Table 10: Baseline Disease Characteristics and Prior Therapy by Treatment Arm. Intent-to-Treat Population. BRF113683 Trial.

	Dabrafenib N= 187 n (%)	DTIC N=63 n (%)
BRAF V600 mutation subtype		
V600E	186 (99)	62 (98)
V600K	1 (1)	1 (2)
ECOG PS at baseline		
0	124 (66)	44 (70)
1	62 (33)	16 (25)
Missing	1 (1)	3 (5)
Stratum at randomization: disease staging		
Unresectable III+IVM1a+IVb	63 (34)	21 (33)
IVM1c	124 (66)	42 (67)
Stratum per e-CRF: disease staging		
Unresectable III+IVM1a+IVb	63 (34)	23 (37)
IVM1c	124 (66)	40 (63)
Baseline LDH		
Above ULN	66 (35)	17 (27)
Equal to or below ULN	116 (62)	40 (63)
Missing	5 (3)	6 (10)
Visceral disease		
Visceral	22 (12)	8 (13)
Non-visceral	50 (27)	20 (32)
Visceral and non-visceral	115 (61)	35 (56)
Number of disease sites		
< 3	94 (50)	35 (56)
≥ 3	93 (50)	28 (44)
Tumor classification at initial diagnosis		
Cutaneous	165 (88)	56 (89)
Non-cutaneous	6 (3)	2 (3)
Other	3 (2)	0
Unknown	13 (7)	5 (8)
Prior therapy		
Radiotherapy	37 (20)	10 (16)
Surgery	179 (96)	61 (97)
Immunotherapy	52 (28)	15 (24)
Biologic Therapy	3 (2)	3 (5)
Chemotherapy	1 (1)	4 (6)
Hormonal Therapy	0	1 (2)

Source: FDA Statistical Review; Review analysis.

REVIEWER COMMENTS:

1. *The randomized population included two patients with BRAF V600K mutation-positive melanoma in spite of the eligibility criteria which limited the trial to patients with the BRAF V600E subtype. Patient BRF113683.0010168 received treatment with dabrafenib whereas Patient BRF113683.0001390, randomized to DTIC, did not receive study treatment.*
2. *The protocol permitted prior use of interleukin-2—a single randomized patient reported prior use of interleukin therapy for advanced or metastatic disease.*
3. *There were no values recorded in the dataset listings for 176/250 (70%) of the randomized patients in regard to prior systemic anti-cancer therapy (i.e., immunotherapy, biologic therapy, chemotherapy, and hormonal therapy). It is uncertain whether these represent missing data or if these patients did not receive prior systemic anti-cancer therapy.*
4. *There were 40 (16%) patients with mismatched stratum (i.e., disease stage) between the IVRS randomization and electronic case report forms (eCRF)s. The FDA primary analysis of PFS used disease stratum at randomization (IVRS).*
5. *See Dr. Yuan's review for additional details in regard to the missing data in the submission as well as discrepancies between documented disease stage stratum on the eCRF and that recorded at the time of randomization by the IVRS.*

6.1.3 Subject Disposition

Screening Phase

The BRF113683 trial screened 733 patients to randomize 250 patients with BRAF V600E mutation-positive melanoma. Reasons for not proceeding to randomization were, in order of decreasing frequency: wild-type BRAF result, ineligible based on other eligibility criteria, BRAF V600K mutation, no tissue sent for biomarker evaluation, and tissue for biomarker status was unevaluable (i.e., quantity not sufficient, no tumor identified, or out of detectable range). Table 11 summarizes the disposition of patients who did not proceed from screening to randomization.

Table 11: Patient Disposition. Screening Population. BRF113683 Trial

	Screening N=733 n (%)
Not Randomized	**483 (66)**
BRAF V600 mutation-positive	159 (22)
BRAF V600E: Other eligibility criteria screening failure	109
V600K result	50
BRAF V600 wild-type result	266 (36)
BRAF V600 mutation status unknown	58 (8)
Unable to identify BRAF status (QNS, NTI, OODR)	28
Subjects who did not send tissue	30
Randomized	**250 (34)**

Source: Applicant response to information request (NDA 202806, eCTD#0055)

REVIEWER COMMENT:
The BRAF V600 mutation-positive subgroup within the screening population consisted of 357/733 (49%) patients with BRAF V600E mutations and 52/733 (7%) patients with BRAF V600K mutations. The overall frequency of BRAF V600E and BRAF V600K mutations in the screening population was 56% (409/733)—a frequency of BRAF V600 mutation-positive melanoma consistent with that reported in the literature.

Randomization/Treatment Phase

The BRF113683 trial randomized 250 patients enrolled at 70 centers in 12 countries. The countries that enrolled the greatest number of patients included: Germany (57 patients), France (36 patients), United States (32 patients), Italy (22 patients), and Spain (21 patients).
Four patients in the ITT population did not receive study treatment, three patients randomized to DTIC and one patient randomized to dabrafenib. In addition, one patient (BRF113683.0007274) randomized to DTIC only received treatment with dabrafenib. This patient is included in the DTIC arm for analyses of efficacy and in the dabrafenib treatment group for analyses of safety.
At the time of data cutoff, 57% on the dabrafenib arm and 22% on the DTIC arm continued on randomized treatment. In addition, 28 patients randomized to DTIC crossed over to receive dabrafenib. Progressive disease was the most reason for treatment discontinuations on the dabrafenib arm [66/80 (83%)] and on the DTIC arm [43/46 (93%)]. Table 12 summarizes the treatment status and reasons for treatment discontinuation for patients in the BRF113683 trial.

Table 12: Summary of Study Treatment Status. Intent-to-Treat and Crossover Populations. BRF113683 Trial.

	Randomized Phase		Crossover
	Dabrafenib N=187 n (%)	DTIC N=63 n (%)	Dabrafenib N=28 n (%)
Treatment status			
Ongoing	106 (57)	14 (22)	21 (75)
Discontinued	80 (43)	46 (73)	7 (25)
Withdrew prior to first dose	1 (1)	3 (5)	
Primary reason for treatment discontinuation[1]			
Disease progression	66 (35)	43 (68)	6 (21)
Adverse event	5 (3)	0	0
Investigator discretion	4 (2)	2 (3)	1 (4)
Decision by subject / proxy	5 (3)	1 (2)	0

Source: RDS.xpt and RIPDISC.xpt
[1] Patients had only one primary reason for treatment discontinuation

The incidence of study withdrawal due to death was 11% on the dabrafenib arm and 14% on the DTIC arm. Study withdrawal for other reasons was infrequent (Table 13).

Table 13: Patient Disposition. Intent-to-Treat Population. BRF113683 Trial.

	Dabrafenib N=187 n (%)	DTIC N=63 n (%)
Subject status		
Died	21 (11)	9 (14)
Ongoing	160 (86)	49 (78)
On randomized study treatment	106 (57)	14 (22)
In follow-up	54 (29)	14 (22)
On crossover study treatment	n/a	21 (33)
Withdrawn from study	6 (3)	5 (8)
Reason for study withdrawal		
Lost to follow-up	2 (1)	1 (2)
Investigator discretion	2 (1)	1 (2)
Withdrew consent	2 (1)	3 (5)

Source: Applicant table verified using RDS.xpt and RIPDISC.xpt
Abbreviations in Table: n/a, not applicable

6.1.4 Analysis of Primary Endpoint(s)

The protocol-specified primary endpoint was PFS, defined as the interval of time between the date of randomization and the earlier of the following:

- date of disease progression based on radiographic or photographic evidence, as assessed by the investigator per RECIST 1.1
- date of death due to any cause

The primary analysis—PFS summarized using Kaplan-Meier estimates and compared between treatment arms (ITT population) using the stratified log-rank test [Stage III (unresectable), M1a, or M1b vs. M1c]—was planned at the time of 102 PFS events (see Section 5.3). The Applicant used a data cutoff of December 19, 2011, for the primary efficacy analysis.

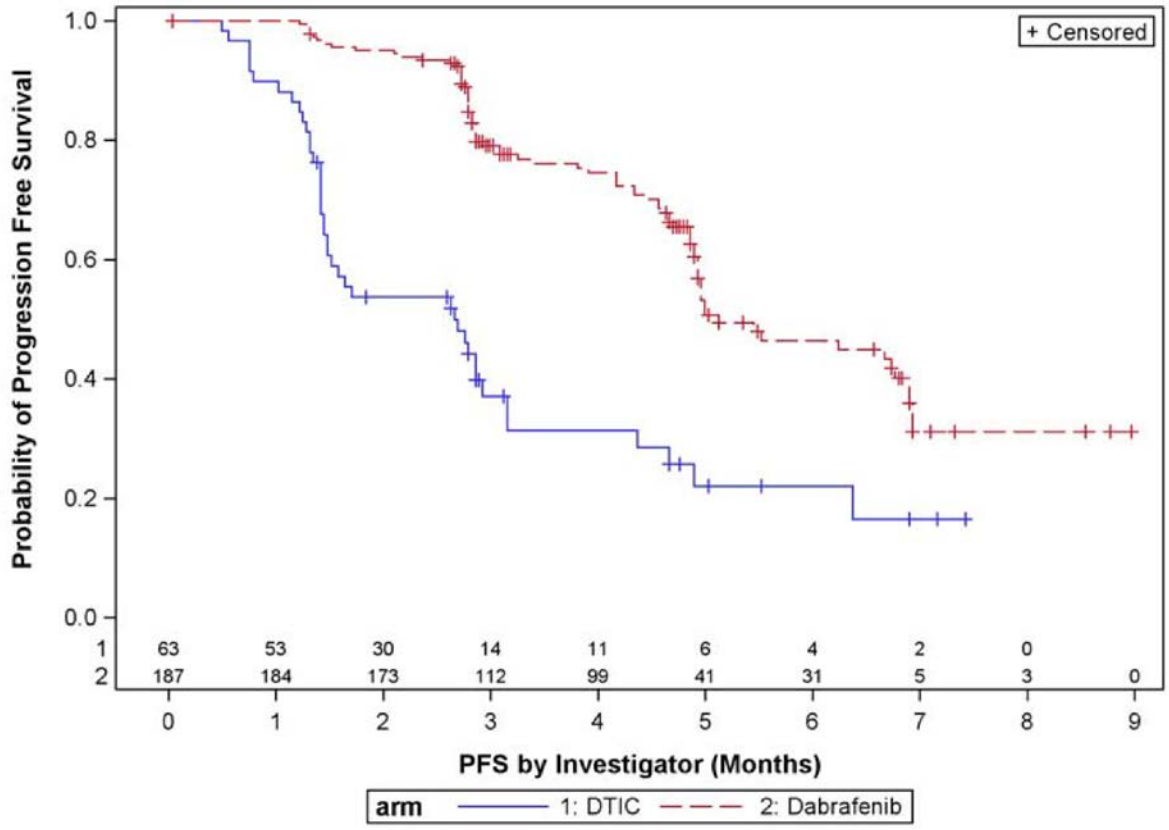
The primary efficacy analysis of the BRF113683 trial demonstrated a statistically significant improvement in investigator-assessed PFS with dabrafenib treatment compared to DTIC treatment. The median PFS was 5.1 months (95% CI: 4.9, 6.9) on the dabrafenib arm and 2.7 months (95% CI: 1.5, 3.2) on the DTIC arm with a HR of 0.33 (95% CI: 0.20, 0.55; 2-sided p-value <0.001). Table 14 and Figure 4 summarize the results of the primary PFS analyses.

Table 14: Primary Efficacy Analysis of Progression-Free Survival. Intent-to-Treat Population. BRF113683 Trial.

	Dabrafenib N = 187	**DTIC** N = 63
Number of Events (%)	78 (42)	41 (65)
Progressive Disease	76	41
Death	2	0
Duration of PFS (months)		
Median PFS (95% CI)	5.1 (4.9, 6.9)	2.7 (1.5, 3.2)
2-sided p-value (stratified log-rank)	< 0.001	
HR (95% CI)[1]	0.33 (0.20, 0.55)	

Source: FDA Statistical Review
[1] by Pike per stratum at randomization

Figure 4: Plots of Kaplan-Meier Estimates for Progression-Free Survival by Treatment Arm. Intent-to-Treat Population. BRF113683 Trial.



Source: FDA Statistical Review

REVIEWER COMMENT:
As per the FDA Guidance for Industry "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics", tumor-assessment endpoints selection should include two judgments: (1) determination whether the endpoint will support either accelerated approval or regular approval and (2) an evaluation for the potential of bias or uncertainty in tumor endpoint assessments. This Guidance recommends that tumor endpoint assessments should be verified by central reviewers blinded to study treatments when the primary study endpoint is based on tumor measurements.

The potential for bias in the PFS assessment in this open-label trial was investigated using analyses conducted based on blinded independent central review assessment of PFS as well as several sensitivity analyses.

Blinded, Independent Central Review Assessment of PFS

The Applicant performed a pre-specified supportive analysis of PFS based on BICR assessment (see Section 5.3). BICR-assessed PFS (based on IR assessments or on combined IR and IO

assessments) demonstrated results consistent with those of the primary efficacy analysis (Table 15).

Table 15: Supportive Analyses of Progression-Free Survival Based on Blinded Independent Central Review Assessments. Intent-to-Treat Population. BRF113683 Trial.

	Primary Analysis		Blinded, Independent Central Review			
	INV		IR		Combined IR and IO	
	Dabrafenib N = 187	DTIC N = 63	Dabrafenib N = 187	DTIC N = 63	Dabrafenib N = 187	DTIC N = 63
Number of Events (%)	78 (42)	41 (65)	61 (33)	29 (46)	68 (36)	33 (52)
Progressive Disease	76	41	56	29	63	33
Death	2	0	5	0	5	0
Duration of PFS, months						
Median PFS (95% CI)	5.1 (4.9, 6.9)	2.7 (1.5, 3.2)	6.7 (5.0, 6.9)	4.4 (1.6, NE)	6.5 (4.9, 6.9)	2.9 (1.5, 4.9)
p-value (2-sided, stratified log-rank)	< 0.001		<0.001		<0.001	
HR(95% CI)[1]	0.33 (0.20, 0.55)		0.36 (0.20, 0.65)		0.36 (0.21, 0.62)	

Source: FDA Statistical Review.
Abbreviations in Table: CI, confidence interval; HR, hazard ratio; INV, investigator; IO, independent oncologist review; IR, independent radiologist review; NE, not estimable; PFS, progression-free survival.
[1] By Pike per stratum at randomization.

REVIEWER COMMENTS:

1. *The FDA analyses of the primary efficacy analysis as well as the supportive analyses of PFS based on blinded, independent central review provide numerically different results than those presented in the clinical study report for the BRF113683 trial. Nonetheless, FDA analyses confirm the treatment effect of dabrafenib, i.e., an improvement in PFS compared to the DTIC arm. Based on NDA submission quality issues, FDA could not validate the Applicant's derivations of tumor response data using the tumor measurement raw data. Rather than using the derived overall tumor response assessment (e.g., complete response, partial response, stable disease, etc.), FDA analyses of PFS re-derived tumor response data according to RECIST version 1.1 using raw datasets containing tumor measurements as documented by the investigator or the independent radiologist.*
2. *The data recorded by the Applicant to support an overall efficacy assessment by the independent oncologist at each timepoint were not adequate for FDA to verify, using raw data, analyses of PFS based on independent oncologist assessments.*
3. *Please see Dr. Yuan's review for details of the submission quality issues which hindered the FDA analyses of PFS.*

4. Dr. Yuan conducted various sensitivity analyses, including analyses based on original data submitted by the Applicant, to evaluate the robustness of the primary analysis results. These sensitivity analyses were:

- *investigator-assessed PFS without censoring for symptomatic PD*
- *investigator-assessed PFS without censoring for start of new anti-cancer therapy*
- *investigator-assessed PFS without censoring for two continuous missing assessments*

These sensitivity analyses of PFS demonstrated results consistent with those from the primary efficacy analysis.

6.1.5 Analysis of Secondary Endpoints(s)

The Applicant's analyses of secondary endpoints used a two-sided α of 0.05 without adjustments to the significance level for multiplicity. All efficacy analyses of secondary endpoints are based on the ITT population unless otherwise noted (see Section 5.3).

Overall Survival

The protocol specified OS as a key secondary endpoint. The definition of OS was the time from randomization to death from any cause. Patients without death events recorded by the investigator were censored at the date that the patient was last known to be alive. The definition of OS included all death events, including those which occurred following the date of crossover from the DTIC treatment to dabrafenib treatment.

Table 16 summarizes the results from the OS analysis. There were a total of 30 death events at the time of the OS analysis, 21 events on the dabrafenib arm and 9 events on the DTIC arm. The estimated HR of death (dabrafenib arm compared to DTIC arm) was 0.67 (95% CI: 0.28, 1.58) and median OS was not estimable for either treatment arm because the OS data were not mature. Figure 5 shows the Kaplan-Meier plots of OS.

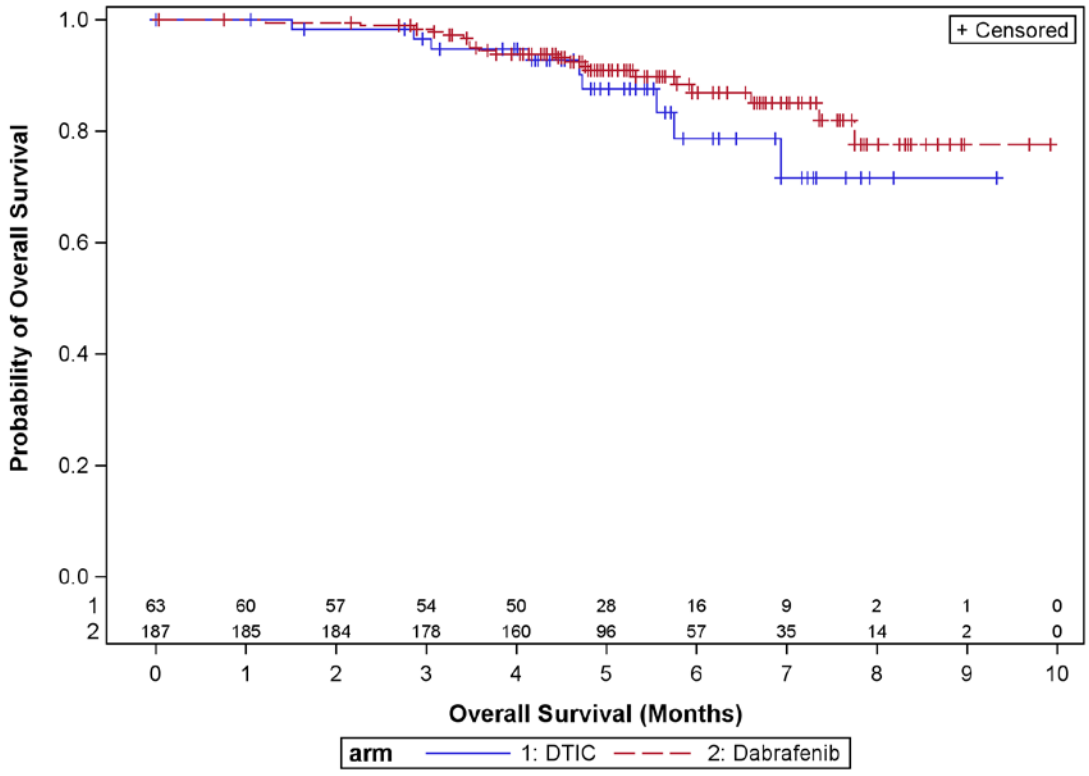
Table 16: Analysis of Overall Survival by Treatment Arm. Intent-to-Treat Population. BRF113683 Trial.

	Dabrafenib N = 187	**DTIC N = 63**
Number of deaths (%**)**	21 (11)	9 (14)
Duration of overall survival		
Median OS, months (95% CI)	NE (6.9, NE)	NE (NE, NE)
p-value (2-sided, unstratified log-rank)	0.31	
HR (95% CI)		
by Cox unstratified	0.67 (0.31, 1.46)	
by Pike unstratified	0.67 (0.28, 1.58)	
by Cox per stratum at randomization	0.69 (0.32, 1.51)	
by Pike per stratum at randomization	0.69 (0.29, 1.62)	
by Cox per stratum on e-CRF	0.61 (0.28, 1.34)	
by Pike per stratum on e-CRF	0.61 (0.25, 1.47)	

Source: FDA Statistical Review, Table 7.
Abbreviations in Table: CI, confidence interval; e-CRF, electronic case report form; HR; hazard ratio; NE, not estimable.

REVIEWER COMMENT: Various analyses based on stratified and unstratified tests using Cox or Pike estimators demonstrate consistent survival HRs. However, the reliability of the point estimate of the HR is uncertain because the OS data are not mature.

Figure 5: Plots of Kaplan-Meier Estimates for Overall Survival. Intent-to-Treat Population. BRF113683 Trial.



Overall Response Rate

The investigator-assessed, confirmed ORR was 52% (95% CI: 45%, 59%) on the dabrafenib arm and 17% (95% CI: 9%, 29%) on the DTIC arm. The median duration of response was 5.6 months (95% CI: 5.4, not estimable) for objective responders on the dabrafenib arm and was not estimable for objective responders on the DTIC arm. The BICR-assessed ORR rates and durations of responses were similar to those based on analyses using investigator assessment (Table 17).

Table 17: Confirmed Objective Response Rates and Duration of Responses as Assessed by Investigator or Blinded Independent Central Review. Intent-to-Treat Population. BRF113683 Trial.

	Investigator		Blinded, Independent Central Review			
			IR		Combined IR and IO	
	Dabrafenib N = 187	**DTIC N =63**	**Dabrafenib N = 187**	**DTIC N =63**	**Dabrafenib N = 187**	**DTIC N =63**
ORR, n (%)	97 (52)	11 (17)	92 (49)	5 (8)	91 (49)	5 (8)
95% CI	(45%, 59%)	(9%, 29%)	(42%, 57%)	(3%, 18%)	(41%, 56%)	(3%, 18%)
CR, n (%)	6 (3)	0	6 (3)	2 (3)	6 (3)	2 (3)
PR, n (%)	91 (49)	11 (17)	86 (46)	3 (5)	85 (45)	3 (5)
Median DoR (95%CI)	5.6 (5.4, NE)	NE (5.0, NE)	5.6 (5.0, 6.9)	NE	5.6 (5.0, 6.9)	NE

Source: FDA Statistical Review, Table 8.
Abbreviations in Table: CI, confidence interval; CR, complete response; DoR, duration of response; IO, independent oncologist; IR, independent radiologist; NE, not estimable, PR, partial response.

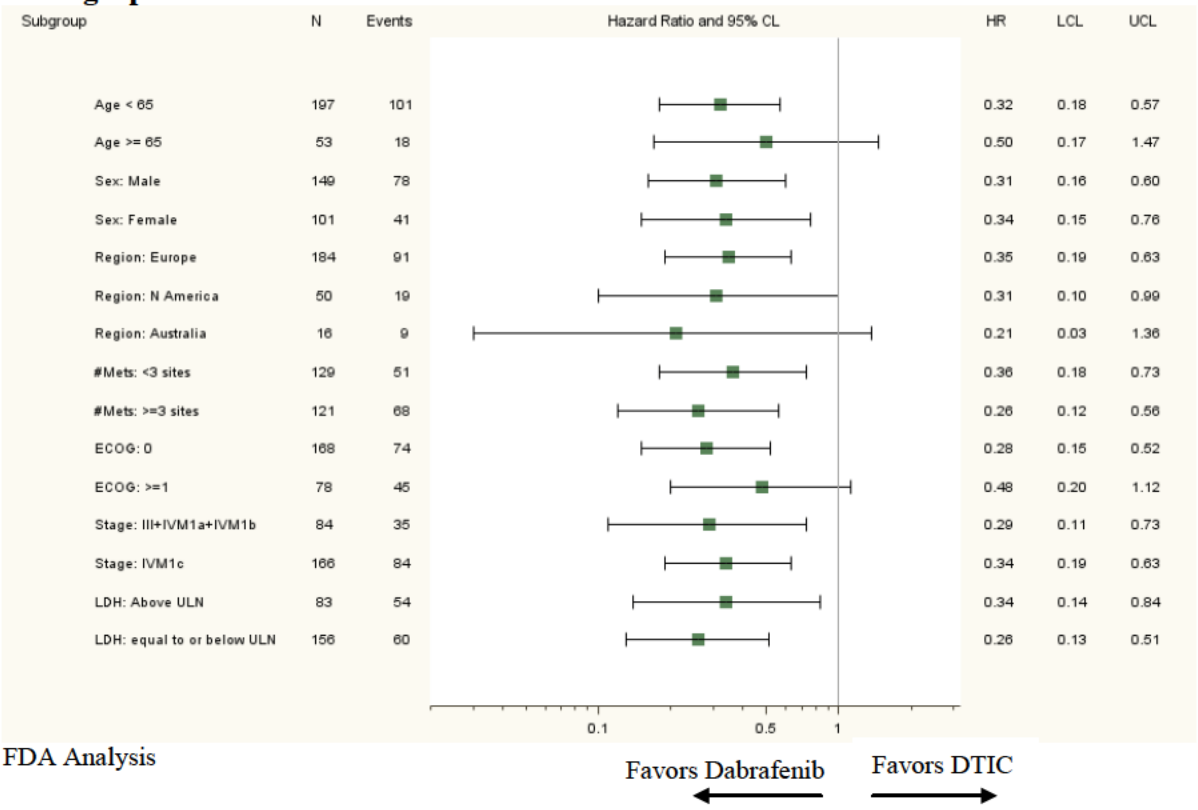
6.1.6 Other Endpoints

The review did not include an analysis of exploratory endpoints for the BRF113683 trial because the Applicant did not propose to include these results in labeling or intend to use these endpoints, as designed, to support the efficacy of dabrafenib.

6.1.7 Subpopulations

Analyses of investigator-assessed PFS by demographic and baseline characteristic subgroups are shown below (Figure 6). The Applicant and FDA did not perform subgroup analyses based on race because the study population was almost entirely Caucasian. Subgroup analyses demonstrated consistent estimates of the PFS HR (dabrafenib compared to DTIC) and in most cases the 95% confidence intervals do not cross 1.0. In subgroups where estimates of PFS HRs crossed 1, there were small numbers of patients and wide confidence intervals (e.g., age ≥65, Australia region).

Figure 6: Subgroup Analyses of Investigator-Assessed Progression-Free Survival by Demographic and Baseline Disease Characteristics. BRF113683 Trial.

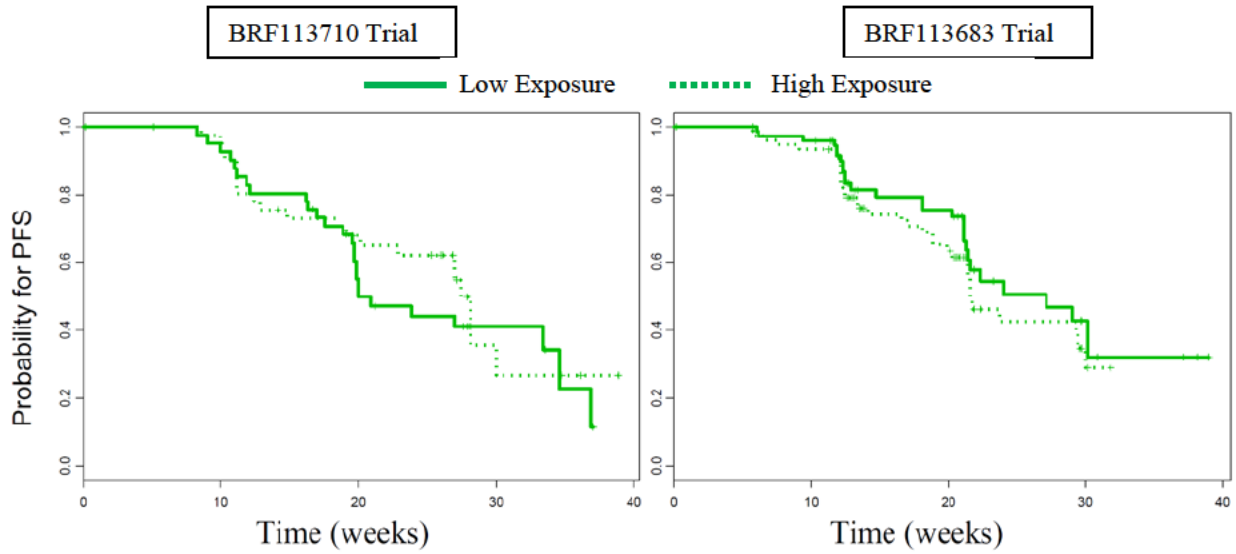


FDA Analysis

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The development program of dabrafenib contains limited data on dose-response. The Applicant has not conducted individual dose-response trials. FDA review included analyses of exposure-response relationships. As shown in Figure 7, plots of Kaplan-Meier estimates for patients with exposures of dabrafenib, including its metabolites, that are above (High Exposure) and below (Low Exposure) the median active concentration (99.6 ng/mL) do not suggest a trend toward increasing PFS with increasing exposure in analyses of the BRF113710 and BRF113683 trials. Please see the FDA Clinical Pharmacology NDA Review for further details.

Figure 7: Plots of Kaplan-Meier Estimates of Progression-Free Survival by Dabrafenib ($C_{min, parent} + C_{min, met}$) Exposure. BRF113710 Trial (Left Plot) and BRF113683 Trial (Right Plot).



Source: Kaplan-Meier Plots Reproduced from FDA Clinical Pharmacology Review of NDA 202806, Figure 1

In the first-in-human, dose-escalation part of the BRF112680 trial, the Applicant summarized the anti-tumor activity of dabrafenib in the subgroup of BRAF and MEK inhibitor naïve patients with BRAF V600 mutation-positive melanoma and measurable disease at baseline. Table 18 summarizes the investigator-assessed, unconfirmed response rates at Week 9 of the trial.

Table 18: Unconfirmed, Investigator-Assessed Objective Response Rates at Week 9. BRAF V600 Mutation-Positive Melanoma Population. Dose-Escalation Phase of the BRF112680 Trial.

	Dabrafenib (Gelatin Capsule) Dose Escalation Cohorts								
Total Daily Dose (mg)	**<=35**	**70**	**140**	**200**	**300**	**300**	**400**	**600**	**150/300[a]**
No. of Daily Divided Doses	**One**	**Two**			**Three**	**Two**			
	N=3	**N=5**	**N=14**	**N=9**	**N=14**	**N=16**	**N=16**	**N=10**	**N=5**
Week 9 assessment									
ORR, n (%)	0	3 (60)	3 (21)	4 (44)	4 (29)	8 (50)	6 (38)	9 (90)	1 (20)
95% CI	-	15, 95	5, 51	14, 79	8, 58	25, 75	15, 65	55, 100	1, 72
CR, n (%)	0	1 (20)	0	0	1 (7)	0	1 (6)	0	0
PR, n (%)	0	2 (40)	3 (21)	4 (44)	3 (21)	8 (50)	5 (31)	9 (90)	1 (20)

Source: BRF112680 CSR, Table 16
Abbreviations in Table: CI, confidence interval; CR, complete response; PR, partial response.
[a] Pharmacodynamic cohort, patients doses with dabrafenib 75 mg orally twice daily for at least 15 days but permitted to escalate to 150 mg orally twice daily thereafter.

REVIEWER COMMENT:
The Applicant analyzed the results of ORR based on unconfirmed objective responses at Week 9 because the protocol permitted intra-patient dose-escalation following this timepoint. As

previously noted, the BRF112680 trial evaluated the gelatin capsule formulation of dabrafenib which results in lower exposure than the HPMC formulation. In an analysis performed by the Applicant, the exposure at steady state of dabrafenib HPMC capsules administered at a 50 mg dose orally twice daily, the lowest dose of dabrafenib administered based on the dose modification schedule in the BRF113683 trial (Table 3), would be consistent with the exposure of dabrafenib gelatin capsule administered at 75 mg orally twice daily, a dose range which demonstrated anti-tumor activity in trial BRF112680.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The ORRs observed with dabrafenib treatment are high (≥ 50%) in patients with BRAF V600E mutation-positive unresectable or metastatic melanoma but the majority of the responses are not sustained—i.e., median duration of an objective response is approximately 5-6 months (see Section 6.1.5 and Section 6.1.10).

The Phase 2 and 3 development program of dabrafenib for treatment of patients with BRAF V600 mutation-positive metastatic melanoma included a plan to analyze biomarkers related to the activity of dabrafenib. Consenting patients had an optional tumor biopsy performed at baseline before receiving dabrafenib as well as at the end of study (e.g., time of disease progression, death, or unacceptable AE). The Applicant intends to evaluate these samples for various biomarkers—such as BRAF, MEK1/2, PTEN, and mutations in other genes—and states that it will submit the results of its analyses in separate reports upon conclusion of the trials.

REVIEWER COMMENT:
Although not fully characterized, several mechanisms of resistance of melanoma to BRAF inhibitors have been described in the literature, including: (1) intrinsic resistance factors such as Cyclin D1 amplification, PTEN loss, and hepatocyte growth factor product; (2) acquired resistance factors leading to ERK activation such as receptor tyrosine kinase upregulation, NRAS mutations, splice variants of mutant BRAF, secondary mutations in MEK, and acquired resistance mutations; and (3), acquired resistance factors leading to activation of non-ERK pathways such as the PI3K pathway through platelet derived growth factor receptor beta or insulin-like growth factor 1 receptor (Reviewed by Sullivan and Flaherty 2013).

6.1.10 Additional Efficacy Issues/Analyses

Single Adequate and Well-Controlled Trial for Effectiveness Claim

The FDA Guidance for Industry "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" identifies the following characteristics of a single adequate and well-controlled trial that could make the study adequate support for an effectiveness claim:

- Large, multicenter study
- Consistency across study subsets
- Multiple studies in a single study

- Multiple endpoints involving different events
- Statistically very persuasive finding

This guidance further acknowledges one of the caveats for reliance on a single, multicenter study is that even a strong result from a single, internally consistent, strong multicenter study can represent "an isolated or biased result, especially if that study is the only study suggesting efficacy among similar studies."

The review of efficacy examined potential limitations of the BRF113683 trial as a single trial to support the efficacy of dabrafenib in the proposed indication.

First, the Applicant conducted an open-label trial using a primary endpoint based on tumor responses as assessed by the investigator, which may be subject to bias. As stated in the FDA Guidance for Industry, "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics", tumor response endpoints should be verified by central reviewers blinded to study treatments, especially important when the study itself is not blinded. Although not the primary efficacy analysis, the Applicant conducted pre-specified PFS analyses based on BICR assessments to investigate potential bias. These results, in addition to sensitivity analyses of investigator-assessed PFS, demonstrate treatment effects of dabrafenib consistent with those of the primary efficacy analysis. The Applicant also minimized the potential for bias by designing the trial as a large, multicenter trial which limited the individual contribution of any one study site in the overall primary efficacy analysis.

REVIEWER COMMENT:
FDA held an Oncologic Drugs Advisory Meeting on July 24, 2012, to discuss the evaluation of radiographic review in randomized trials using PFS as a primary endpoint. FDA presented its analysis of 28 trials which reported investigator- and BICR-assessed PFS results for nine primary tumor types; this analysis demonstrated a high degree of correlation, irrespective of investigator blinding, between investigator–assessed and BICR-assessed PFS treatment effects as measured by HR (Sridhara 2012).

Second, the Applicant designed the trial to evaluate multiple secondary endpoints, including objective response rate and OS. The SAP, however, did not include a plan to adjust the significance level for multiplicity based on testing of multiple secondary endpoints. Thus, comparative analyses of secondary endpoints are considered exploratory (see Dr. Yuan's Statistical Review for details). In addition to issues regarding multiplicity, results of the overall survival analysis, a key secondary endpoint of the BRF113683 trial, are unable to serve as supportive evidence of clinical benefit because the OS data are not mature. Nevertheless, the PFS treatment effect of dabrafenib is supported by the large magnitude of the confirmed ORR (≥ 50%) concurrent with moderate response durations in this disease. The large magnitude of ORR [59% (95% CI: 48%, 70%)] observed in the BRF113710 trial (n=92), a trial conducted in a previously treated BRAF V600E mutation-positive melanoma patient population, provides external validation of the anti-tumor activity of dabrafenib (see Table 19 below).

Third, the Applicant did not design the trial using multiple studies within the same trial, e.g., a three-arm trial evaluating different doses of dabrafenib compared to the DTIC arm. However, the primary efficacy analysis of PFS demonstrated a statistically very persuasive result (see Section 6.1.4) which reduces greatly the probability that a positive effect of dabrafenib on PFS, when compared to DTIC, is due to chance.

Effectiveness Claim Regardless of BRAF V600 Mutation Subtype

The review of efficacy also examined the limitations of the BRF113683 trial to support the Applicant's proposed indication which includes BRAF V600 mutation-positive disease regardless of BRAF V600 mutation subtype.

Melanoma harboring BRAF V600K mutations consists of a substantial proportion of patients with BRAF V600 mutation-positive melanoma, approximately 5-30% (Rubinstein, Sznol, et al. 2010). Within the population of BRAF V600 mutation-positive melanoma patients, the BRAF V600K mutation-positive subgroup appears to have distinct clinicopathologic features when compared to the BRAF V600E mutation-positive subgroup, such as site of primary melanoma (e.g., higher proportion arising on the head and neck region vs. extremity), higher association with chronic sun damaged skin, and older age at diagnosis of metastatic disease (Menzies, Haydu, et al. 2012). The Applicant used the clinical trial IUO assay, which distinguishes BRAF V600E and BRAF V600K mutations, to centrally screen patients for enrollment onto Applicant-sponsored clinical trials including BRF113710, BRF113929, and BRF113683.

Patients with BRAF V600K mutation-positive melanoma were not eligible for the BRF113683 trial. However, the Applicant conducted two open-label, multicenter, activity-estimating trials (BRF113710 and BRF113929) which enrolled patients with BRAF V600E or BRAF V600K mutation-positive metastatic melanoma. The eligibility criteria for these activity-estimating trials were similar to those required for enrollment in the BRF113683 trial with the following key exceptions:

- The BRF113710 trial inclusion criteria permitted enrollment of patients who received prior systemic chemotherapy for metastatic melanoma as well as patients with melanoma containing BRAF V600K mutations
- The BRF113929 trial inclusion criterion permitted enrollment of patients with asymptomatic brain metastases, either previously untreated (Cohort A) or previously treated (Cohort B), as well as patients with melanoma containing BRAF V600K mutations

<u>BRF113710 Trial</u>

The BRF113710 trial was a single-arm, open-label, multicenter trial conducted in 92 patients with histologically confirmed, BRAF V600E or V600K mutation-positive metastatic (Stage IV) melanoma. Patients received dabrafenib (gelatin capsule) 150 mg orally twice daily and continued treatment until disease progression, death, or unacceptable AEs. The primary analysis

was ORR in patients with BRAF V600E mutation-positive metastatic melanoma defined as the percentage of patients with a confirmed CR or PR by investigator assessment per RECIST version 1.1. A secondary endpoint was ORR in patients with V600K mutation-positive metastatic melanoma.

REVIEWER COMMENT:
In the original BRF113710 protocol, the primary efficacy population included patients with BRAF V600K and BRAF V600E mutation-positive melanoma. The Applicant amended the BRF113710 trial with Amendment 2 to limit the primary analysis population to patients with BRAF V600E mutation-positive melanoma; the Applicant modified the statistical design to include in the secondary endpoints analyses of anti-tumor activity in patients with BRAF V600K mutation-positive melanoma.

The median age of patients enrolled in the BRF113710 trial was 55.5 years (range 22 to 83). The majority of patients enrolled in the BRF113710 trial were male (53%) and Caucasian (99%). Eighty-four percent of patients received at least one prior therapy for metastatic disease. The study population consisted of 76 (83%) patients with BRAF V600E mutation-positive melanoma and 16 (17%) patients with BRAF V600K mutation-positive melanoma.

The investigator-assessed ORR was 59% (95% CI: 48%, 70%) in the BRAF V600E mutation-positive subgroup and 13% (95% CI: 0, 29%) in the BRAF V600K mutation-positive subgroup. Table 19 summarizes the confirmed ORRs of patients with BRAF V600 mutation-positive metastatic melanoma by BRAF V600 mutation subtype (V600 E or K).

Table 19: Investigator-Assessed, Confirmed Objective Response Rates by BRAF V600 Mutation Subtype. BRF113710 Trial.

	BRAF V600E+ N=76	**BRAF V600K+ N=16**
INVESTIGATOR		
ORR, n (%) 95% CI	45 (59) (48%, 70%)	2 (13) (0%, 29%)
CR, n (%)	5 (7)	0
PR, n (%)	40 (53)	2 (13)
Median DoR (95% CI), months	5.2 (4, NR)	5.3 (3.7, 6.8)
IRR		
ORR, n (%) 95% CI	31 (41) (30%, 52%)	4 (25) (4%, 46%)
CR, n (%)	2 (3)	0
PR, n (%)	29 (38)	4 (25)
Median DoR (95% CI), months	6.2 (5.1, NR)	5 (3.4, NR)

Source: BRF113710 CSR, Tables 13, 15, 16, 19, 20.

Abbreviations in Table: CI, confidence interval; DoR, Duration of Response; IRR, independent radiologic review; NR, not reached; ORR, objective response rate.

REVIEWER COMMENTS:

1. *The BRF113710 trial included relatively few patients with BRAF V600K mutation-positive melanoma. The two BRAF V600K mutation-positive patients who experienced an investigator-assessed confirmed objective response subsequently experienced disease progression, one patient after 16.1 weeks and the other after 29.6 weeks. Of the 45 BRAF V600E mutation-positive patients who experienced investigator-assessed confirmed objective responses, follow-up was ongoing for 24 (53%) patients and these patients were censored in the duration of response analysis.*
2. *Differential anti-tumor activity of dabrafenib in BRAF V600E and BRAF V600K mutation subtypes would not be predicted based on the demonstration of similar inhibitory concentrations (IC50) of dabrafenib in these BRAF V600 mutation subtypes (see 4.4.1 Mechanism of Action). BRAF V600 mutation-positive melanoma potentially consists of clinically relevant subpopulations based on BRAF V600 mutation subtype. Patients with BRAF V600K mutation-positive melanoma possess distinct clinicopathologic characteristics when compared to those with BRAF V600E mutations as discussed earlier in Section 6.1.10. In analyses of demographic data for the BRF113710 and BRF113929 trials by BRAF V600 mutation subgroups, patients with BRAF V600K mutation-positive melanoma were older and a higher percentage were men compared to those with BRAF V600E mutation-positive melanoma (see Dr. Grimstein's Genomics Group Review, Section 4.2 of the FDA Review of Clinical Pharmacology). As patients with melanoma harboring these two BRAF V600 mutation subtypes appear to have distinct clinicopathologic features, it is possible that the apparent disparity in clinical anti-tumor activity of dabrafenib between patients with melanoma and BRAF V600E mutations and those with BRAF V600K mutations may exist based on factors intrinsic to the tumor microenvironment or to resistance mechanisms within melanoma harboring a BRAF V600K mutation. Similarly, tumor cell lines harboring the same BRAF V600 mutation subtype, BRAF V600E, but arising from different primary sites (i.e., melanoma and colon cancer) demonstrate intrinsic differences in tumor resistance resulting from feedback activation of EGFR following BRAF inhibitor treatment, an in vitro finding which may shed light on the marginal anti-tumor activity of BRAF inhibitor therapy in patients with BRAF V600E mutation-positive metastatic colorectal cancer (Kopetz, Desai, et al. 2010; Prahallad, Sun, et al. 2012).*

BRF113929 Trial

The BRF113929 trial was a two-arm, open-label, multicenter, non-randomized trial conducted in 172 patients with histologically confirmed, BRAF V600 (V600E or V600K) mutation-positive melanoma with metastases to the brain. Patients received dabrafenib (HPMC capsules) 150 mg orally twice daily and continued treatment until disease progression, death, or unacceptable AEs. Patients enrolled into Cohort A must not have received prior local therapy for brain metastases; those enrolled into Cohort B must have had prior local therapy for brain metastases which may have included surgical resection, whole-brain radiotherapy (WBRT) or stereotactic radiosurgery. In both Cohorts, progression of brain metastases was not an eligibility requirement unless located

at the site of prior local therapy. In addition, patients were eligible if immediate local therapy was clinically not indicated or if not a suitable candidate to receive immediate local therapy.

Additional key inclusion criteria included the following: (1) up to two previous systemic treatment regimens for extracranial metastatic melanoma; (2) at least one measurable intracranial target lesion from ≥5 mm up to 4 cm in diameter, (3) ECOG PS of 0-1; (4) stable or decreasing dose of corticosteroids for ≥ 3 weeks (Cohort A) or ≥ 2 weeks (Cohort B) prior to first dose of dabrafenib; and (5) no prophylactic or preventive anti-epileptic therapy (Cohort A only).

Key exclusion criteria included the following: (1) neurological symptoms related to brain metastasis, (2) previous treatment with a BRAF or MEK inhibitor, and (3) presence of leptomeningeal disease or primary dural metastases.

The primary analysis was overall intracranial response rate (OIRR) as assessed by the investigator in each of the two cohorts of patients with BRAF V600E mutation-positive metastatic melanoma. The protocol defined OIRR as the percentage of patients who had a confirmed best intracranial response of CR or PR as assessed by the investigator per RECIST version 1.1. Secondary endpoints included OIRR in patients with V600K mutation-positive metastatic melanoma as well as ORR in patients with BRAF V600E or V600K mutation-positive melanoma.

REVIEWER COMMENT:
In the original protocol for the BRF113929 trial, the primary analysis population in each cohort included patients with BRAF V600K and BRAF V600E mutation-positive melanoma. Based on preliminary evidence from the BRF112680 trial, which according to the Applicant showed that patients with V600E mutation-positive melanoma respond at a higher rate than those with the V600K mutation subtype, the Applicant amended the BRF113929 trial with Amendment 2 to limit the primary analysis population to patients with BRAF V600E mutation-positive melanoma and to increase the sample size of the trial to accrue 60 patients per cohort with the BRAF V600E mutation subtype. The Applicant modified the statistical design to include the anti-tumor activity analyses of patients with BRAF V600K mutation-positive melanoma in the secondary endpoints.

In total, the BRF113929 trial enrolled 172 patients: 83 patients without prior local treatment to brain metastases (Cohort A) and 89 patients with prior local treatment to brain metastases (Cohort B). Cohort A consisted of 74 (83%) patients with BRAF V600E mutation-positive melanoma and 15 (17%) patients with BRAF V600K mutation-positive melanoma. Cohort B consisted of 65 (78%) patients with BRAF V600E mutation-positive melanoma and 18 (22%) patients with BRAF V600K mutation-positive melanoma. The median age of patients enrolled in the BRF113929 trial by mutation type was 51 years (range 19 to 76) in patients with BRAF V600E mutations and 62 years (range 31-87) in patients with BRAF V600K mutations. The majority of patients enrolled in the BRF113929 trial were male (70% overall; 68% in BRAF V600E subgroup and 79% in BRAF V600K subgroup) and Caucasian (99%). Sixty-two percent of patients with BRAF V600E mutation-positive melanoma and 39% of patients with BRAF V600K mutation-positive melanoma were ECOG PS of 0. Twenty-nine percent of patients in

Cohort A and 48% of patients in Cohort B received at least one prior systemic therapy for advanced or metastatic disease. The number of intracranial target lesions present at baseline was 1 or 2 in most patients, 71% of the BRAF V600E subgroup and 66% of the BRAF V600K subgroup. Overall, 89% of patients had measurable extra-cranial disease at baseline. In addition, approximately 17% of patients enrolled in Cohort A and 42% of patients enrolled in Cohort B were receiving dexamethasone at baseline.

Table 20 summarizes the confirmed OIRR and ORR of patients with BRAF V600 mutation-positive metastatic melanoma by BRAF V600 mutation subtype (V600 E or K) and prior local treatment for intra-cranial metastases (Cohort A or B).

Table 20: Investigator- and Independent Radiologist-Assessed Confirmed Overall Intracranial Response Rates and Confirmed Objective Response Rates By BRAF V600 Mutation Subtype. BRF113929 Trial.

	BRAF V600E+		**BRAF V600K+**	
	COHORT A[2] N=74	**COHORT B[3] N=65**	**COHORT A[2] N=15**	**COHORT B[3] N=18**
OIRR				
Investigator				
CR+PR, n (%)	29 (39)	20 (31)	1 (7)	4 (22)
95% CI	28.0%, 51.2%	19.9%, 43.4%	0.2%, 31.9%	6.4%, 47.6%
CR, n (%)	2 (3)	0	0	0
DoR (95% CI)[1]	4.7 (2.8, NR)	6.5 (4.7, 6.5)	2.9 (NR, NR)	3.8 (NR, NR)
Independent radiologist				
CR+PR, n (%)	15 (20)	12 (18)	0	2 (11)
95% CI	11.8%, 31.2%	9.9%, 30.0%	0, 21.8%	1.4%, 34.7%
CR, n (%)	1 (1)	0	0	0
DoR (95% CI)[1]	4.7 (4.5, 6.5)	4.7 (4.2, 4.7)	-	NR (NR, NR)
ORR				
Investigator				
CR+PR, n (%)	28 (38)	30 (31)	0	5 (28)
95% CI	26.8%, 49.9%	19.9%, 43.4%	0, 21.8%	9.7%, 53.5%
CR, n (%)	0	0	0	0
DoR (95% CI)[1]	5.1 (3.7, NR)	4.7 (4.6, 6.5)	-	3.1 (2.8, NR)
Independent Radiologist				
CR+PR, n (%)	21 (28)	15 (23)	0	2 (11)
95% CI	18.5%, 40.1%	13.5%, 35.2%	0, 21.8%	1.4%, 34.7%
CR, n (%)	0	0	0	0
DoR (95% CI)[1]	4.7 (4.3, NR)	4.7 (2.8, NR)	-	NR (NR, NR)

Source: BRF113929 CSR
Abbreviations in Table: CR, complete response; DoR, duration of response; NR, not reached; OIRR, overall intracranial response rate; ORR, objective response rate; PR, partial response.
[1] months
[2] Cohort A, no prior local therapy for brain metastasis
[3] Cohort B, prior local therapy for brain metastasis

REVIEWER COMMENTS:

1. *There was substantial discordance between the investigator and independent radiologist in regard to the number of confirmed intracranial responses (CR and PR) in both Cohorts—the investigator-assessed OIRR was nearly twice the OIRR based on blinded independent radiologist assessment. The Applicant conducted a post-hoc third-party adjudication of all discordant cases—reasons for this discordance included the following:*
    - *selection of different lesions as target lesions*
    - *necrosis or hemorrhage of the lesions following treatment which limited reproducibility of lesion measurements*
    - *identification of new lesions due to variability in the image acquisition technique and the large number of MRI series, and borderline response and progression*
    - *borderline response and progression*

    In 68% of discordant cases, the third party adjudicator selected the investigator's response assessment.
2. *Neither the BRF113710 trial nor the BRF113929 trial meet the definition of an adequate and well-controlled trial as described in 21 CFR 314.126 to serve as substantial evidence for the purpose of effectiveness claims. Inasmuch as these two activity-estimating trials do not demonstrate tumor response rates of similar magnitude between patients with BRAF V600E and those with BRAF V600K mutation-positive melanoma, and as there is no information in regard to the activity (or efficacy) of dabrafenib in patients with BRAF V600K mutation-positive melanoma from randomized controlled trials based on exclusion of these patients from enrolling in the BRF113683 trial, this reviewer recommends that the dabrafenib label specify the BRAF V600 mutation subtype in the indication, i.e., treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test (see Section 1.1). Similarly, from a regulatory perspective, the Applicant's proposed inclusion of OIRR results from the BRF113929 trial in the Clinical Studies section of the label constitutes a de facto efficacy claim; therefore, under 21 CFR 201.57, indications or uses must not be implied or suggested in Sections of the label if not included in the Indications and Usage Section. Moreover, all indications listed in the indications and Usage Section of labeling must be supported by substantial evidence of effectiveness based on adequate and well-controlled trials.*
3. *The results of the BRF113929 trial with dabrafenib monotherapy in patients with BRAF V600E mutation-positive melanoma and asymptomatic brain metastases suggests an encouraging albeit imprecise degree of anti-tumor activity in melanoma metastases involving the brain. The role of dabrafenib and its clinical benefit in this important subpopulation of melanoma patients requires further evaluation. Consistent with the indications of other FDA-approved products for treatment of metastatic melanoma, the proposed indication for dabrafenib does not preclude its use in patients with brain metastases.*

7 Review of Safety

Safety Summary

The review of safety primarily focused on analyses of data submitted for the BRF113683 trial because it is the only randomized, comparative trial submitted by the Applicant to support the safety of dabrafenib and it administered the to-be-marketed formulation of dabrafenib (HPMC formulation) whereas the Phase 1 trials (BRF112680 and BRF113220) and Phase 2 trial (BRF113710)— trials conducted in patients with advanced melanoma without active brain metastases (similar to the study population enrolled in trial BRF113683)—administered the gelatin capsule formulation, a formulation of dabrafenib which demonstrated lower bioavailability and decreased exposure following single dose administration compared to the HPMC formulation. The geometric LS ratio (90% CI) of dabrafenib HPMC formulation compared to gelatin capsule formulation was 2.02 (1.42, 2.87) for C_{max} and 1.80 (1.32, 2.46) for $AUC_{(0-\infty)}$. The Applicant states that the difference between HPMC and gelatin formulation is smaller after repeat dosing (see the FDA Clinical Pharmacology NDA review for details). The size of the integrated safety database and duration of dabrafenib exposure were sufficient to characterize the safety of dabrafenib for treatment of a serious and life-threatening condition.

The BRF113683 trial was an open-label, multicenter, international, randomized (3:1) controlled trial of 250 patients with previously untreated, advanced (unresectable Stage III) or metastatic (Stage IV) BRAF V600E mutation-positive melanoma. Patients were allocated to receive dabrafenib 150 mg orally twice daily (n=187) or DTIC 1000 mg/m^2 IV every 3 weeks (n=63) until disease progression or intolerable toxicity. The median duration on treatment was 4.9 months in the dabrafenib treatment group (n=187 patients) and 2.8 months in the DTIC treatment group (n=59 patients). The mean daily dose intensity for dabrafenib was 95% and the mean relative weekly dose intensity (mg/m^2/week) for DTIC was 93%. Eighteen percent of dabrafenib-treated patients required at least one dose reduction and 3% required treatment withdrawal for AEs.

Overall, the most frequent (≥20%) AEs with dabrafenib were hyperglycemia on laboratory testing (50% of dabrafenib-treated patients vs. 42% of DTIC-treated patients), hyperkeratosis (37% vs. 0), hypophosphatemia on laboratory testing (35% vs. 14%), headache (32% vs. 8%), pyrexia (28% vs. 10%), arthralgia (27% vs. 2%), papilloma (27% vs. 2%), alopecia (22% vs. 2), and palmar-plantar erythrodysesthesia syndrome (20% vs. 2%).

Serious adverse events occurred in 23% of dabrafenib-treated patients and in 22% of DTIC-treated patients. The most significant SAEs experienced by dabrafenib-treated patients were new primary malignancies, including cutaneous squamous cell carcinoma/keratoacanthoma and new primary melanomas, as well as serious febrile drug reactions, defined as fever complicated by hypotension, dehydration, severe rigors/chills, or renal failure in the absence of another identifiable etiology (e.g., infection).

The rate of treatment withdrawals, dose reductions, and dose interruptions was similar between treatment groups. Approximately 3% of dabrafenib-treated patients experienced AEs leading to treatment withdrawal. Dose reductions for AEs occurred in 18% of dabrafenib treated patients, most frequently for pyrexia (9% in the dabrafenib treatment group vs. 0 in the DTIC treatment group), palmar-plantar erythrodysesthesia syndrome (3% vs. 0), chills (3% vs. 0), fatigue (2% vs. 0), and headache (2% vs. 0). Adverse events led to withholding treatment without requirement for dose reduction in 16% of dabrafenib-treated patients, most commonly for pyrexia (6% vs. 0). Grade 3 or 4 AEs occurred in 33% of dabrafenib-treated patients—the most frequent were pyrexia (3%), squamous cell carcinoma (3%), and back pain (3%).

The reviewer does not recommend a REMS based on the information provided in the submission but does recommend a Medication Guide primarily based on the risk of cutaneous squamous cell carcinoma and the potential risk of other new primary malignancies.

7.1 Methods

Analyses in the review of safety of the integrated summary of safety (ISS) database were based on the data cutoff dates for the 120-Day safety update. The ISS database comprises safety data from the following trials:

- BRF113683 (n=187 patients in randomized phase and 35 additional patients who crossed over from DTIC)
- BRF113710 (n=92 patients)
- BRF113929 (172 patients)
- BRF113220 (Part C, dabrafenib monotherapy arm; n=53 patients)
- BRF112680 (n= 47 patients)

The review of safety primarily focused on the BRF113683 trial data based on the following:

- The BRF113683 trial is the only randomized, comparative trial submitted by the Applicant to support the safety of dabrafenib
- The BRF113683 trial used the to-be-marketed formulation of dabrafenib (HPMC) whereas the Phase 1 trials (BRF112680 and BRF113220) and Phase 2 trial (BRF113710)—all trials conducted in patients without active brain metastases similar to trial BRF113683—administered the gelatin capsule formulation which demonstrated decreased exposure compared to the HPMC formulation
- The BRF113929 trial, which used the HPMC formulation of dabrafenib, was conducted entirely in patients with previously untreated or recurrent brain metastases, a population with supportive care requirements and background rate of AEs due to disease sequelae which may confound an analysis of the adverse reaction profile in the absence of a comparator arm

In the BRF113683 trial, safety assessments at the baseline/screening visit included documentation of medical history including concomitant medications, oncologic history

including prior therapy; organs involved with metastatic disease; physical examination; vital signs assessment; blood sampling for laboratory safety variables; blood sample collection for cardiac troponin I; documentation of an ECOG PS; ECG testing; echocardiogram testing; radiologic examination including an MRI of the brain; dermatologic skin assessment examination (performed by the investigator or may be referred to a dermatologist at the discretion of the Investigator); serum pregnancy testing (if applicable); and documentation of AEs. On-treatment safety assessments performed on Day 1 of each Cycle included documentation of concomitant medications, brief physical examination, vital signs assessments, ECOG PS, blood sampling for laboratory safety variables (hematology and clinical chemistry); on Week 3 (ECG only), 6, 12, and every 9 weeks thereafter included echocardiogram and ECG; and on Weeks 3, 6, and every 9 weeks thereafter included dermatologic skin assessment examinations. Follow-up post-treatment discontinuation included collection of AEs until 28 days post-treatment discontinuation (regardless of initiation of a new cancer therapy or transfer to hospice).

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The Applicant submitted five trials as listed in Table 8 to evaluate the safety of dabrafenib for treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation-positive disease. Safety analyses of the BRF113683 trial used the data cutoff date of December 19, 2011. The review of safety also included an evaluation of major safety findings (e.g., deaths, SAEs) and AEs of interest using pooled data (n=586) from the five trials based on the data cutoff date used in the 120-day safety cutoff date, i.e., June 25, 2012 (BRF113683, BRF113929, BRF113710), May 31, 2013 (BRF113220), and March 19, 2012 (BRF112680). The review of safety did not include extensive analyses of pooled data to evaluate the severity of specific AEs because the trials used different versions of the NCI CTCAE and different formulations of dabrafenib.

7.1.2 Categorization of Adverse Events

The Applicant mapped and coded verbatim AE terms for the BRF113683 trial using MedDRA version 14.1.The Applicant graded the severity of AE toxicities encountered on trial BRF113683 using NCI CTCAE version 4.

REVIEWER COMMENT:
The review of safety assessed the adequacy of the Applicant's mapping of AE verbatim terms to MedDRA preferred terms (PT) for 100% of the BRF113683 raw AE dataset. Of the 2,436 AE line listings in the RAE.xpt dataset (BRF116383 trial), the review used programmatic matching of identical verbatim and MedDRA PTs (n=637 line listings) as well as manual evaluation of the remaining verbatim terms (n=1799 line listings) to assess the acceptability of the Applicant's mapping from the verbatim term to MedDRA PT. The MedDRA PTs listed in the datasets adequately represented the investigator recorded term (i.e., verbatim term) with minor differences that did not alter the reliability and interpretation of the safety data.

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

The integrated safety database included AE data from five trials (see Section 7.1.1 and Table 8). The Applicant's integrated summary of safety presented the most common (≥10% of patients) treatment-emergent adverse events (TEAE) reported in dabrafenib-treated patients in the BRF113683 trial as well as in the entire ISS database. Hyperkeratosis, palmar-plantar erythrodysesthesia syndrome, and asthenia occurred at a higher incidence (≥5%) in the BRF113683 trial than in the ISS database. Fatigue, nausea, vomiting, diarrhea, extremity pain, and decreased appetite occurred at a higher incidence (≥5% difference) in the ISS database than in the BRF113683 trial. This analysis is presented in the Table 21 below.

Table 21: Incidence of Treatment-Emergent Adverse Events (>10%) by Toxicity Grade in Dabrafenib-Treated Patients. BRF113683 Trial and ISS Database.

	Number (%) of Subjects					
	Dabrafenib (BRF113683 Trial) (N=187)			Dabrafenib (ISS Database) (N=586)		
	Any Grade[1]	Grade 3	Grade 4	Any Grade[2]	Grade 3	Grade 4
ANY EVENT	185 (99)	55 (29)	7 (4)	566 (97)	220 (38)	30 (5)
Hyperkeratosis	69 (37)	1 (1)	1 (1)	188 (32)	3 (1)	1 (<1)
Headache	59 (32)	0	0	177 (30)	8 (1)	0
Pyrexia	52 (28)	6 (3)	0	176 (30)	11 (2)	0
Arthralgia	51 (27)	2 (1)	0	172 (29)	6 (1)	0
Papilloma[3]	51 (27)	0	0	130 (22)	0	0
Alopecia	41 (22)	0	0	136 (23)	1 (<1)	0
PPES	37 (20)	4 (2)	0	81 (14)	8 (1)	0
Fatigue	36 (19)	2 (1)	0	151 (26)	8 (1)	0
Nausea	35 (19)	0	1 (1)	149 (25)	5 (1)	1 (<1)
Asthenia	33 (18)	1 (1)	0	66 (11)	1 (<1)	0
Rash	31 (17)	0	0	115 (20)	0	0
Vomiting	23 (12)	1 (1)	1 (1)	107 (18)	6 (1)	1 (<1)
Cough	23 (12)	0	0	78 (13)	0	0
Back pain	22 (12)	5 (3)	0	65 (11)	8 (1)	0
Constipation	21 (11)	2 (1)	1 (1)	61 (10)	2 (<1)	1 (<1)
Diarrhea	20 (11)	1 (1)	0	91 (16)	3 (1)	0
Myalgia	20 (11)	0	0	86 (15)	1 (<1)	0
Nasopharyngitis	19 (10)	0	0	54 (9)	0	0
Chills	17 (9)	0	0	77 (13)	1 (<1)	0
Pain in extremity	16 (9)	1 (1)	0	92 (16)	2 (<1)	0
Decreased appetite	16 (9)	0	0	82 (14)	5 (1)	0

Source: RAE.xpt (BRF113683), Module 5.3.5.3.28, integrated summary of safety (ISS), Tables 8 & 9
Abbreviations in Table: PPES, palmar-plantar erythrodysesthesia syndrome
[1] NCI CTCAE version 4
[2] NCI CTCAE version 3 (BRF112680 trial) and version 4 (BRF113683, BRF113710, BRF113929, BRF113220)
[3] Composite term for skin papilloma, papilloma, and blepharal papilloma.

REVIEWER COMMENT: An analysis of only those studies which used NCI CTCAE version 4 to grade toxicity severity demonstrated similar AE incidences of all grade as well as Grade 3-4

toxicities. Overall, the incidences of the most common TEAEs occurring on the primary trial, BRF113683, were similar to the incidences of TEAEs in the integrated safety database with the exception of the TEAEs previously noted.

7.2 Adequacy of Safety Assessments

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

In the BRF113683 trial, 187 patients received treatment with dabrafenib and 59 patients received treatment with DTIC in the randomized phase. Patients treated with dabrafenib remained on treatment longer than patients treated with DTIC (median of 4.9 vs. 2.8 months). The mean and median daily dose intensity for dabrafenib was 284.9/300 mg (95%) and 300/300 mg respectively. The mean and median relative weekly dose intensity (mg/m^2/week) for DTIC was 311.6 (93%) and 332, respectively. Table 22 summarizes the exposure to investigational product for each treatment group in the BRF113683 trial.

Table 22: Summary of Exposure to Dabrafenib and DTIC. Safety Population. BRF113683 Trial.

		Randomized Phase	
		Dabrafenib (N=187)	**DTIC (N=59)**
Average GSK2118436 daily dose (mg)	**n**	**187**	**N/A**
	Mean	284.9	N/A
	sd	33.54	N/A
	Median	300.0	N/A
	Min.	118.0	N/A
	Max.	300.0	N/A
DTIC dose intensity (mg/m2/week)	**n**	**N/A**	**59**
	Mean	N/A	311.6
	sd	N/A	34.23
	Median	N/A	332.0
	Min.	N/A	204.0
	Max.	N/A	350.0
Time on study treatment (months)	**n**	**187**	**59**
	Mean	5.0	3.2
	sd	1.86	2.12
	Median	4.9	2.8
	Min	0.1	0.7
	Max.	10.3	9.9
Number of Subjects (%)	<3 months	33 (18)	32 (54)
	3-6 months	105 (56)	21 (36)
	>6-12 months	49 (26)	6 (10)

Source: BRF113683 CSR, Table 28
Abbreviations in Table: Min, minimum; max, maximum; n/a, Not applicable; sd, standard deviation.

Table 23 summarizes the number of dabrafenib-treated patients requiring at least one, two, or three dose reductions.

Table 23: Incidence of Dose Reductions by Treatment Group. Safety Population. BRF113683 Trial.

	Dabrafenib (N=187) n (%)	DTIC (N=59) n (%)
Subjects with Any Dose Reductions	52 (28)	10 (17)
Total number of dose reductions, n	123	12
Number of dose reductions		
0	135 (72)	49 (83)
1	24 (13)	8 (14)
2	16 (9)	2 (3)
3 or more	12 (6)	0
Reasons for reduction[1,2]		
n	123	12
Adverse event	47 (38)	11 (92)
Subject non-compliance	67 (54)	0
Other	9 (7)	1 (8)

Source: Verified with REXPOSUR.xpt
[1] A patient may be counted multiple times in the same 'reason' row if the patient had multiple reductions/escalations/interruptions/delays for the same reason.
[2] Expressed as a % of number of reductions/escalations or interruptions/delays

REVIEWER COMMENT: The incidence of dose reductions in Table 23 above in the dabrafenib treatment group is misleading because data entry system specifications required investigators to record any missed doses as dose reductions. See Table 38 for dose reductions due to AEs.

The mean daily dabrafenib dose was similar between the crossover dabrafenib treatment group (n=28 patients) and the dabrafenib randomized treatment group (292.6 vs. 284.9 mg), but the median duration of dabrafenib exposure was shorter in the crossover dabrafenib treatment group (2.8 vs. 4.9 months) at the time of data cutoff.

Within the ISS database, a total of 586 patients received a median daily dose of dabrafenib of 299.17 mg with a median time on study treatment of 5.47 months (minimum 0.07 months, maximum 22.6 months). One hundred eighty-one patients (31%) were on study treatment between 6 and 12 months and 86 patients (15%) were on study treatment for more than 12 months.

7.2.2 Explorations for Dose Response

The dabrafenib development program did not include dose-response trials. See Section 7.5.1 for explorations of exposure-response relationships for AEs.

7.2.3 Special Animal and/or In Vitro Testing

See the summary of the pharmacology/toxicology review in Section 4.3**.**

7.2.4 Routine Clinical Testing

Please refer to sections 7.4.2-7.4.4.

7.2.5 Metabolic, Clearance, and Interaction Workup

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

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

The Applicant initiated the BRF113683 trial on February 2, 2011, six months prior to FDA approval of vemurafenib (August 17, 2011). A prominent drug toxicity of the BRAF inhibitor class is the development of cutaneous squamous cell carcinoma. The safety monitoring plan to mitigate the risk of cutaneous squamous cell carcinoma was similar in the BRF113683 trial (dabrafenib) to that specified in the primary trial supporting FDA approval of vemurafenib.

7.3 Major Safety Results

7.3.1 Deaths

Individual deaths will not be listed in a table because OS was an effectiveness outcome for the primary trial, BRF113683.

Table 24 summarizes the primary causes of death reported as recorded by investigators on the BRF113683 trial eCRFs. Overall, 21 patients randomized to the dabrafenib arm (11%) and 9 patients (11%) randomized to the DTIC arm (4 patients after initial progression on DTIC and crossover to treatment with dabrafenib) died at the time of the clinical data cutoff. Disease under study was the most commonly reported primary cause of death and accounted for all but one death in the dabrafenib treatment group and all deaths in the DTIC treatment group. Overall, treatment-emergent deaths (within 30 days of investigational product dosing) occurred in 4% of the patients in the dabrafenib treatment group and 7% of the patients in the DTIC treatment group.

Table 24: Survival Follow-up Status and Primary Causes of Death by Treatment Group. Safety Population. BRF113683 Trial.

	Dabrafenib (N=187) n (%)	DTIC N=59 n (%)
Subject status		
Dead	21 (11)	9 (15)
Alive at last contact, follow-up ended	5 (3)	2 (3)
Alive at last contact, follow-up ongoing	161 (86)	48 (81)
Primary cause of death		
Disease under study	20 (11)	9 (15)
Other	1 (1)	0
Unknown	0	0
SAE possibly related to study treatment	0	0
Time to death from last dose		
Within 30 days	9 (5)	1 (2)

Source: BRF113683 CSR, Table 8.2012

REVIEWER COMMENT: In a 100% audit of the raw dataset (RDEATH.xpt) and corresponding CRF of deaths for the BRF113683 trial, there was one patient with a discrepancy between the reported cause of death on the CRF and the value listed for the cause of death in the variable "DTHCSCD" in the raw dataset. The CRF recorded the primary cause of death for patient BRF113683.0007350 as "Other, specify" which was specified as an SAE unrelated to study medication. The line listing in the RDEATH.xpt dataset identified the reported cause of death for this patient as "disease under study." The details in regard to the death of patient BRF113683.0007350 was further reviewed in the analysis of Grade 5 (fatal) AEs below. This discrepancy is the result of different data cutoff dates used by the Applicant for information captured in the dataset and for information submitted in the CRF pdf documents (see Section 3.1).

Two patients in the BRF113683 trial experienced a Grade 5 AE—one patient randomized to the dabrafenib arm and another randomized to the DTIC arm who crossed over to receive dabrafenib—both occurring within 28 days of the last dose of dabrafenib.

- Patient BRF113683.0000054, a 42-year-old man with Stage IV (M1c) melanoma with metastases involving the left chest wall and lung, a history of prior radiotherapy to a solitary brain metastasis, and no other significant past medical history (PMH) or concomitant medication history, died from euthanasia. Euthanasia occurred on Study Day 36, 22 days after his last dose of dabrafenib.
- Patient BRF113683.0007350, a 50-year-old woman with metastasis stage M1c melanoma and PMH significant for asthma, tobacco use, and sinus bradycardia, experienced progression of disease, initially with DTIC treatment (administered on Days 1-23) and then with dabrafenib treatment (administered Days 23-78), followed by Grade 5 hypoxemic respiratory failure (Study Day 86). The event occurred while the patient was in hospice care following a hospital admission (Study Day 84) for septic shock

complicated by an aspiration event. The investigators attributed none of the SAEs experienced by this patient, including Grade 5 hypoxemic respiratory failure, to DTIC or dabrafenib.

Of the 274/586 (47%) deaths listed in the ISS database, the most frequent cause of death was disease under study [266/274 ((97%)]. Eighty-seven of the 274 deaths (32%) occurred within 30 days of the last dabrafenib dose. Eight patients in the ISS database experienced a Grade 5 SAE (Table 25).

Table 25: All Grade 5 Adverse Events. Dabrafenib-Treated Patients. ISS Database.

Patient ID	Age / Sex	Grade 5 Adverse Event	Last dose (Day)	Onset AE (Day)	Death (Day)	Investigator Reported Primary Cause of Death
BRF113683.d007350	50/F	Hypoxemic respiratory failure	54	64	64	Other, specify: SAE unrelated to study medication
BRF113683.0000054	42/M	Euthanasia	15	36	36	Other, specify: Euthanasia
BRF113683.0000667	77/M	Myocardial infarction Acute coronary syndrome	166	149 165	172	Disease under study
BRF113929.0000808	56/F	Intracranial hemorrhage	5	5	10	Disease under study
BRF113929.0001058	65/F	Cerebral hemorrhage	97	97	103	Disease under study
BRF113929.0000610	32/F	Cerebral hemorrhage	48	47	49	Disease under study
BRF113929.0000553	71/M	Acute renal failure; Pulmonary embolism; Urinary tract infection; Cardiac arrest	292	305 305 305 309	309	Disease under study
BRF113929.0000011	39/M	Metastases to meninges	226	220	240	Disease under study

Source: AE.xpt
Abbreviations in Table: AE, adverse event; F, female; M, male

The investigators reported that the Grade 5 AEs were unrelated to the study drug with the exception of myocardial infarction and acute coronary syndrome, both AEs experienced by Patient BRF113683.0000667; in this case, the investigator reported the primary cause of death for this patient as disease under study. The following are descriptions of the six additional cases of Grade 5 AEs reported in the 120-Day safety update:

- Patient BRF113683.0000667, a 77-year-old man with metastatic melanoma with a PMH significant for hyperlipidemia, hypertension, and syncope, was diagnosed with new left ventricular hypokinesis on Study Day 148. Further work-up revealed calcification of the left coronary artery on a coronary CT scan. On Day 164, the patient developed an ST elevation myocardial infarction with cardiac insufficiency. Following readmission on Day 171 for syncope and coronary stent obstruction, the patient expired on Day 172.
- Patient BRF113929.0000808, a 56-year-old woman with melanoma with metastases involving the brain status post gamma-knife radiosurgery—treatment she received two months prior to starting the investigational product—and a PMH significant for hypertension, hyperlipidemia, and pulmonary embolism (PE), developed an intracranial

hemorrhage 5 days after the first dose of dabrafenib. Of note, the intracranial hemorrhage occurred six days after enoxaparin was initiated for treatment of PE. The patient died of the intracranial hemorrhage as well as disease progression on Study Day 10.

- Patient BRF113929.0000610, a 32-year-old woman with melanoma with metastases involving the brain and no other significant PMH, developed a cerebral hemorrhage on Day 47. The investigator assessed this hemorrhage to be most likely due to a responding lesion in the brain, but the investigator also considered it possible that the event was due to progressive disease. Of note, the last tumor response assessment at Week 4 demonstrated a partial response of the brain lesions with a 33% decrease in the sum of the diameters.
- Patient BRF113929.001058, a 65-year-old woman with melanoma with metastases involving the brain and a PMH significant for hypertension, developed multiple supratentorial hemorrhages on Study Day 97 and died due to the disease under study on study Day 103. The patient's clinical course was significant for administration of cyberknife radiosurgery to metastatic lesions in the medial occipital lobe, right frontal lobe, and left frontal midline on Study Days 66 and 67, continued administration of dabrafenib in the context of radiographic disease progression in the brain, and initiation of corticosteroids for development of neurologic symptoms approximately two weeks prior to the SAE.
- Patient BRF113929.0000553, a 71-year-old man with melanoma with metastases involving the brain and a PMH significant for chronic renal failure, diabetes, hypertension, hyperlipidemia, and obesity, developed cardiac arrest and expired on Study Day 309 following discontinuation of study drug due to progression of disease on Study Day 293. Cardiac arrest occurred while hospitalized for evaluation of dyspnea and suspicion of pulmonary embolism as well as urinary tract infection complicated by acute on chronic renal failure.
- Patient BRF113929.0000011, a 39-year-old man with melanoma with metastases involving the brain, was hospitalized on Study Day 220 for confusion and diagnosed with carcinomatous meningitis on Study Day 225. He discontinued dabrafenib on Study Day 226, and expired on Study Day 240 from carcinomatous meningitis.

REVIEWER COMMENT: Five of the eight deaths occurred in the BRF113929 trial. In the absence of a control arm in this trial, it is uncertain whether cerebral hemorrhages are consistent with the background SAE event rates in the selected study population. The above limitations notwithstanding, review of the data provided for these eight Grade 5 AEs as individual cases suggest that these deaths were possibly related to underlying metastatic melanoma, including sequelae thereof, underlying comorbidities, or medical interventions which possibly contributed to the death as in the case of Patient BRF113929.0000808.

7.3.2 Nonfatal Serious Adverse Events

In the BRF113683 trial, non-fatal SAEs occurred in 23% (42/187) of patients in the dabrafenib treatment group and 22% (13/59) of DTIC-treated patients. The most frequently reported, non-

fatal SAEs in the dabrafenib treatment group compared to the DTIC treatment group were squamous cell carcinoma (4% vs. 0), pyrexia (4% vs. 0), squamous cell carcinoma of skin (2% vs. 0), and melanoma (2% vs. 0). Table 26 summarizes the non-fatal SAEs which occurred in the dabrafenib-treated patients.

Table 26: Incidence of Non-Fatal SAEs (≥1 in Dabrafenib-Treated Patient) by Treatment Group. Safety Population. BRF113683 Trial.

	Dabrafenib N=187 n (%)	DTIC N=59 n (%)
PATIENTS WITH AT LEAST ONE SAE	42 (23)	13 (22)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	12 (6)	0
Squamous cell carcinoma	7 (4)	0
Malignant melanoma	3 (2)	0
Squamous cell carcinoma of skin	3 (2)	0
Basal cell carcinoma	1 (1)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	8 (4)	1 (2)
Pyrexia	7 (4)	0
Chills	1 (1)	0
Influenza like illness	1 (1)	0
GASTROINTESTINAL DISORDERS	6 (3)	2 (3)
Vomiting	2 (1)	1 (2)
Constipation	1 (1)	1 (2)
Hemorrhoidal hemorrhage	1 (1)	0
Ileus	1 (1)	0
Nausea	1 (1)	1 (2)
Pancreatitis	1 (1)	0
Small intestinal perforation	1 (1)	0
METABOLISM AND NUTRITION DISORDERS	5 (3)	0
Dehydration	1 (1)	0
Diabetes mellitus	1 (1)	0
Diabetes mellitus inadequate control	1 (1)	0
Hyperlipasemia	1 (1)	0
Hyponatremia	1 (1)	0
Hypophosphatemia	1 (1)	0
CARDIAC DISORDERS	4 (2)	1 (2)
Atrial fibrillation	2 (1)	0
Cardiac failure congestive	1 (1)	0
Myocardial infarction	1 (1)	0
INFECTIONS AND INFESTATIONS	3 (2)	2 (3)
Erysipelas	1 (1)	0
Localized infection	1 (1)	0
Pleural infection	1 (1)	0
Sepsis	0	1 (2)
INVESTIGATIONS	3 (2)	1 (2)
Ejection fraction decreased	2 (1)	0
Blood creatinine increased	1 (1)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE	3 (2)	0

	Dabrafenib N=187 n (%)	DTIC N=59 n (%)
DISORDERS		
Back pain	1 (1)	0
Joint effusion	1 (1)	0
Muscular weakness	1 (1)	0
Pain in extremity	1 (1)	0
NERVOUS SYSTEM DISORDERS	3 (2)	1 (2)
Presyncope	1 (1)	0
Syncope	1 (1)	0
Transient ischemic attack	1 (1)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3 (2)	1 (2)
Hypoxia	1 (1)	0
Pleural effusion	1 (1)	0
Pleuritic pain	1 (1)	0
Pulmonary embolism	1 (1)	1 (2)
Pulmonary edema	1 (1)	0
Respiratory distress	1 (1)	0
VASCULAR DISORDERS	3 (2)	0
Hypotension	2 (1)	0
Hemorrhage	1 (1)	0

Source: RAE.xpt

REVIEWER COMMENT:
The 3:1 randomization scheme in a trial of this size minimizes the number of patients available for comparison of background event rates in the population under study. Thus, the review of safety included extensive manual evaluation of clinically important AEs, even if occurring as isolated cases, in order to identify safety signals of dabrafenib.

The review further analyzed the following SAEs:

- New primary malignancies
- Cardiac disorders
- Pyrexia
- Diabetes mellitus and hyperglycemia
- Hemorrhage
- Pancreatitis

New primary malignancies

New primary malignancies are a particular concern with BRAF inhibitors based on nonclinical and clinical evidence. Nonclinical studies of BRAF inhibitors demonstrated hyperproliferative lesions in animal models in vivo as well as paradoxical MAPK pathway activation in vitro with increased proliferation of cell lines containing wild-type BRAF with or without RAS mutations (Carnahan, Beltran, et al. 2010; Hatzivassiliou, Song, et al. 2010; Poulikakos, Zhang, et al.

2010). In addition, clinical data with vemurafenib demonstrated an increased incidence of new primary malignancies, i.e., cutaneous squamous cell carcinoma/keratoacanthoma developed in 24% of patients receiving vemurafenib (Zelboraf USPI). Cutaneous squamous cell carcinomas developing in patients receiving BRAF inhibitor therapy appear to have a distinct mutational profile and higher frequency of RAS mutations when compared to tumors arising in patients unexposed to BRAF inhibitors (Oberholzer, Kee, et al. 2012; Su, Viros, et al. 2012)

Cutaneous Squamous Cell Carcinoma (cuSCC)
Nine patients (5%) in the dabrafenib treatment group compared to no patients in the DTIC treatment group developed squamous cell carcinoma (composite of AE preferred terms squamous cell carcinoma and squamous cell carcinoma of the skin). The median time to onset was 12 weeks (range 3.3 to 21 weeks). There were no patients who required dose interruptions or dose reductions for cuSCC and the outcome of the event was "recovered/resolved" in all patients. An additional five dabrafenib-treated patients developed keratoacanthoma whereas no patients in the DTIC treatment group developed keratoacanthoma.

In an analysis of the composite term cuSCC (squamous cell carcinoma, squamous cell carcinoma of the skin, Bowen's disease, and keratoacanthoma) in the ISS database, 110 cases of cuSCC occurred in 64 patients (10.9%). The median time to onset of first occurrence was 9.4 weeks (range 1.3 to 52.9 weeks). Twenty-one of 64 patients (33%) experienced at least one recurrence of cuSCC. The median time between occurrences was 6 weeks (range 0.7 weeks to 24 weeks). Treatment continued unmodified in 108 cases, treatment was withheld in one case, and treatment modification was not applicable in one case. The outcome was "not recovered/not resolved" in seven patients, five with keratoacanthoma and two with squamous cell carcinoma.

REVIEWER COMMENTS:

1. *The Applicant stated that, for all 110 events of squamous cell carcinoma (including keratoacanthoma), the location and clinical presentation were consistent with a cutaneous origin.*
2. *In addition, of the seven patients reported to have ongoing cuSCC (including keratoacanthoma), three patients had excision and resolution of the events following the data cutoff date for the ISS database and four patients had discontinued the study resulting in no additional information available in regard to the status of cuSCC.*
3. *The Applicant did not systematically collect information in regard to high-risk features of cuSCC.*

New Primary Malignant Melanoma

New melanoma lesions occurred in three (2%) dabrafenib-treated patients compared to none of the DTIC-treated patients. All lesions resolved with excision; none required dose modifications or interruptions of dabrafenib.

In the ISS database, the incidence of new primary melanomas in dabrafenib-treated patients was 1% (6/586). The median time to onset was 12 weeks (range 5 to 46 weeks) and the investigators recorded all cases as resolved with excision. Of the six cases of new primary melanoma in the dabrafenib treatment group, the Applicant reported that the BRAF V600 mutation status was wild-type in three cases and unknown in the remaining cases. The safety update also reported one case of a new primary melanoma in a DTIC-treated patient (Patient BRF113683.0003957). This patient had a Grade 2 abdominal skin atypical hyperchromic lesion at baseline. Sixteen days after the first dose of DTIC, the patient had an excisional skin biopsy performed for a lesion on the right abdominal wall which demonstrated a Stage 1, non-ulcerated, superficial spreading melanoma.

Other Treatment-emergent Malignancies

No patients randomized to DTIC developed a treatment-emergent, non-cutaneous malignancy in the randomized phase or crossover phase.

Basal cell carcinoma was reported in five (3%) dabrafenib-treated patients and in none of the DTIC-treated patients. Three of the five patients were diagnosed in the first month of treatment (minimum 22 days, maximum 87 days). Basal cell carcinoma was resolved in all patients as of the data cutoff date and none required treatment modification of dabrafenib.

In addition, there was one case of treatment-emergent mycosis fungoides (MF). Patient BRF113683.0001488, a 67-year-old Caucasian man with melanoma metastases involving the liver and soft tissue and no other significant PMH, developed Stage I MF 44 days after initiating dabrafenib. Treatment for MF included methylprednisolone and was ongoing.

REVIEWER COMMENT:
In cutaneous T-cell lymphoma patients, including patients with MF and Sezary syndrome, NRAS and KRAS mutations have been infrequently identified in tumor specimens (Keibling, Oberholzer, et al. 2011). No information was available in regard to RAS mutation testing of the MF tumor specimen from Patient BRF113683.0001488.

In the ISS database, the Applicant reported occurrence of four treatment-emergent non-cutaneous malignancies in dabrafenib-treated patients. These were acute myeloid leukemia, myelodysplastic syndrome, adenocarcinoma of the breast, and adenocarcinoma of the cervix (Table 27).

Table 27: All Cases of Non-Cutaneous New Primary Malignancies in Dabrafenib-Treated Patients. ISS Database.

Patient ID	Age / Sex	New Primary Malignancy	Onset (Day)	Comment
BRF113683.0000600	81/F	Breast adenocarcinoma	42	This patient had melanoma metastases involving the subcutaneous tissue and was status post multiple excisions of melanoma and PMH of Grade 1 thyroid neoplasm. She discovered a mass in her left breast approximately 11 months after initiating dabrafenib. She underwent a breast biopsy (Day 350) which demonstrated infiltrating ductal adenocarcinoma with one positive sentinel lymph node, ER+PR+Her2+ (amplified). The Applicant reported that review of the past scans demonstrated a visible mass on Day 42. The patient underwent an excisional biopsy on Day 385. This patient had not had mammography performed for the previous eight years .
BRF113683.0010630	40/F	Cervical adenocarcinoma	186	This patient had a PMH significant for melanoma metastases involving the lymph nodes and a PMH significant for former tobacco use. She developed a new primary melanoma (Day 36) which on biopsy demonstrated a malignant spitzoid melanoma. The tumor stage was a T2a lesion which extended to the periphery and deep margins. On Study Day 186, a Papanicolaou (Pap) test was abnormal, and an endometrial biopsy showed adenocarcinoma of the endocervix. The patient underwent endometrial curettage (Day 219) and loop electrosurgical excision procedures (Days 233 and 317). Pathology from the first specimen showed moderate to poorly-differentiated adenocarcinoma of the endocervix with extension to the excisional margin. The patient had no prior Pap tests or testing for HPV. The patient continued dosing with dabrafenib and the event was reported as resolved on Day 233.
BRF113710.0000155	45/M	Acute myeloid leukemia (AML)	181	This patient had a PMH significant for anemia at baseline and prior treatment history which included interferon, interleukin-2, vinblastine, cisplatin, temozolomide, and ipilimumab. Grade 2 pancytopenia was diagnosed on Study Day 35. He discontinued treatment on Day 162 due to worsening pancytopenia. On Day 181, he was diagnosed with AML, monocytic differentiation. Bone marrow aspirate and biopsy revealed abnormal karyotype (47,XY,+11[20]) by cytogenetics and an extra MLL gene locus signal was identified. Patient initiated treatment with azacytidine and AML was ongoing.
BRF112680.0005202	70/M	Myelodysplastic syndrome	198	Patient had baseline cytopenias (anemia, neutropenia, leukopenia). Treatment was interrupted for fatigue secondary to anemia on Day 174 prior to the Grade 3 MDS diagnosis (refractory anemia with ringed sideroblasts subtype) considered unrelated to dabrafenib. The patient restarted dabrafenib on Day 223 and MDS was ongoing.

Based on a data cutoff of March 6, 2013, the Applicant reported that across the entire development program of dabrafenib (monotherapy or administered in combination) there were

seven additional cases of non-cutaneous new primary malignancies—myelodysplastic syndrome, gastric adenocarcinoma, invasive ductal carcinoma of the breast, renal cell carcinoma, squamous cell carcinoma of the head and neck, glioblastoma, pancreatic carcinoma—and one case of progression of a BRAF wild-type, KRAS mutation-positive metastatic colon adenocarcinoma which occurred in a patient with a history of a previously resected, KRAS mutation-positive Dukes B colon adenocarcinoma (see Appendix 9.4).

REVIEWER COMMENTS:

1. *The mechanisms of paradoxical activation of the MAPK pathway by RAF kinase inhibitors are being elucidated in the literature (Cichowski and Janne 2010). Activation of the RAS pathway through mutation in RAS or through upstream events involving receptor tyrosine kinases appears important in this process.*
2. *Most cases of non-cutaneous new primary malignancies occurring in dabrafenib-treated patients are confounded by pre-existing lesions, prior anti-cancer treatment, and background event rates in patients with a cancer history. Few of these new primary tumors have undergone mutational analyses, including testing for mutations in RAS. In addition to the KRAS mutation identified in the recurrent colorectal cancer (consistent with this patient's primary), the Applicant identified one new primary malignancy, a case of pancreatic adenocarcinoma, with a RAS mutation which was identified as KRAS G12D (see Appendix 9.4).*
3. (b) (4)
4. *This reviewer recommends that the Applicant conduct postmarketing trials to define the risk of non-cutaneous, new primary malignancies. These trials should better inform prescriber and patient labeling to enhance risk communication with patients, identify appropriate safety monitoring to mitigate risk of non-cutaneous, new primary malignancies in patients prescribed dabrafenib, and guide appropriate development of dabrafenib in patients with earlier stages of melanoma and in patients with other malignancies.*

Cardiac Disorders

Overall, cardiac disorder AEs occurred in 18 (10%) patients treated with dabrafenib and in 3 (5%) patients treated with DTIC. These AEs were serious in four (2.1%) dabrafenib-treated patients and in one (1.7%) DTIC-treated patient (Table 28). Two serious cases of decreased ejection fraction (1.1%), both Grade 2 in severity and reported as important medical events, and one serious case of congestive cardiac failure (<1%), which required hospitalization, occurred in the dabrafenib treatment group. In addition, two serious cases of atrial fibrillation (1.1%) and one case of myocardial infarction (<1%) occurred in the dabrafenib treatment group. There was one SAE involving a cardiac disorder reported in the DTIC treatment group, a case of Grade 3 angina pectoris which required hospitalization.

Table 28: All Cases of Cardiac Disorders Reported as Serious Adverse Events. BRF113683 Trial.

Patient ID	Group	Age/ Sex	Cardiac RF / Hx	Verbatim Term	Grade	Study Day	Intervention	Outcome	Dur (days)	Dose Modification/ Interruption
BRF113683.0010605	Dabrafenib	75/F	DM; HTN; HLD	Congestive Heart Failure	3	7	IV diuretics; electrolytes	Recovered /resolved	5	Not applicable[1]
BRF113683.0003964	Dabrafenib	68/M	none	Ischemic heart attack	3	118	Cardiac stent placement	Recovered /resolved	5	Withdrawn
BRF113683.0001751	Dabrafenib	44/F	Arrhyth-mia; PE	Paroxysmal atrial fibrillation	3	113	IV and PO anti-arrhythmics	Recovered /resolved	2	None
BRF113683.0001488	Dabrafenib	67/M	HTN; HLD; MV	Tachy-arrhythmia absoluta atrial fibrillation	2	156	Cardioversion; anti-arrhythmics; anti-coagulants	Recovered /resolved	12	Dose reduction
BRF113683.0000598	DTIC	68/M	HTN; Brady-cardia	Angina pectoris	3	63	Cardiac stent placement; thienopyridine; anticoagulant	Recovered /resolved	12	Not applicable[2]

Source: BRF11683 narratives, CRFs, AE.xpt, and RAE.xpt datasets
Abbreviations in Table: DM; diabetes mellitus; Dur, duration; HLD, hyperlipidemia; HTN, hypertension; Hx, History; IV, intravenous; MV, mitral valve insufficiency; PE, pulmonary embolism; PO, oral; RF, risk factor;
[1] Patient discontinued dabrafenib prior to event on Day 5 due to muscular weakness
[2] Patient discontinued DTIC prior to event on Day 45 due to progression of disease

The Applicant provided further details of the case of congestive heart failure. Patient BRF113683.0010605, a 75-year-old woman with melanoma metastases involving the lymph nodes, bone, and left adrenal gland and PMH significant for diabetes, hyperlipidemia, hypertension, and anemia, discontinued dabrafenib on Day 5 for muscular weakness. She also reported a fall in association with neurologic symptoms. Imaging studies, including head CT, MRI of spine, and chest x-ray, were normal. The patient was febrile to 40.5º C, dehydrated, and hypophosphatemic. The patient received dibasic sodium phosphate and the hypophosphatemia resolved. The patient's condition initially improved (Day 6) but she required hospitalization on Day 7 for congestive heart failure and Raoultella terrigena infection. The laboratory evaluation demonstrated increased CKs but normal troponins. A chest x-ray on Day 7 revealed pulmonary edema. Her condition improved with intravenous diuretics, antibiotics, and intravenous hydration. On Day 9, an echocardiogram demonstrated a normal LVEF of 65%. The investigator reported that the congestive heart failure was unrelated to dabrafenib.

In the safety monitoring plan, the Applicant included routine echocardiographic assessments of LVEF and of valvular function on Weeks 6, 12, 21, 30 and every nine weeks thereafter. The

Applicant included these assessments in the BRF113683 trial based on the safety profile of other tyrosine kinase inhibitors and the results of nonclinical toxicology studies with dabrafenib demonstrating valvular abnormalities in dogs (see the FDA Pharmacology/Toxicology NDA review). As listed in Table 29, there were three (2%) patients in the dabrafenib treatment group and no patients in the DTIC treatment group who met LVEF stopping criteria, i.e., a ≥10% decrease in LVEF that is also less than the institutional lower limit of normal (LLN). The Applicant reported that a fourth patient experienced a 10% decrease in LVEF in association with a Grade 3 decrease in LVEF.

Table 29: All Cases Meeting LVEF Stopping Criteria per Investigator Assessment. Dabrafenib Treatment Group. BRF113683 Trial.

Patient ID[1]	Age / Sex	Cardiac History[2]	LVEF			AEs Temporally Associated with LVEF Decrease	Disposition
			Screen (LLN), %)	Worst (%)	Study Day		
BRF113683 .00015292	53/M	-	74 (55)	52	164	None	Withheld dabrafenib, event reported as not resolved
BRF113683 .0000675	33/M	-	72 (60)	59	121	None	Discontinued dabrafenib on Day 126 for PD; repeat Echo Day 147 showed improvement to 62%
BRF113683 .0003964	68/M	-	60 (50)	47	118	Myocardial infarction	Discontinued on Day 119 due to myocardial infarction
BRF113683 .0004686	71/F	+[3]	45 (40)	35	40	Mitral and tricuspid valve disease (Grade 2)	Discontinued Day 43 due to worsening valvular disease; Decreased LVEF resolved Day 68

Abbreviations in Table: F, female; LLN, institutional lower limit of normal; LVEF, left ventricular ejection fraction; M, male.
[1] All cases occurred in the dabrafenib treatment group.
[2] -, negative; +, positive.
[3] Relevant cardiac history —Grade 1 valvular disease (aortic, mitral, and tricuspid); Grade 2 decreased LVEF, myocardial infarction, paroxysmal atrial fibrillation, ventricular tachycardia, and circulatory arrest.

In analyses of the ISS database, the incidence of heart failure was 0.5% (3/586). In addition to the serious case of heart failure (Patient BRF113683.0010605) described in Table 28, there were two additional heart failure cases reported in the ISS database, both were non-serious:

- Patient BRF113683.0005215, an 84-year-old man with melanoma metastases involving the lymph nodes, lung, and subcutaneous tissue and PMH significant for prior smoking, hypertension, hyperlipidemia, hyperthyroidism, hyperglycemia, and venous insufficiency, developed Grade 2 heart failure starting on Day 247. The patient received oral diuretics and continued on the same dose of dabrafenib without interruption. Therapy for the heart failure was complicated by Grade 1 renal failure and dabrafenib was subsequently withheld, reportedly for heart failure, from Days 253 to Day 259. The

patient restarted dabrafenib without dose reduction on Study Day 260. The investigator reported that heart failure was unrelated to dabrafenib and had resolved on Day 274.

- Patient BRF113683.0001511, a 95-year-old man with a PMH of hypertension, hyperlipidemia, myocardial hypertrophy, and sclerosis of the mitral and tricuspid valves developed Grade 2 cardiac decompensation on Day 100. The patient continued on dabrafenib without dose modification or interruption and the AE, cardiac decompensation, resolved on Day 148.

REVIEWER COMMENT:
In all three cases, patients had underlying comorbidities which may have contributed to the events. In addition, two of the three cases had negative rechallenge data with dabrafenib; the investigators reported that heart failure was unrelated to dabrafenib in all three cases. Of note, analyses of LVEF in serial echocardiograms do not establish an effect of dabrafenib on cardiac function in patients with normal LVEFs prior to treatment.

Pyrexia

Overall, the incidence of pyrexia, serious as well as non-serious AEs, was increased in dabrafenib-treated patients compared to that in DTIC-treated patients, 28% (53/187) vs. 10% (6/59), respectively. Serious adverse events of pyrexia developed in seven (3.4%) patients in the dabrafenib treatment group and in none of the patients in the DTIC treatment group (see Table 30). The median time to onset of first occurrence of pyrexia (serious or non-serious) was two weeks in dabrafenib-treated patients and three weeks in DTIC-treated patients with a median duration of 3 and 4 days, respectively. No cases of pyrexia led to treatment withdrawal; however, 16 (8.6%) and 12 (6.4%) dabrafenib-treated patients required either dose reductions or dose interruptions for pyrexia, respectively. Twenty-six dabrafenib-treated patients and two DTIC-treated patients received medications for pyrexia. In the dabrafenib treatment group, these medications included NSAIDS (n=11), acetaminophen (n=12), antibiotics (n=9), aspirin (n=1), and corticosteroids (n=1). Pyrexia resolved in 52 of 53 dabrafenib-treated patients and 6 of 6 patients treated with DTIC.

Table 30: All Serious Adverse Events of Pyrexia. Dabrafenib Treatment Group. BRF113683 Trial.

Patient ID[1]	Age / Sex	SAE Type	Verbatim Term(s)	Grade	Study Day	AEs or Symptoms Temporally Associated With Pyrexia	Interventions	Outcome	Dur (d)	Disposition
BRF113683.0000064	47/M	HOSP	fever	2	74	SVT (Gr 2; D 74)	Antibiotics (IV and PO); acetaminophen	Recovered /resolved	2	Dose not changed
		HOSP	fever	2	88	Fatigue (Gr 2; D84); Chills; Renal failure	Antibiotics (PO)	Recovered /resolved	8	Dose not changed
		HOSP	fever	3	116	Vomiting; Cough	acetaminophen	Recovered /resolved	5	Dose reduced
BRF113683.0003452	41/M	IMP	Pyrexia with rigors	3	25	Upper abdominal pain (Gr 2; D26); Vomiting (Gr 1; D28)	acetaminophen	Recovered /resolved	4	Dabrafenib withheld Day 29-33 and restarted at reduced dose Day 34 and discontinued Day 39 due to PD
BRF113683.0003456	46/M	HOSP	Complicated fever	2	189	Influenza-like illness (Gr 3;D186); Rigors;, Difficulty breathing	acetaminophen	Recovered /resolved	3	Dabrafenib withheld Day 190-195 and restarted at reduced dose Day 196
BRF113683.0004012	74/M	HOSP	FUO	1	58	Confusion (Gr 1, D57); Tremor (Gr 1, D57); Constipation (Gr 1, D60); AST increased (Gr 1, D60); Hypotension (Gr 1, D65)	Antibiotics (PO); acetaminophen	Recovered /resolved	7	Dabrafenib withheld Day 60-70

Patient ID[1]	Age / Sex	SAE Type	Verbatim Term(s)	Grade	Study Day	AEs or Symptoms Temporally Associated With Pyrexia	Interventions	Outcome	Dur (d)	Disposition
BRF113683.0005151	37/F	HOSP	FEVER	2	85	Vomiting (Gr 3, D84); Constipation (Gr 3, D84); Stomatitis (D85, Gr 1); Anxiety (Gr 3, D88); Oliguria (Gr 1, D89); Hypotension (Gr 1, D99) Oliguria (Gr 1, D89	Antibiotics (IV); NSAID (IV)	Recovered /resolved	19	Dabrafenib discontinued prior to pyrexia; Another BRAF inhibitor started seven days prior to episode of hypotension
BRF113683.0007455	75/M	PROT	fever	1	102	Hypotension (Gr 2, D 99;Gr 1, D101);, Syncope (Gr 3, D 99); Dehydration (Gr 2, D 99); Fatigue	Corticosteroid (PO)	Recovered /resolved	2	Dabrafenib withheld Days 103-109 then restarted without dose reduction
		PROT	fever	2	157	Chills (Gr 2, D 157): Hypotension (Gr 2, D 157)	Increased corticosteroid dose (PO)	Recovered /resolved	3	Dabrafenib withheld Days 157-163 and then restarted without dose reduction
BRF113683.0010632	41/F	PROT	Pyrexia	1	125	Rigors (Gr 1, D125); Arthralgia Myalgia;	Corticosteroids	Recovered /resolved	1	Dabrafenib withheld Day 125-134, then restarted at a reduced dose

Abbreviations in Table: d, days; D, Study Day; Dur, duration; F, female; FUO, fever of unknown origin; Gr, Toxicity Grade; HOSP, hospitalization; IMP, important medical event; IV, intravenous; M, male; PO, oral; PROT, protocol specific event; SAE, serious adverse event; Term, verbatim term reported by investigator.
[1] All cases of serious adverse events of pyrexia occurred in the dabrafenib treatment group.

In the ISS database, the incidence of pyrexia (any Grade) was 33% (194/586). The median time to initial onset of pyrexia was 22 days (range 1 to 383 days). The median duration of pyrexia (initial and recurrent episodes) was 3 days (range 1 to 297 days). Of the 315 cases of pyrexia, dabrafenib required dose reduction in 45 cases, dose interruption in 54 cases, no changes in 216

cases (recorded as not applicable for 9 of 216). In total, 5% (30/586) of the patients required a dose reduction of dabrafenib for pyrexia.

As listed in Table 31, there were 39 serious cases of pyrexia and 2 serious cases of influenza like illness for a total incidence of serious pyrexia events of 6% (35/586). The most frequent criteria for classifying pyrexia as a serious adverse event was hospitalization (n=30 cases) followed by protocol defined event (n=6 cases), other important medical event (n=4 cases), or both a protocol defined event and other important medical event (n=1 case).

Table 31: All Serious Cases of Pyrexia in Dabrafenib-Treated Patients. ISS Database.

Patient ID	AGE	SEX	Pyrexia Serious Adverse Event				Associated AEs in Definition of Non-infectious Febrile Event			
			Verbatim Term	Grade	Start (Day)	End (Day)	AE or Symptoms	Grade	Start (Day)	End (Day)
BRF112680.0003121[a]	55	M	Fever of unknown origin.	2	28	38	Hypotension	1	28	38
BRF112680.0003122[a]	44	F	Pyrexia of unknown origin	2	5	8	Rigors	1	5	7
							Hypotension	2	7	7
							Dehydration	2	7	8
BRF112680.0003202	58	M	Fever	2	606	606	-	-	-	-
BRF112680.0003208[a]	82	M	Fever	2	17	23	-	-	-	-
			Fever	2	42	46	Dehydration	2	42	49
							Syncopal episode	3	42	42
BRF112680.0004106	26	M	Pyrexia	1	295	297	-	-	-	-
BRF112680.0005202	70	M	Fever	1	105	107	Volume depletion	1	105	107
BRF112680.0005206	65	M	Pyrexia	3	18	18	-	-	-	-
			Fever	2	156	157	-	-	-	-
BRF113220.0000669	49	F	Pyrexia	1	5	14	Chills	1	5	14
BRF113683.0000064[a]	47	M	Fever	2	74	75	-	-	-	
			Fever	2	88	95	Renal failure	-	-	-
			Fever	3	116	120	-	-	-	-
BRF113683.0001415	49	F	Fever	1	59	60	Chills	1	59	60
BRF113683.0003452	41	M	Pyrexia with rigors	3	25	28	-	3	25	28
BRF113683.0003456	46	M	Complicated fever	2	189	191	Flu like symptoms	3	189	191
BRF113683.0004012	74	M	Fever of unknown origin	1	58	64	Hypotension	1	65	71

Patient ID	AGE	SEX	Pyrexia Serious Adverse Event				Associated AEs in Definition of Non-infectious Febrile Event			
			Verbatim Term	Grade	Start (Day)	End (Day)	AE or Symptoms	Grade	Start (Day)	End (Day)
BRF113683.0005151	37	F	Fever	2	84	103	Hypotension	1	99	-
BRF113683.0007153[a]	47	F	Flu-like symptoms	4	22	32	-	4	22	32
BRF113683.0007455[a]	75	M	Fever	1	102	103	Hypotension	1	101	146
			Fever	2	157	159	Hypotension	2	157	159
							Chills	2	157	159
BRF113683.0010632	41	F	Pyrexia	1	125	125	Rigors	1	125	125
BRF113683.0012368	71	M	Fevers	2	159	164	Rigors	2	159	164
BRF113683.D012326	26	M	Episodic fevers	2	32	46	-	-	-	-
BRF113710.0000002	44	M	Fever	2	139	153	-	-	-	-
BRF113710.0001017	41	M	Fever	1	178	186	-	-	-	-
BRF113710.0002007	66	F	Fever	2	17	26	Rigors	1	17	26
							Chills	1	20	28
BRF113929.0000010	69	M	Pyrexia with chills	2	14	17	-	2	14	17
BRF113929.0000334	58	M	Fever	2	110	111	Hypotension	3	110	110
BRF113929.0000501[a]	40	F	Fever	3	23	27	Dehydration	1	23	27
							Chills	3	23	27
BRF113929.0000506	48	F	Pyrexia of unknown origin	2	31	34	-	-	-	-
BRF113929.0000553	71	M	Fevers	2	2	3	Rigors	2	2	7
			Fever	2	292	294	Rigors	1	292	293
BRF113929.0000556	50	F	Fevers	2	162	163	Rigors	1	162	163
BRF113929.0000557[a]	62	M	Fever	1	24	28	Dehydration	1	25	25
							Rigors	1	24	26
BRF113929.0000566	41	M	Fever	1	53	54	-	-	-	-
BRF113929.0000574	66	M	Fever	1	243	254	-	-	-	-
BRF113929.0000807[a]	68	M	Pyrexia	2	29	47	Hypotension	2	31	44
BRF113929.0000861	63	F	Flu like symptoms	3	28	49	Hypotension	2	28	49
BRF113929.0000904	68	M	Fever	2	21	22	Hypotension	3	22	26
							Rigors	2	22	22

Patient ID	AGE	SEX	Pyrexia Serious Adverse Event				Associated AEs in Definition of Non-infectious Febrile Event			
			Verbatim Term	Grade	Start (Day)	End (Day)	AE or Symptoms	Grade	Start (Day)	End (Day)
BRF113929.0000957	45	F	Fever	1	140	144	Chills	-	-	-

Source: BRF113683 CSR, BRF113929 CSR, BRF113710 CSR, BRF112680 CSR, BRF113220 CSR, ISS, ISS 120-Day Safety Update, AE.xpt (ISS database-120-Day Safety Update)
Abbreviations in Table: AE, adverse event; F, female; M, male.
[a] Identified by Applicant as a serious non-infectious febrile drug reaction

The Applicant performed a retrospective, manual evaluation of serious pyrexia cases to identify serious non-infectious febrile events. In the original NDA, the Applicant defined serious non-infectious febrile events as SAEs of pyrexia complicated by hypotension, dehydration, circulatory collapse, or renal failure in the absence of another identifiable etiology (e.g., infection). In analyses of the ISS database (120-day safety update), the Applicant defined serious non-infectious febrile events as SAEs of pyrexia complicated by hypotension, dehydration, severe rigors/chills, or renal failure in the absence of another identifiable etiology (e.g., infection). In the final ISS database, the Applicant identified a total of nine (1.5%) dabrafenib-treated patients who met criteria for serious non-infectious febrile events.

REVIEWER COMMENTS:

1. *The Applicant reported that the etiology of these serious febrile drug reactions are unknown but posited that it may be immune-mediated and possibly related to cytokine release.*
2. *The Applicant updated its definition of serious non-infectious febrile events in the ISS submitted in the 120-Day safety update. In analyses of the ISS, the reviewer identified an additional 13 potential cases of serious non-infectious febrile drug reactions based on the broad criteria listed by the Applicant to define these events. This highlights the uncertainty in retrospective review to define serious non-infectious febrile events as a distinct clinical syndrome as well as to report an observed incidence for the purposes of labeling. Of note, serious cases of pyrexia were associated with a diverse range of symptoms not included in the Applicant's definition of serious non-infectious febrile drug reaction indicating that this may not represent a single clinical entity.*
3. *In the ISS, the Applicant stated that in an ad hoc analysis it could not determine the impact of management guidelines for pyrexia (see Appendix 9.5, Table F) based on the similar low rates of recurrence of pyrexia pre- and post-implementation of the protocol amendments containing this standardized management guidance, 3% and 4%, respectively.*

Diabetes mellitus and Hyperglycemia

Medical history of diabetes was systematically recorded at baseline, 12 (6.4%) patients in the dabrafenib treatment group and four (6.8%) patients in the DTIC treatment group reported a

current history of diabetes; additionally, one patient in the dabrafenib treatment group reported a past history of diabetes. Of these 13 dabrafenib-treated patients reporting current or past diabetes at baseline, two patients (1.1%) experienced serious exacerbations of diabetes mellitus; no patients in the DTIC treatment group experienced serious exacerbations or new onset diabetes.

- Patient BRF113683.0000600, an 81-year-old woman with history of diabetes and Grade 1 hyperglycemia at baseline, but no reported medications for the treatment of diabetes, developed inadequate control of diabetes beginning on Day 20. The patient initiated an oral hypoglycemic on Study Day 8 and increased the dose twice on Day 14 and Day 29. She experienced Grade 2 hyperglycemia beginning Day 20 which increased to Grade 3 beginning on Day 42. The patient initiated insulin on Day 61 which was ongoing at the time of data cutoff. This event resulted in prolongation of a hospitalization from Day 61-64. Dosing with dabrafenib was withheld from Days 63 to 70 and she restarted dabrafenib at a reduced dose (100 mg BID) on Day 71 following resolution of inadequate control of diabetes on Day 69. Of note, the patient had received prednisone for an iodine allergy from Days 37-42.
- Patient BRF113683.0004660, a 59-year-old woman with melanoma with metastases to subcutaneous tissue and lymph nodes and a PMH significant for diabetes requiring oral hypoglycemic medications, developed worsening diabetes with Grade 3 hyperglycemia on Day 22. The patient required hospitalization for the event and initiated insulin therapy on Day 25. In addition, the patient withheld dabrafenib dosing from Day 23-37. The AE worsening diabetes resolved on Day 31 and the patient restarted dabrafenib at a reduced dose (100 mg BID) beginning on Day 38. Insulin therapy was ongoing at the time of data cutoff.

Overall, fifteen cases of hyperglycemia or diabetes mellitus (any Grade) occurred in 10 (5.7%) patients in the dabrafenib treatment group compared to one (1.7%) case of hyperglycemia or diabetes in the DTIC treatment group, a single case of Grade 3 hyperglycemia. Of the 15 cases in dabrafenib-treated patients, the Applicant coded thirteen of the 15 cases as hyperglycemia AEs and two cases as diabetes mellitus (both SAEs as described above). The incidence of Grade 3 hyperglycemia/diabetes mellitus in dabrafenib-treated patients was 2.7%—no patients experienced Grade 4 hyperglycemia/diabetes mellitus. Of these ten patients with diabetes or hyperglycemia AEs in the dabrafenib treatment group, six had a history of diabetes mellitus (n=3) or hyperglycemia (n=3; all Grade 1) at baseline. The outcome of hyperglycemia was not resolved in four cases, recovered with sequelae in two cases, and recovered/resolved in seven cases. Both patients with SAEs of diabetes required dose reductions of dabrafenib; no additional patients required treatment modification of dabrafenib for hyperglycemia.

As summarized in Table 32, the review included an analysis of patients receiving oral hypoglycemic medications or insulin therapy at baseline or at any time while on treatment. Of the 12 dabrafenib-treated patients with a medical history of current diabetes at baseline, five (42%) required an increase in therapy while on treatment. In addition, one dabrafenib-treated patient (Patient BRF113683.0003981) without a reported history of diabetes required initiation of oral hypoglycemic therapy while on treatment with dabrafenib. In cases requiring change in

diabetic treatment, nearly all occurred within the first two months of starting dabrafenib treatment. None of the DTIC-treated patients required an increase or change in treatment for diabetes.

Table 32: Hyperglycemia at Baseline and Worst Case On-Treatment. Subgroup of Patients on Glucose Lowering Medications (Baseline or On-Treatment). BRF113683 Trial.

	BL Meds	Glucose[1]		Action(s)	Start, Day	End, Day
		BL	Max			
DABRAFENIB						
BRF113683.0000600	None	1	3	New Medication (SU) Dose Increase (SU) New Medication (IN)	8- 29 61	 61 Ongoing
BRF113683.0004660	SU BG	1	3	New Medication (IN) Dose Increase (BG)	25 32	Ongoing Ongoing
BRF113683.0001475	TZ/BG SU	2	3	Dose Increase (SU)	22	Ongoing
BRF113683.0003981	None	1	3	New Medication (BG)	46	Ongoing
BRF113683.0006796	BG	1	3	Dose Increase (BG)	148	Ongoing
BRF113683.0007001	BG	2	3	New Medication (SU)	56	Ongoing
BRF113683.0000182	BG/SU	2	3	None	-	-
BRF113683.0001487	IN	0	2	None	-	-
BRF113683.0001530	BG	1	3	None	-	-
BRF113683.0001587	SU	1	3	None	-	-
BRF113683.0001646	BG	1	3	None	-	-
BRF113683.0005171	BG	1	1	None	-	-
BRF113683.0007460	SU	1	2	None	-	-
DTIC						
BRF113683.0012328	TZ/BG SU	3	2	None	-	-
BRF113683.0000632	BG	1	0	None	-	-
BRF113683.0000670	SU	1	2	None	-	-
BRF113683.0001454	DP/BG	1	2	None	-	-

Abbreviations in Table: BG, biguanide; BL, Baseline, DP, dipeptidyl peptidase inhibitor; IN, insulin; IP, investigational product; M, maximum on-treatment toxicity grade; SU, sulfonylurea, TZ, thiazolidinedione
[1] Laboratory Glucose Testing, Toxicity Grade

REVIEWER COMMENT:
Concomitant treatments that could impair glucose control, e.g., use of corticosteroids in a supportive care role as was the case for BRF113683.0000600, may have contributed in few cases but do not appear to explain this safety concern.

In an analysis of routine and unscheduled blood glucose testing, the incidence of treatment-emergent hyperglycemia (increase of ≥ 1 toxicity grade) was 50% in the dabrafenib treatment group compared to 42% in the DTIC treatment group. The incidence of Grade 3 or 4 hyperglycemia was 6.4% in the dabrafenib treatment group. There were no DTIC-treated patients with treatment-emergent Grade 3 or 4 hyperglycemia based on laboratory testing of blood glucose.

REVIEWER COMMENT:
The importance of the RAS/RAF/MEK/ERK pathway in glucose metabolism is being elucidated in tumors and in normal cells (reviewed by Osborne, Zaganjor et al. 2012). The review of safety supports diabetes/hyperglycemia as an adverse reaction of dabrafenib, a reaction that can be serious as it was in two cases in the BRF113683 trial. Worsening glucose control required initiation of insulin therapy, addition of oral hypoglycemic medications, increased dose of oral hypoglycemic medications, and/or initiation of oral hypoglycemic medications in patients on the dabrafenib arm. This reviewer recommends adding information concerning risk of hyperglycemia/worsening glucose control to the label as well as recommendations for routine glucose monitoring in populations at increased risk.

Hemorrhage

There were two SAEs of hemorrhage in the BRF113683 trial, both observed in the dabrafenib treatment group:

- Patient BRF113683.0012330, a 65-year-old man with melanoma metastases involving the abdomen/abdominal wall and a PMH significant for hemorrhoids, experienced a Grade 2 hemorrhoidal hemorrhage on Day 16 requiring hospitalization. He continued the same dose of dabrafenib uninterrupted and the event resolved after 9 days with use of stool softeners and laxatives.
- Patient BRF113683.0000636, a 79-year-old woman with a history of a left inguinal lymph node excision and melanoma lesions in the left iliac and femoral lymph nodes at baseline, experienced a Grade 1 inguinal lymph node hemorrhage on Day 170—five days after discontinuing dabrafenib for progression of disease—which required radiotherapy as hemostatic treatment and resolved after six days.

REVIEWER COMMENT:
Clinical review of these two cases does not support bleeding as an adverse reaction of dabrafenib. In addition, the overall incidence of AEs related to bleeding was not increased in the dabrafenib treatment group compared to the DTIC treatment group, 5.4% vs. 10.2%, respectively.

Pancreatitis

There was one serious case of pancreatitis and one serious case of hyperlipasemia, both occurring in the dabrafenib treatment group:

- Patient BRF113683.0012362, a 38-year-old man with metastatic melanoma and a PMH significant for tobacco use and alcohol use (14 units/week), developed upper abdominal pain on Day 4 with biochemical and radiological evidence of pancreatitis. The patient reported his most recent use of alcohol as Day 2. The patient withheld dosing with dabrafenib on Day 6 and he improved rapidly with conservative management. Rechallenge with the same dose of dabrafenib was negative.
- Patient BRF113683.0003482, a 54-year-old man with a PMH significant for Grade 1 elevated lipase at baseline, developed on Day 22 an asymptomatic Grade 3 hyperlipasemia, an event classified as an important medical event. The patient initially withheld dabrafenib on Days 40-41 but the investigator determined that the event was unrelated to dabrafenib and he restarted dabrafenib at the same dose on Day 42. The outcome of the event was not recovered/not resolved. There were no associated increases in LFTs or in amylase. The patient discontinued dabrafenib on Day 78 for disease progression and died due to disease under study on Day 87.

The review of pancreatitis as an adverse reaction of dabrafenib included analyses of the ISS database. There was one additional case of pancreatitis reported. Patient 113929.0000502, a 64-year-old man with metastatic melanoma and a PMH significant for diabetes, gout, hyperlipidemia and no alcohol use, required hospitalization on Day 10 following an episode of syncope (Day 8) and prolonged immobility (2 days). This event was complicated by dehydration and rhabdomyolysis. An imaging evaluation demonstrated a small bowel obstruction and raised the possibility of pancreatitis; laboratory testing revealed a Grade 4 elevation of lipase. The outcome of the event was recovered/resolved and the patient restarted dabrafenib at a reduced dose on Day 24.

REVIEWER COMMENT:
The data provided are insufficient to support inclusion of pancreatitis as an adverse reaction of dabrafenib. The reviewer requested that the Applicant provide additional evidence to support attribution of this AE as an adverse reaction of dabrafenib, e.g., a risk-difference or relative risk of a specific magnitude, challenge-rechallenge data, rarity and severity of the adverse reaction in the patient population under study, a plausible biological mechanism of action, etc.

7.3.3 Dropouts and/or Discontinuations

Forty-three percent (57/187) and 76% (24/59) of patients treated with dabrafenib and DTIC, respectively, had treatment discontinued at the time of data cutoff for the BRF113683 trial as summarized (Table 33). The incidence of treatment discontinuations for adverse event was 3% (5/187) in the dabrafenib treatment group and nil in the DTIC treatment group.

Table 33: Summary of Treatment Discontinuations. Safety Population. BRF113683 Trial.

	Dabrafenib N=187 n (%)	DTIC N=59 n (%)
Total Discontinued	81 (43)	45 (76)
Disease Progression	67 (36)	42 (71)
Adverse Event	5 (3)	0
Investigator Discretion	4 (2)	2 (2)
Decision by subject or proxy	5 (3)	1 (2)

Source: IPDISC.xpt and RIPDISC.xpt.

Table 34 lists the patients who discontinued treatment based on the discretion of the investigator or on the decision by subject of proxy.

Table 34: All Patients Discontinuing Treatment for Investigator Discretion or Subject Decision. BRF113683 Trial.

Patient ID	Treatment	Reason	Comment
BRF113683.0010650	Dabrafenib	I	Withdrawn for disease progression
BRF113683.0010168	Dabrafenib	I	Withdrawn when patient began hospice care
BRF113683.0000064	Dabrafenib	I	Withdrawn due to intolerance to study medication
BRF113683.0000587	Dabrafenib	I	Withdrawn as patient was in a complete response
BRF113683.0007352	Dabrafenib	S	Pursue additional anti-cancer therapy
BRF113683.0001766	Dabrafenib	S	Pursue additional anti-cancer therapy
BRF113683.0001490	Dabrafenib	S	Discontinue treatment to go to another clinic
BRF113683.0000054[a]	Dabrafenib	S	Unknown
BRF113683.0000600	Dabrafenib	S	Asthenia
BRF113683.0000588	DTIC	I	Withdrawn as patient was in a complete response
BRF113683.0000634	DTIC	I	Withdrawn as patient was in a complete response
BRF113683.0005204	DTIC	I	Withdrew during first day of the study

Source: RIPDISC.xpt
Abbreviations in Table: I, Investigator assessment, I; S , Decision by subject or proxy,
[a] Primary cause of death in this patient was euthanasia (see Table 25)

REVIEWER COMMENT: Based on the ambiguity of comment "withdrawn due to intolerance to study medication" for Patient BRF113683.0000064, the review of safety further evaluated the reason for treatment discontinuation in this patient. The patient is a 47-year-old man with melanoma metastases involving the peritoneum/omentum who experienced three episodes of serious pyrexia—episodes requiring hospitalization on Study Days 74, 84, and 116—prior to discontinuation of dabrafenib on Study Day 128. On Study 84, the investigator first reduced the dose of dabrafenib to 100 mg twice daily for Grade 2 fatigue and then to 75 mg twice daily on Study Day 126 following the third occurrence of serious pyrexia. Insufficient information is available in the narratives, CRFs, and AE datasets to determine the specific intolerance which led the investigator to withdraw treatment with dabrafenib. However, fatigue was the only AE considered related to dabrafenib that was ongoing at the time of treatment discontinuation.

On review of the AE datasets, AEs led to treatment discontinuation in 3% (5/187) of dabrafenib-treated patients and 3% (3/59) of DTIC-treated patients. Table 35 lists all AEs leading to treatment discontinuation.

Table 35: All Cases of Treatment Discontinuations Due To Adverse Events. BRF113683 Trial.

Patient ID	Age[1]/ Sex	Treatment Group	Adverse Event	Onset (Day)	Dur (days)	Serious	Outcome
BRF113683.0001470	63/M	Dabrafenib	Constipation	84	14	Y	R
BRF113683.0001587	72/M	Dabrafenib	Hepatic pain	41	3	Y	R
BRF113683.0003964	68/M	Dabrafenib	Myocardial infarction	118	5	Y	R
BRF113683.0004686	71/F	Dabrafenib	Mitral valve/ Tricuspid valve disease	40	n/a	N	O
BRF113683.0010605	75/F	Dabrafenib	Muscular weakness	4	12	Y	R
BRF113683.0000591	29/F	DTIC	Hepatic pain Subileus Abdominal pain	31	n/a	Y	O
BRF113683.0004653	52/M	DTIC	Hematuria	64	5	Y	R

Source: RAE.xpt, AE.xpt
Abbreviations in Table: F, female; M, male; n/a, not applicable; N, No; O, ongoing; R, resolved/recovered; Y, Yes;
[1] Age in years

The incidence of AEs leading to treatment discontinuation in dabrafenib-treated patients within the ISS database (3%) was consistent with that observed in the dabrafenib treatment group in the BRF113683 trial (3%). In the analysis of the ISS database (Table 36), there were few overlapping AEs leading to treatment discontinuation; AEs reported in more than one patient were pancytopenia (n=2) and myocardial infarction (n=2).

Table 36: All Cases of Adverse Events Leading to Treatment Discontinuation in Dabrafenib-Treated Patients. ISS database.

SYSTEM ORGAN CLASS Patient ID	Verbatim Term	Onset (Day)	Dur (days)	Outcome
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
BRF113710.0000155	Pancytopenia	35	-	Ongoing
BRF113929.0000702	Pancytopenia	57	12	Resolved
BRF113929.0000333	Lymphocytopeny	1	-	Ongoing
CARDIAC DISORDERS				
BRF113683.0004686	Mitral valve disease	40	-	Ongoing
	Tricuspid valve disease	40	-	Ongoing
BRF113683.0000667	Asymptomatic myocardial infarct	149	24	Fatal
	Acute coronary syndrome	165	8	Fatal
BRF113683.0003964	Ischemic heart attack	118	5	Recovered
GASTROINTESTINAL DISORDERS				
BRF113683.0001470	Severe abdominal pain with constipation	84	14	Recovered
HEPATOBILIARY DISORDERS				
BRF113683.0001587	Glisson´s capsule pain	41	3	Recovered
INVESTIGATIONS				
BRF113220.0000451	Elevated creatinine	309		Ongoing
BRF113710.0002007	Elevated liver function tests	21	22	Recovered
BRF113929.0000709	Decreased LVEF	280	85	Recovered
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
BRF113683.0010605	Muscle weakness	4	12	Recovered
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)				
BRF113929.0000403	Intracranial hemorrhage due to brain metastases bleeding	81	-	Ongoing
NERVOUS SYSTEM DISORDERS				
BRF113683.D004677	Procedures for planning of radiotherapy (increased intracranial pressure due to progression);	108	2	Recovered
BRF113929.0000265	Epileptic seizures	190	-	Ongoing
BRF113929.0000610	Cerebral Hemorrhage	47	3	Fatal
METABOLISM AND NUTRITION DISORDERS / PSYCHIATRIC DISORDERS				
BRF113710.0000093	Hyponatremia	320	12	Recovered
	Altered Mental Status	320	-	Ongoing

7.3.4 Significant Adverse Events

Adverse Events Leading to Treatment Modifications

Table 37 summarizes the incidence of treatment modifications (discontinuations, dose interruptions/delays, and dose reductions) due to AEs in the BRF113683 trial. The overall incidence of treatment modifications (including treatment withdrawals, dose reductions, and dose

interruptions) was similar between the dabrafenib treatment group in the BRF113683 trial and the dabrafenib-treated patients in the ISS database.

Table 37: Incidence of Treatment Modifications for Adverse Events by Treatment Group. BRF113683 Trial and ISS Database.

	Dabrafenib N=187 n (%)	DTIC N=59 n (%)	Dabrafenib ISS N=586 n (%)
Any treatment modification	57 (31)	17 (29)	207 (35)
Investigational product withdrawn	5 (3)	2 (3)	17 (3)
Dose Reduction	34 (18)	10 (17)	99 (17)
Treatment Interruption	30 (16)	10 (17)	136 (23)

Source: RAE.xpt and AE.xpt datasets, BRF113683; AE.xpt dataset (120-Day safety update)

The incidence of AEs leading to dose reduction was similar between the dabrafenib treatment group (18%) and the DTIC treatment group (17%). The most frequent AEs leading to dose reduction of dabrafenib were pyrexia (9% in the dabrafenib treatment group vs. 0 in the DTIC treatment group), palmar-plantar erythrodysesthesia syndrome (3% vs. 0), chills (3% vs. 0), fatigue (2% vs. 0), and headache (2% vs. 0). Table 38 summarizes the AEs leading to dose reduction in dabrafenib-treated patients.

Table 38: Incidence of Adverse Events Resulting in Dose Reduction (≥1 Dabrafenib-Treated Patient) by Treatment Group. Safety Population. BRF113683 Trial.

	Dabrafenib N=187 n (%)	DTIC N=59 n (%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Pyrexia	16 (9)	0
Chills	5 (3)	0
Fatigue	4 (2)	0
Asthenia	1 (1)	0
Influenza like illness	1 (1)	0
Pain	1 (1)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Palmar-plantar erythrodysesthesia	6 (3)	0
Hyperkeratosis	2 (1)	0
Hyperhidrosis	1 (1)	0
NERVOUS SYSTEM DISORDERS		
Headache	3 (2)	0
Migraine	1 (1)	0
Syncope	1 (1)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Arthralgia	2 (1)	0
Myalgia	2 (1)	0
Musculoskeletal pain	1 (1)	0

	Dabrafenib N=187 n (%)	DTIC N=59 n (%)
GASTROINTESTINAL DISORDERS		
Vomiting	2 (1)	0
Diarrhea	1 (1)	0
Nausea	1 (1)	1 (2)
CARDIAC DISORDERS		
Atrial fibrillation	1 (1)	0
INFECTIONS AND INFESTATIONS		
Influenza	1 (1)	0
INVESTIGATIONS		
Alanine aminotransferase increased	1 (1)	0
Aspartate aminotransferase increased	1 (1)	0
METABOLISM AND NUTRITION DISORDERS		
Diabetes mellitus	1 (1)	0
Diabetes mellitus inadequate control	1 (1)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Pulmonary edema	1 (1)	0
Respiratory distress	1 (1)	0

Source: RAE.xpt and AE.xpt datasets

In the ISS database, the incidence of AEs leading to dose reductions of dabrafenib was 17%. The most frequent AEs (>1%) leading to dabrafenib dose reductions were:

- Pyrexia (4.9%)
- Palmar-plantar erythrodysesthesia syndrome (1.5%)
- Chills (1.4%)
- Fatigue (1.4%)
- Hypophosphatemia (1.4%)

Adverse events leading to treatment interruptions/delays without requiring dose reductions occurred in 16% of patients in the dabrafenib treatment group and 17% of patients in the DTIC treatment group. Pyrexia was the most frequent adverse event leading to treatment interruptions of dabrafenib (6% in the dabrafenib treatment group vs. 0 in the DTIC treatment group). In addition to pyrexia, AEs occurring in more than one patient which led to interruption of dabrafenib treatment were pleural effusion (1% vs. 0), ALT increase (1% vs. 0), hypophosphatemia (1% vs. 0), and vomiting (1% vs. 0). Table 39 summarizes the incidence of AEs leading to dose delays/interruptions in the dabrafenib treatment group.

Table 39: Incidence of Adverse Events Leading to Treatment Interruption/Delay (≥1 Dabrafenib-Treated Patient) by Treatment Group. Safety Population. BRF113683 Trial.

	Dabrafenib N=187 n (%)	DTIC N=59 n (%)
ALL	30 (16)	10 (17)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Pyrexia	12 (6)	0
Fatigue	1 (1)	0
Malaise	1 (1)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Pleural effusion	2 (1)	0
Oropharyngeal pain	1 (1)	0
INVESTIGATIONS		
Alanine aminotransferase increased	2 (1)	0
Blood alkaline phosphatase increased	1 (1)	1 (2)
Ejection fraction decreased	1 (1)	0
Gamma-glutamyltransferase increased	1 (1)	1 (2)
METABOLISM AND NUTRITION DISORDERS		
Hypophosphatemia	2 (1)	0
Hyperlipasemia	1 (1)	0
GASTROINTESTINAL DISORDERS		
Vomiting	2 (1)	1 (2)
Abdominal distension	1 (1)	0
Abdominal pain upper	1 (1)	0
Constipation	1 (1)	0
Diarrhea	1 (1)	0
Ileus	1 (1)	0
Nausea	1 (1)	1 (2)
Pancreatitis	1 (1)	0
Small intestinal perforation	1 (1)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Neutropenia	1 (1)	4 (7)
Thrombocytopenia	1 (1)	2 (3)
EYE DISORDERS		
Cataract	1 (1)	0
INFECTIONS AND INFESTATIONS		
Gastrointestinal infection	1 (1)	0
Localized infection	1 (1)	0

	Dabrafenib N=187 n (%)	DTIC N=59 n (%)
Otitis media	1 (1)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Back pain	1 (1)	0
Muscle spasms	1 (1)	0
Musculoskeletal stiffness	1 (1)	0
Myalgia	1 (1)	0
NERVOUS SYSTEM DISORDERS		
Headache	1 (1)	0
RENAL AND URINARY DISORDERS		
Urinary bladder polyp	1 (1)	0
Urinary retention	1 (1)	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
Menstrual disorder	1 (1)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Hyperkeratosis	1 (1)	0
Pemphigoid	1 (1)	0
VASCULAR DISORDERS		
Hypotension	1 (1)	0

Source: RAE.xpt and AE.xpt datasets

In the ISS database, the incidence of AEs leading to treatment interruption was 23%. The most frequent AEs (>1%) leading to interruptions of dabrafenib dosing were:

- Pyrexia (7%)
- Chills (1.7%)
- Hypophosphatemia (1.4%)
- Vomiting (1.4%)
- Anemia (1.2%)

Grade 3 or 4 Adverse Events

Overall, fewer patients in the dabrafenib treatment group experienced any Grade 3 or 4 TEAEs than those in the DTIC treatment group, 33% vs. 42%, respectively (Table 40). The most frequent (> 2%) Grade 3 or 4 TEAEs in the dabrafenib treatment group were pyrexia (3% in dabrafenib treatment group vs. 0 in DTIC treatment group), squamous cell carcinoma (3% vs. 0), and back pain (3% vs. 0). The incidence of Grade 4 TEAEs was lower (4%) in the dabrafenib treatment group compared to the DTIC treatment group (15%).

Table 40: Incidence of Grade 3 and 4 Treatment-Emergent Adverse Events (>1% Dabrafenib-Treated Patients). Safety Population. BRF113683 Trial.

	Dabrafenib N=187 n (%)			DTIC N=59 n (%)		
	Grade 3 (%)	Grade 4 (%)	Grade 3-4 (%)	Grade 3 (%)	Grade 4 (%)	Grade 3-4 (%)
ALL	55 (29)	7 (4)	62 (33)	16 (27)	9 (15)	25 (42)
Cutaneous squamous cell carcinoma[1]	8 (4)	0	8 (4)	0	0	0
Pyrexia	6 (3)	0	6 (3)	0	0	0
Back pain	5 (3)	0	5 (3)	0	0	0
PPES	4 (2)	0	4 (2)	0	0	0
Hypophosphatemia	4 (2)	0	4 (2)	0	0	0
Constipation	2 (1)	1 (1)	3 (2)	0	0	0
Hyperglycemia	3 (2)	0	3 (2)	1 (2)	0	1 (2)
Alanine aminotransferase increased	3 (2)	0	3 (2)	0	0	0
Gamma-glutamyltransferase increased	3 (2)	0	3 (2)	1 (2)	0	1 (2)
Hyperkeratosis	1 (1)	1 (1)	2 (1)	0	0	0
Arthralgia	2 (1)	0	2 (1)	0	0	0
Fatigue	2 (1)	0	2 (1)	0	0	0
Vomiting	1 (1)	1 (1)	2 (1)	0	0	0
Dyspnea	2 (1)	0	2 (1)	0	0	0
Influenza like illness	1 (1)	1 (1)	2 (1)	0	0	0
Hypokalemia	2 (1)	0	2 (1)	0	0	0
Muscular weakness	2 (1)	0	2 (1)	0	0	0
Malignant melanoma	2 (1)	0	2 (1)	0	0	0

Source: RAE.xpt and AE.xpt datasets
Abbreviations in Table: PPES, Palmar-plantar erythrodysesthesia syndrome;
[1] cutaneous squamous cell carcinoma includes preferred terms squamous cell carcinoma, and squamous cell carcinoma of the skin

The review further analyzed the following significant AEs:

- Palmar-plantar erythrodysesthesia syndrome (PPES)
- Uveitis

Palmar-Plantar erythrodysesthesia syndrome (PPES)

PPES occurred in 37 (20%) dabrafenib-treated patients and in one (2%) DTIC-treated patient. There were no cases of serious or Grade 4 PPES AEs reported. Four dabrafenib-treated patients

(2%) compared to no DTIC-treated patients experienced Grade 3 PPES. The median time to onset of first occurrence of PPES was 22 days (range 1 to 100 days) in dabrafenib-treated patients. No cases of PPES led to treatment withdrawal. Six (3%) patients required dose reduction of dabrafenib whereas the remaining patients with PPES continued on the same dose of dabrafenib uninterrupted. Of the 37 dabrafenib-treated patients with PPES, the outcome was not resolved in 62% and resolved in 32%.

Uveitis

One patient treated with dabrafenib developed iritis compared to no patients treated with DTIC. In addition, blurred vision occurred in three dabrafenib-treated patients and in none of the DTIC-treated patients. In the ISS database, there were six (1%) patients treated with dabrafenib who developed uveitis as listed in Table 42.

Table 41: All Cases of Uveitis. Dabrafenib Treatment Group. ISS Database.

Patient ID	Study Day	Grade	Intervention	Outcome	Duration (days)	Dose modification/
BRF113683.00007455	9	1	None	Resolved	16	None
BRF113929.00000652	195	2	Steroids and dilating eye drops	Resolved	35	Dose interrupted
BRF113929.00000852	65	2	Steroid and dilating eye drops	Ongoing	n/a	Dose interrupted
BRF113929.00001058	43	2	Steroid eye drops	Resolved	11	Dose reduced
BRF113710.00001026	190	2	Steroid and dilating eye drops	Resolved	19	None
BRF112680.00008201	67	2	Steroid and non-steroidal anti-inflammatory eye drops	Resolved	140	None

Abbreviations in Table: ID, Identification; n/a, not applicable

7.3.5 Submission Specific Primary Safety Concerns

Cardiac Valvular Disease

In a nonclinical toxicology study of dogs administered dabrafenib at doses of 50 mg/kg/day (approximately 9 times the human exposure at the recommended dose based on AUC) or greater for up to four weeks, cardiac atrioventricular valve hypertrophy/hemorrhage was observed. Patients with abnormal cardiac valve morphology (≥ Grade 2) or moderate valvular thickening as documented by echocardiogram were not eligible for the BRF113683 trial.

Four AEs related to cardiac valvular abnormalities occurred in three patients (2%) in the dabrafenib treatment group compared to none in the DTIC treatment group. Table 42 lists the cardiac valvular AEs reported in the BRF113683 trial.

Table 42: All Cases of Treatment-Emergent Adverse Events of Valvular Heart Disease. Dabrafenib Treatment Group. BRF113683 Trial.

Patient ID[1]	Age/ Sex	Cardiac History (Grade)	AE	Grade	Onset (Day)	Duration (days)	Action	Outcome
BRF113683.0004686	71/F	MV disease (1) AV disease (1) TV disease (1) LVEF decrease (2) Myocardial infarction Ventricular tachycardia	MV disease TV disease	2 2	40 40	-	Treatment withdrawn	Ongoing
BRF113683.0003083	41/F	None	MV incom-petence	1	85	72	None	Resolved/ recovered
BRF113683.0000600	81/F	Ventricular hypertrophy, Myocardial infarction	MV incom-petence	1	41	-	None	Ongoing

Abbreviations in Table: AE, adverse event; AV, aortic valve; F, female; LVEF, left ventricular ejection fraction; MV, mitral valve; TV, tricuspid valve.
[1] All cases occurred in the dabrafenib treatment group

REVIEWER COMMENTS:

1. *Two of the patients with cardiac valvular disease AEs, Patients BRF113683.0004686 and BRF113683.0000600, had cardiac disease at baseline. The third patient, Patient BRF113683.0003083, experienced mitral valve incompetence which the Applicant reported had resolved with continuation of dabrafenib without dose interruption or dose reduction.*
2. *Protocol BRF113683 provided specific treatment modifications for occurrence of cardiac valvular abnormalities (see Appendix 9.5, Table D); however, data pertaining to valvular abnormalities were not systematically collected. A general narrative data field in the eCRF was available to the investigator to record any findings considered abnormal, either clinically significant or not clinically significant. The BRF113683 protocol and SAP did not plan to conduct specific safety analyses of cardiac valvular toxicities.*

To examine the effect of dabrafenib on cardiac valvular function, the Applicant performed a blinded, centralized analysis of available echocardiograms from trial BRF113710. Cardiologists, blinded to the sequence of imaging and timepoint designation, assessed each cardiac valve for reduced excursion, regurgitation, stenosis, and valvular thickening as well as any cardiac wall motion abnormalities. Of note, there were no cardiac valvular abnormalities reported as AEs in the BRF113710 trial. Table 43 summarizes the results of the blinded, centralized independent analysis of echocardiograms from trial BRF113710.

Table 43: Blinded Central Analysis of Valvular Abnormalities on Serial Echocardiograms. BRF113710 Trial.

	Baseline	Week 6	Week 12	Week 20	Week 28	Week 36	Worst case on therapy[1]
	N=73 n (%)	N=67 n (%)	N=62 n (%)	N=46 n (%)	N=32 n (%)	N=8 n (%)	N=81 n (%)
Abnormal Cardiac Wall Motion							
Present	1 (1)	0	0	1 (2)	0	0	1 (1)
Aortic Valve							
Excursion reduced	2 (3)	1 (1)	2 (3)	1 (2)	2 (6)	2 (25)	4 (5)
Regurgitation	10 (14)	8 (12)	7 (11)	4 (9)	1 (3)	1 (13)	12 (15)
Thickening	8 (11)	7 (10)	9 (15)	8 (17)	4 (13)	3 (38)	16 (20)
Stenosis	2 (3)	1 (1)	1 (2)	2 (4)	2 (6)	2 (25)	3 (4)
Mitral Valve							
Excursion reduced	0	0	0	0	0	0	0
Regurgitation	22 (30)	26 (39)	18 (29)	17 (37)	9 (28)	0	42 (52)
Thickening	0	0	0	1 (2)	2 (6)	0	3 (4)
Stenosis	0	0	0	0	0	0	0
Pulmonic Valve							
Excursion reduced	0	0	0	0	0	0	0
Regurgitation	15 (21)	9 (13)	12 (19)	6 (13)	5 (16)	2 (25)	20 (25)
Thickening	0	0	0	0	0	0	0
Stenosis	0	0	0	0	0	0	0
Tricuspid Valve							
Excursion reduced	0	0	0	0	0	0	0
Regurgitation	29 (40)	29 (43)	27 (44)	19 (41)	14 (44)	5 (63)	46 (57)
Thickening	0	0	0	0	0	0	1 (1)
Stenosis	0	0	0	0	0	0	0

Source: BRF113710 CSR, Table 38
[1] Worst case on therapy may include unscheduled visits that were analyzed centrally but are not shown elsewhere in the table.

REVIEWER COMMENTS:

1. *The reviewer performed a worst-case analysis of valvular regurgitation by toxicity severity grade which demonstrated that, of the 49 patients with baseline assessments of valvular regurgitation, 21 patients had a post-baseline increase (≥ 1 grade) in toxicity grade in at least one cardiac valve. Of these, the review identified six events in four patients with a ≥ 2 Grade increase from baseline in valve regurgitation. Confounders in this analysis include valvular disease present at baseline and/or prior use of chemotherapy associated with cardiac toxicity.*

2. *The Applicant did not include valvular abnormalities in its risk management proposal based on the observation of these abnormalities in a minority of patients in the integrated population and on its determination that the central analysis of echocardiograms in BRF113710 presented in Table 43 was not representative of a drug effect.*
3. *The results of the centralized analysis of valvular abnormalities in BRF113710 may not be extrapolated to patients receiving the HPMC formulation of dabrafenib (i.e., to-be-marketed formulation) based on its increased bioavailability compared to the gelatin capsule formulation of dabrafenib, the formulation administered in trial BRF113710.*
4. *Taken together, the data submitted are insufficient to conclude that dabrafenib causes valvular toxicities. However, the data support further evaluation of this potentially serious condition as a postmarketing requirement.*

Renal Failure

The Applicant identified renal failure as an AE of special interest. The incidence of renal events did not appear to be increased among patients treated with dabrafenib compared to patients treated with DTIC in trial BRF113683; no dabrafenib-treated patients or DTIC-treated patients experienced renal failure and neither treatment group developed Grade 3 or 4 elevations in creatinine based on laboratory monitoring. In an analysis of the ISS database, the Applicant identified seven patients (1.2%) with renal failure. According to the review of the submitted data, identification of renal failure as an adverse drug reaction based on direct effects of dabrafenib on the kidney rather than as sequelae of other adverse reactions of dabrafenib (e.g., serious febrile drug reactions and dehydration) is considered inconclusive.

Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

Patients with known G6PD deficiency were not eligible to receive dabrafenib, a sulfonamide, in the melanoma development program because of a theoretical risk of hemolytic anemia. However, the proposed labeling of dabrafenib does not communicate this potential risk. The Applicant states that, unlike sulfamethoxazole, primaquine, dapsone, dabrafenib does not contain an aryl amine that can undergo oxidation to hydroxylamine and potentially cause hemolytic anemia; furthermore, the Applicant reports that amino-pyrimidine nitrogen of dabrafenib does not readily undergo oxidation and there has been no evidence of metabolic oxidation or other metabolism at this position in vitro or in vivo.

REVIEWER COMMENT:
Based on discussions with the FDA Clinical Pharmacology and Pharmacology/Toxicology reviewers, the Applicant has not provided adequate evidence to support the proposed exclusion of this potential risk.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most frequent affected (≥ 10% in either treatment group) MedDRA System Organ Classes (SOCs) in either treatment group in the BRF113683 trial were:

- Skin and subcutaneous disorders (80% in the dabrafenib group vs. 24% in the DTIC group)
- General disorders and administration site conditions (64% vs. 49%)
- Musculoskeletal and connective tissue disorders (54% vs. 27%)
- Nervous system disorders (50% vs. 22%)
- Gastrointestinal disorders (47% vs. 68%)
- Neoplasms benign, malignant and unspecified (incl cysts and polyps) (43% vs. 3%)
- Infections and Infestations (32% vs. 27%)
- Respiratory, thoracic and mediastinal disorders (28% vs. 19%)
- Metabolism and nutrition disorders (18% vs. 12%)
- Vascular disorders (15% vs. 12%)
- Investigations (14% vs. 15%)
- Eye disorders (11% vs. 9%)
- Cardiac disorders (10% vs. 5%)
- Injury, poisoning and procedural complication (9% vs. 10%)
- Psychiatric disorders (7% vs. 12%)
- Blood and lymphatic system disorders (6% vs. 27%)

Table 44 lists TEAEs occurring at ≥5% incidence in the dabrafenib treatment group. The most common TEAEs (≥10%) occurring more frequently (≥5%) in the dabrafenib group compared to DTIC were hyperkeratosis (37% vs. 0), headache (32% vs. 8%), pyrexia (28% vs. 10%), arthralgia (27% vs. 2%), papilloma (27% vs. 2%), alopecia (22% vs. 2), palmar-plantar erythrodysesthesia syndrome (20% vs. 2%), rash (17% vs. 0), cough (12% vs. 5%), back pain (12% vs. 7%), myalgia (11% vs. 0), and nasopharyngitis (10% vs. 3%). Nausea, vomiting, neutropenia, abdominal pain, anemia, and leukopenia occurred less frequently in the dabrafenib treatment group.

Table 44: Incidence of Treatment-Emergent Adverse Events (≥5% of Dabrafenib-Treated Patients) by Treatment Group. Safety Population. BRF113683 Trial.

	Dabrafenib N=187 n (%)		DTIC N=59 n (%)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Hyperkeratosis	69 (37)	2 (1)	0	0
Headache	59 (32)	0	5 (8)	0
Pyrexia	52 (28)	6 (3)	6 (10)	0
Arthralgia	51 (27)	2 (1)	1 (2)	0
Papilloma[1]	51 (27)	0	1 (2)	0
Alopecia	41 (22)	0	1 (2)	0
PPES	37 (20)	4 (2)	1 (2)	0
Fatigue	36 (19)	2 (1)	14 (24)	0
Nausea	35 (19)	1 (1)	29 (49)	0
Asthenia	33 (18)	1 (1)	9 (15)	1 (2)
Rash	31 (17)	0	0	0
Vomiting	23 (12)	2 (1)	15 (25)	0
Cough	23 (12)	0	3 (5)	0
Back pain	22 (12)	5 (3)	4 (7)	0
Constipation	21 (11)	3 (2)	8 (14)	0
Diarrhea	20 (11)	1 (1)	7 (12)	0
Myalgia	20 (11)	0	0	0
Nasopharyngitis	19 (10)	0	2 (3)	0
Chills	17 (9)	0	1 (2)	0
Pain in extremity	16 (9)	1 (1)	7 (12)	0
Decreased appetite	16 (9)	0	5 (9)	2 (3)
Dry skin	16 (9)	0	0	0
Erythema	14 (8)	0	1 (2)	0
cuSCC[2]	14 (7)	8 (4)	0	0
Musculoskeletal pain	13 (7)	0	2 (3)	0
Dyspnea	12 (6)	2 (1)	2 (3)	0
Actinic keratosis	12 (6)	0	0	0
Paresthesia	11 (6)	1 (1)	2 (3)	0
Seborrheic keratosis	10 (5)	0	0	0
Pruritus	10 (5)	0	1 (2)	0
Upper abdominal pain	9 (5)	0	1 (2)	0
Peripheral edema	9 (5)	0	5 (9)	0
Weight decreased	9 (5)	0	1 (2)	0

	Dabrafenib N=187 n (%)		DTIC N=59 n (%)	
	All Grades	Grades 3-4	All Grades	Grades 3-4
Acrochordon	9 (5)	0	0	0
Melanocytic nevus	9 (5)	0	0	0
Oropharyngeal pain	9 (5)	0	1 (2)	0
Skin lesion	9 (5)	0	0	0

Source: RRAND.xpt, RRANDALL, RAE.xpt, RExposur.xpt, AE.xpt
Abbreviations in Table: PPES, palmar-plantar erythrodysesthesia syndrome
[1] Composite term for AEs of skin papilloma, papilloma.
[2] Composite term for AES of squamous cell carcinoma of the skin, squamous cell carcinoma, keratoacanthoma.

Of note, analysis of abdominal pain based on a composite of MedDRA preferred terms (i.e., abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal tenderness) demonstrated a lower incidence of abdominal pain (all Grade and Grade 3-4) in the dabrafenib treatment group compared to the DTIC treatment group, 9% vs. 20% for all Grades and <1% vs. 3%, respectively.

The review of safety evaluated additional potential toxicities of dabrafenib through analyses of the incidence of AEs based on hierarchical composites of MedDRA preferred terms (i.e., high level terms) and a hierarchical composites of MedDRA high-level terms (i.e., high-level group terms) in each treatment group. As summarized in Table 45, the following additional potential toxicities, based on the analysis of HLTs, occurred more frequently in the dabrafenib treatment group compared to the DTIC treatment group: upper respiratory tract infections (16% vs. 7%), skin neoplasms malignant and unspecified (excl melanoma) (7% vs. 0), and bacterial infections (5% vs. 0). The "skin neoplasms malignant and unspecified (excl melanoma) HLT consisted of fourteen patients, all treated with dabrafenib, who encountered the following treatment-emergent malignant or unspecified skin neoplasms: cutaneous squamous cell carcinoma (n=3), basal cell carcinoma (n=5), keratoacanthoma (n=5), and an unspecified skin neoplasm (n=1).

Table 45: Incidence of Treatment Emergent Adverse Events (≥ 10% of Dabrafenib-Treated Patients or ≥5% Higher in Dabrafenib Treatment Group) by High Level Term. Safety Population. BRF113683 Trial.

HLT	Dabrafenib N=187 n (%)	DTIC N=59 n (%)
Hyperkeratoses	71 (38)	0
Skin neoplasms benign	68 (36)	1 (2)
Asthenic conditions	66 (35)	23 (39)
Headaches NEC	59 (32)	5 (8)
Joint related signs and symptoms	54 (29)	1 (2)
Musculoskeletal and connective tissue pain and discomfort	53 (28)	12 (20)
Febrile disorders	52 (28)	6 (10)
Nausea and vomiting symptoms	47 (25)	35 (59)
Alopecias	43 (23)	1 (2)
Dermal and epidermal conditions NEC	37 (20)	2 (3)
Skin and subcutaneous conditions NEC	37 (20)	1 (2)
Rashes, eruptions and exanthems NEC	34 (18)	0
Upper respiratory tract infections	30 (16)	4 (7)
Coughing and associated symptoms	26 (14)	4 (7)
Feelings and sensations NEC	21 (11)	1 (2)
Gastrointestinal atonic and hypomotility disorders NEC	21 (11)	8 (14)
Diarrhea (excl infective)	20 (11)	7 (12)
Muscle pains	20 (11)	0
Paresthesias and dysesthesias	19 (10)	2 (3)
Erythemas	16 (9)	1 (2)
Skin neoplasms malignant and unspecified (excl melanoma)	14 (7)	0
Neoplasms benign site unspecified NEC	13 (7)	0
Pruritus NEC	13 (7)	1 (2)
Skin preneoplastic conditions NEC	12 (6)	0
Bacterial infections NEC	10 (5)	0

Table 46 summarizes the incidence of HLGTs occurring in ≥ 10% of dabrafenib treated patients or occurring more frequently (≥5%) in the dabrafenib treatment group compared to the DTIC treatment group.

Table 46: Most Common Treatment Emergent Adverse Events (≥ 10% of Dabrafenib-Treated Patients or ≥5% Higher in Dabrafenib Treatment Group) by High Level Group Term by Treatment Group. Safety Population. BRF113683 Trial.

HLGT	Dabrafenib N=187 n (%)	DTIC N=59 n (%)
General system disorders NEC	92 (49)	27 (46)
Epidermal and dermal conditions	89 (48)	9 (15)
Cornification and dystrophic skin disorders	76 (41)	0
Cutaneous neoplasms benign	68 (36)	1 (2)
Headaches	60 (32)	5 (8)
Gastrointestinal signs and symptoms	59 (32)	37 (63)
Skin appendage conditions	57 (30)	6 (10)
Joint disorders	56 (30)	1 (2)
Musculoskeletal and connective tissue disorders NEC	55 (29)	14 (24)
Body temperature conditions	53 (28)	6 (10)
Respiratory disorders NEC	49 (26)	7 (12)
Infections - pathogen unspecified	44 (24)	14 (24)
Gastrointestinal motility and defecation conditions	38 (20)	12 (20)
Skin and subcutaneous tissue disorders NEC	37 (20)	1 (2)
Neurological disorders NEC	35 (19)	9 (15)
Muscle disorders	23 (12)	2 (3)
Skin neoplasms malignant and unspecified	17 (9)	0
Miscellaneous and site unspecified neoplasms benign	14 (7)	0
Bacterial infectious disorders	13 (7)	0

7.4.2 Laboratory Findings

Laboratory testing of clinical chemistry parameters (sodium, potassium, BUN, creatinine, glucose, calcium, magnesium, phosphate, ALT, AST, alkaline phosphatase, total bilirubin, and LDH), cardiac troponin I (drawn at baseline and subsequently if clinically indicated, serum β-hCG (at baseline if indicated), hematology parameters [white blood cell count (WBC) with differential, hemoglobin, hematocrit, platelet count, and absolute neutrophil count (ANC)] was performed at baseline and on Day 1 of each treatment Cycle. The most common (≥10%) laboratory abnormalities (all Grades), which represented an increase from baseline in toxicity grade, in the dabrafenib treatment group compared to DTIC were hyperglycemia (50% vs. 42%), hypophosphatemia (35% vs. 14%), anemia (21% vs. 36%), increased alkaline phosphatase (19% vs. 14%), lymphopenia (18% vs. 27%), leukopenia (11% vs. 44%), and increased ALT (11% vs. 22%). Grade 3 or 4 laboratory abnormalities occurring more frequently in dabrafenib-treated patients include hyperglycemia (6% vs. 0) and decreased phosphorus (5% vs. 2%).

Table 47: Incidence of Treatment-Emergent (Increased from Baseline) Grade 1-4 Laboratory Abnormalities (≥10% of Dabrafenib-Treated Patients) by Treatment Group. Safety Population. BRF113683 Trial.

	Dabrafenib N=187 n (%)		DTIC N=59 n (%)	
	All Grades	**Grades 3-4**	**All Grades**	**Grades 3-4**
Hyperglycemia	93 (50)	12 (6)	25 (42)	0
Hypophosphatemia	66 (35)	9 (5)	8 (14)	1 (2)
Anemia	40 (21)	1 (1)	21 (36)	3 (5)
Increased Alkaline phosphatase	36 (19)	0	8 (14)	1 (2)
Lymphopenia	33 (18)	7 (4)	16 (27)	5 (9)
White blood cell count	21 (11)	0	26 (44)	8 (14)
Increased alanine aminotransferase	21 (11)	2 (1)	13 (22)	0

Source: LAB.xpt

REVIEWER COMMENTS:

1. *There were no Grade 4 liver function abnormalities in either treatment group. Increases from baseline in toxicity grade of total bilirubin were uncommon in both treatment groups, 4/187 (2.1%) in the dabrafenib treatment group and 1/59 (2%) in the DTIC treatment group, and all limited to Grade 1 elevations. The two patients (Patient BRF113683.0004043 and BRF113683.0010607) with Grade 3 ALT elevations, both in the dabrafenib treatment group, also had liver metastases.*
2. *This reviewer's analysis of the laboratory datasets of the BRF113683 trial and the ISS database laboratory dataset did not identify any Hy's Law cases.*

7.4.3 Vital Signs

In the BRF113683 trial, vital signs were collected at baseline and every three weeks thereafter. With the exception of body temperature, there were no clinically meaningful changes in vital signs based on analyses of central tendency as well as in analyses of categorical changes in vital signs from baseline. Pyrexia, including clinically meaningful events, occurred more frequently in the dabrafenib treatment group compared to the DTIC treatment group (see Section 7.3.2).

The incidence of fever (body temperature ≥38ºC) was increased in the dabrafenib treatment group compared to the DTIC treatment group, 12% vs. 7%, respectively, in an analysis of the worst case change from baseline in body temperatures (Table 48).

Table 48: Worse Case Change from Baseline in Temperature by Treatment Group. Subgroup of Patients with ≥1 On-Study Temperature Measurement. BRF113683 Trial.

	Dabrafenib N=185				DTIC N=57			
Worst On-study Temp, °C:	≤35	>35-<38	≥38	Total	≤35	>35-<38	≥38	Total
Baseline Temp, °C								
≤35	0	1 (<1%)	0	1 (<1%)	0	0	0	0
>35-<38	0	158 (85%)	22 (12%)	180 (97%)	0	53 (93%)	4 (7%)	57 (100%)
≥38	0	1 (<1%)	0	1 (<1%)	0	0	0	0
Missing	0	3 (2%)	0	3 (2%)	0	0	0	0
Total	0	163 (88%)	22 (12%)	185 (100%)	0	53 (93%)	4 (7%)	57 (100%)

Source: BRF113683 CSR, pages Page 1592, 1596
Abbreviations in Table: C, Celsius; Temp, temperature

7.4.4 Electrocardiograms (ECGs)

The BRF113683 trial collected serial ECGs using an ECG machine that automatically calculated heart rate and measured PR, QRS, QT, and corrected QT (QTc) intervals at baseline, Week 3, Week 6, Week 12, Week 21, and every nine weeks thereafter. The protocol required collection of triplicate ECGs if the initial test was abnormal.

Of the 187 patients treated with dabrafenib and the 59 patients treated with DTIC, 159 (85%) and 43 (73%), respectively, had a corrected QT interval assessed based on Bazett's formula (QTcB). Six patients (4%) in the dabrafenib treatment group and two patients (5%) in the DTIC treatment group developed a QTcB value greater than 480 msec and less than 500 msec. No patient in either treatment group developed a QTcB value > 500 msec. In addition, there were no patients with elevations in corrected QT intervals using methods other than QTcB.

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

REVIEWER COMMENT:
According to review of the submitted data, the effect of dabrafenib on the QT interval is inconclusive. The Applicant is performing a dedicated, placebo-controlled, blinded trial (BRF113773) to evaluate the effect of dabrafenib and its metabolites on cardiac repolarization.

Completion of the BRF113773 trial and submission of the final study report with the primary data will be a post-marketing requirement.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

No formal immunogenicity studies were required or were conducted by the Applicant. An analysis of anaphylactic / anaphylactoid shock conditions using Standard MedDRA Queries terminology (SMQ/Narrow) for the BRF113683 trial did not identify any dabrafenib-treated patients who met the criteria for this SMQ.

In the ISS database, the Applicant reported several dabrafenib-related hypersensitivity reactions:

- Patient 22201, a 68-year-old man with NSCLC, enrolled in trial BRF113928 experienced a Grade 2 blistering rash on the limbs on the same day as the start of dabrafenib 150 mg orally twice daily. The rash resolved after withholding dabrafenib. On Day 8, the patient was rechallenged with a single dose of dabrafenib and a Grade 2 blistering rash recurred 4 hours post-dose. The patient discontinued use of dabrafenib.
- Patient 101206, a 67-year-old man enrolled in a rollover trial for dabrafenib, was noted to have an elevated creatinine. A renal biopsy showed granulomatous interstitial nephritis, consistent with a drug hypersensitivity reaction. The investigator concluded that the nephritis and renal insufficiency were attributable to the study drug. The patient discontinued use of dabrafenib. The Applicant reported that the event was ongoing.
- Patient BRF113220.0000518, a 31-year-old woman with metastatic melanoma, developed on Day 2 a Grade 2 rash on her back, thighs, face and neck followed by flu-like symptoms (Grade 1) in association with eyelid swelling on Day 3 while receiving dabrafenib monotherapy. The patient also developed a Grade 2 fever on Day 5. On Days 3-4, the patient received a reduced dose of dabrafenib due to this event, and she returned to full doses of dabrafenib on Day 5. The flu-like symptoms resolved on Day 5.
- Patient BRF113683.D000177, a 57-year-old woman with metastatic melanoma, on crossover therapy with dabrafenib, developed on Day 2 a Grade 1 “allergic reaction on IP [investigational product] (fever, burning and hyperemia of the face skin)” which increased to Grade 2 on Day 5 before resolving on Day 7. The patient withheld dabrafenib dosing on Days 6 and 7. Upon rechallenge with dabrafenib, the same adverse reaction recurred beginning on Day 8 requiring further treatment interruption (Days 12 to 20) followed by administration of a reduced dose of dabrafenib beginning on Day 21. This AE resolved on Day 19.

REVIEWER COMMENT:
According to review of the submitted data, the reviewer agrees with the Applicant's proposed inclusion of hypersensitivity in the Adverse Reactions section of labeling under the clinically important adverse reaction observed in < 10% of patients treated with dabrafenib.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

According to the Clinical Pharmacology NDA review, population pharmacokinetic (PK) and exposure-response (E-R) analyses using PK data from Phase 1-3 trials in patients did not identify significant covariates influencing dabrafenib PK or evident E-R relationships for effectiveness and safety.

Please see the FDA Clinical Pharmacology NDA review for additional details.

7.5.2 Time Dependency for Adverse Events

Please see sections 7.3.2 (cutaneous squamous cell carcinoma, new primary melanoma, pyrexia), 7.3.4 (palmar-plantar erythrodysesthesia), and 7.3.5 (cardiac valvular AEs) for analyses of time dependency for AEs.

7.5.3 Drug-Demographic Interactions

In the BRF113683 trial, patients age 65 years or older represented 21% and 20% of the dabrafenib- and DTIC treatment groups, respectively, whereas female patients represented 40% and 42% of the dabrafenib- and DTIC treatment groups, respectively. The incidence of any AE (all grades) was similar across these demographic subgroups within each treatment arm. The incidence of Grade 3 or 4 AEs was similar in female and male patients within each treatment group, 29% vs. 36% in the dabrafenib treatment group and 44% vs. 41% in the DTIC treatment group, respectively. However, the incidence of Grade 3 or 4 AEs was higher in patients age 65 years or older compared to patients younger than 65 years, 50% vs. 29% and 58% vs. 38% in the in the dabrafenib- and DTIC treatment groups, respectively. The incidence of serious AEs was higher in patients age 65 years or older and in men, a finding which was similar in both treatment groups. Table 49 summarizes the incidence of AEs by toxicity grade as well as serious AEs by age and gender subgroups.

Table 49: Incidence of Major Safety Findings by Treatment Group. Age (< 65 vs. ≥65) and Gender Subgroups. BRF113683 Trial.

	Age Subgroup				Gender Subgroup			
	Dabrafenib		DTIC		Dabrafenib		DTIC	
	<65 N=147 n (%)	≥65 N=40 n (%)	<65 N=47 n (%)	≥65 N=12 n (%)	Female N=75 n (%)	Male N=112 n (%)	Female N=25 n (%)	Male N=34 n (%)
ALL GRADE AE	145 (99)	40 (100)	43 (91)	11 (92)	74 (99)	111 (99)	23 (92)	31 (91)
Grade 3-4	42 (29)	20 (50)	18 (38)	7 (58)	22 (29)	40 (36)	11 (44)	14 (41)
Grade 4	7 (5)	0	9 (19)	0	2 (3)	5 (4)	3 (12)	6 (18)
Any SAE	30 (20)	13 (33)	9 (19)	4 (33)	12 (16)	31 (28)	3 (12)	10 (29)
AE leading to withdrawal	1 (1)	4 (10)	2 (4)	0	2 (3)	3 (3)	1 (4)	1 (3)

Abbreviations in Table: AE, adverse event, SAE, serious adverse event.

REVIEWER COMMENTS:

1. *The safety review included analyses of Grade 3 or 4 TEAEs at the level of MedDRA preferred terms within age and gender subgroups. Several exploratory analysis methods, including analyses of attributable and relative risk, did not identify any substantial differential effects of dabrafenib (compared to DTIC) on the occurrence of specific Grade 3 or 4 AEs in age or gender demographic subgroups. The strength of these analyses was limited by the small numbers in the comparator DTIC subgroups enrolled in the BRF113683 trial.*
2. *Ninety-nine percent (243/246) of the patients in the safety population were Caucasians which precluded safety analyses based on racial subgroups.*

7.5.4 Drug-Disease Interactions

Please refer to the FDA Clinical Pharmacology NDA review for details. This review recommends that the Applicant perform trials in patients with impaired renal and hepatic function as post-marketing requirements.

7.5.5 Drug-Drug Interactions

Please refer to Section 4.4.3 and to the FDA Clinical Pharmacology NDA review for details.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The Applicant did not conduct carcinogenicity studies with dabrafenib. Of note, dabrafenib increased the risk of cutaneous squamous cell carcinomas in patients in clinical trials (see Section 7.3.2).

7.6.2 Human Reproduction and Pregnancy Data

There are no data available on the use of dabrafenib in pregnant or lactating women.

7.6.3 Pediatrics and Assessment of Effects on Growth

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

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Applicant defined an overdose of dabrafenib as doses > 300 mg as a single dose or > 600 mg daily based on the administration of dabrafenib at doses up to 300 mg twice daily in the first-in-human trial, BRF112680. In the ISS database, there were no patients who received a dabrafenib dose in excess of these thresholds. In the development program of dabrafenib monotherapy, the Applicant identified one patient who received repeated, total daily doses of 900 mg of dabrafenib (administered as 300 mg three times daily) for 47 out of 48 days. The Applicant reported that this patient did not experience any AEs during this time period.

7.7 Additional Submissions / Safety Issues

Safety analyses of the BRF113683 trial based on Standardized MedDRA Queries (Narrow Based) did not identify additional safety signals.

8 Postmarket Experience

Not applicable to this new molecular entity with no prior approval history.

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

Please refer to the package insert of Tafinlar.

9.3 Advisory Committee Meeting

The Division did not obtain the advice of the Oncologic Drugs Advisory Committee (ODAC) for this application.

9.4 Non-cutaneous New Primary Malignancies/Malignancy Progression

Table A: All Cases of Non-cutaneous New Primary Malignancies / Malignancy Progression in Development Program of Dabrafenib as Monotherapy (b) (4) (Excludes Cases in the ISS Database).

Study/ Pt ID/ Age/Sex	Other IP	Study Day	New Primary Tumor	Additional Features	Treatment/ Outcome/ Disposition	Molecular and Other Analyses Performed	Comments
BRF114144/ 101113/ 50/F	None	115	Myelodysplastic syndrome	NR	NR/ Unresolved/ Dabrafenib continued	NR	Patient was heavily pretreated with chemotherapeutics including alkylating agents
BRF113252/ IT78/ 72/M	None	42	Gastric adenocarcinoma	Elevated tumor markers (CEA= 9.6 / CA 19-9=54)	Surgery/ NR/ Dabrafenib continued	NR	-
BRF113252/ US5/ 64/F	None	365	Invasive ductal carcinoma of the breast	NR	Surgery, radiotherapy, and anti-estrogen therapy/ Unresolved / Dabrafenib continued	ER positive, HER2 negative	Lesion in breast present prior to starting therapy
BRF113220/ 951/ 48/M	GSK1120212 (trametinib)	BL[1]	Renal cell carcinoma	Fuhrman Grade 2	NR/ Unresolved/ NR	NR	Lesion in kidney present at baseline--only site of patient's widespread disease that had not responded.
BRF113220/ 2183/ 62/M	GSK1120212 (trametinib)	426	Squamous cell carcinoma of the head and neck	1/31 lymph nodes positive	Surgery/ Resolved/ NR	HPV 16(+), p16(+); bcl-2(-); RAS wild type	-
BRF113220/ 2442/ 55/F	GSK1120212 (trametinib)	213	Glioblastoma	PNET-like foci present; SOX-2(+), WT-1(+), GFAP (+), IDH-1(-), P53(+ in 1%)	Surgery/ Resolved/ NR	Negative for: EGFR amplification, PTEN deletion, Deletion of 1P or 19Q	Baseline MRI of brain was unremarkable; Follow-up MRI after 5 months showed an atypical appearance
BRF113220/ 2858/ 62/M	GSK1120212 (trametinib)	362	Pancreatic adenocarcinoma	CA19.9=1,893 IU/mL	Palliative stent/ Unresolved/ IPs Discontinued	KRAS (G12D); ERBB4 (R103C)	Whipple planned but disease was too widespread at laparotomy

Study/ Pt ID/ Age/Sex	Other IP	Study Day	New Primary Tumor	Additional Features	Treatment/ Outcome/ Disposition	Molecular and Other Analyses Performed	Comments
BRF113220/ 2918 BRF113252/ AUS66 57/M	GSK1120212 (trametinib)	95	Recurrent metastatic colon adenocarcinoma	CEA elevated in pleural fluid	Surgery and radiation/ NR/ IPs Discontinued	KRAS mutant (consistent with primary tumor), BRAF wild type	Dukes B CRC diagnosed surgically resected 3y prior; Brain met resected as only site of PD and found to be CRC.

Abbreviations in Table: CRC, colorectal cancer; F, female; IP, investigational product; M, male; NR, not reported
[1] RCC diagnosed on Day 485 but lesion was present at baseline (BL)

REVIEWER COMMENT:
All cases reported in Table A occurred in patients with melanoma with the exception of Patient 101113 who was being treated for ovarian carcinoma. Stage information for the new primary malignancies was not reported in all but one case.

9.5 Treatment Modification Plan for Toxicity, BRF113683 Protocol

GSK2118436 (Dabrafenib) Treatment Modification Guidelines:

- Rash (Table B)
- Hand-foot skin reaction (Table C)
- Ejection fraction changes (Table D)
- Renal insufficiency (Table E)
- Fever (Table F)
- Neutropenia (Table G)
- Liver function testing abnormalities.

Table B: Rash. GSK2118436 Dose Modification and Management Guidelines. BRF113683 Protocol.

Skin Toxicity Grade	Management	Dose Modification[1]
1	Topical corticosteroids (mometasone, betamethasone, or fluocinonide creams)	None
2	As for Grade 1, with the addition of diphenhydramine oral prednisone (short course)[2]	None: if unacceptable to patient or medically concerning then hold until recovery to ≤ Grade
≥3		Hold until recovery to ≤ Grade 1.Then reduce the dose by one dose level

[1]If no recovery after 2 weeks of holding drug, patients must be withdrawn from study treatment unless in the opinion of the investigator and GSK medical monitor, there is a reason to believe that the patient will experience clinical benefit from future treatment.
[2]For patients with Grade 3 or 4 extensive or symptomatic dermatologic event, or chronic, persistent or recurring lower grade skin events, dermatology consult is encouraged.

Table C: Hand-Foot Skin Reaction. GSK2118436 Dose Modification and Management Guidelines. BRF113683 Protocol.

Grade	Occurrence	Management and Dose Modification[1]
1	Any	• Continue treatment with GSK2118436 and start topical therapy[b] for symptomatic relief
2	1st	• Continue treatment with GSK2118436 and start topical therapy[2] for symptomatic relief. • Instruction on life-style modifications.[3] • If no improvement within 28 days, see below
	No improvement within 28 days or additional occurrence	• Interrupt GSK2118436 treatment until toxicity resolves to Grade 0-1. • Decrease GSK2118436 dose by one dose level. • Continue topical therapy[b] for symptomatic relief. • Instruction on life-style modifications.[c]
	4th	• Discontinue GSK2118436
3 (or intolerable 2)	1st or 2nd	• Interrupt GSK2118436 treatment until toxicity resolves to Grade 0-1. • Decrease GSK2118436 dose by one dose level. • Continue topical therapy[b] for symptomatic relief. • Instruction on life-style modifications.[c]
	3rd	• Discontinue GSK2118436

[1]. No dose adjustment is required on the basis of patient age, gender, or body weight.
[2]. Topical therapy includes the following options; keratolytics (e.g. urea 40%), emollients, high potency corticosteroids, (fluocinonide, clobetasol) oral analgesia (non-steroidal anti-inflammatories or narcotics)
[3]. Lifestyle modifications include; avoidance of excessive temperatures, exercise, and ill-fitting clothing/shoes.

Table D: LVEF And Valvular Toxicity. GSK2118436 Dose Modification and Management Guidelines. BRF113683 Protocol.

Toxicity Description	Management	Dose Adjustment of GSK2118436
LVEF Asymptomatic, absolute decrease of >10% in LVEF compared to baseline and the EF is < the institution's lower limit of normal (LLN) VALVULAR Asymptomatic, Moderate regurgitation or stenosis by ECHO (Grade 2 mitral/tricuspid/aortic valvular toxicity)	• Interrupt GSK2118436 • Repeat evaluation of LVEF in 1 week • Repeat ECHO every 1-2 weeks for 4 weeks or until toxicity resolves[1]	Toxicity resolves[a] within 4 weeks • Restart on reduced dose and monitor by ECHO after 2, 4, 8, 12, 16 weeks then per protocol Toxicity does not recover within 4 weeks • Permanently discontinue and consider evaluation by a cardiologist. Perform monitoring by ECHO every 4 weeks for 16 weeks or until resolution
Grade 3 or 4 (symptomatic) LVEF Grade 3 or 4 left ventricular cardiac dysfunction VALVULAR Severe regurgitation/stenosis by imaging with symptoms controlled by medical intervention	• Discontinue GSK2118436 • Monitor LVEF every 4 weeks for 16 weeks or until resolution	Toxicity resolves[a] within 4 weeks • Restart GSK2118436 at reduced dose in consult with medical monitor

[1] LVEF, recover to above institutional LLN and within 10% of baseline; Valvular, recovers to baseline and symptom resolution (for severe valvular toxicity)

Table E: Renal Insufficiency. Dose Modification and Management Guidelines of GSK2118436. BRF113683 Protocol.

Category	Management
For patients with creatinine increase >0.2 mg/dL (18 umol/L) but ≤0.5 mg/dL (44 umol/L)	1. Re-check within 1 week 2. If patient has fever (T ≥ 38.5ºC): treat pyrexia as per guidelines (please note NSAIDs can induce renal insufficiency, especially in patients with dehydration); encourage oral fluids
Creatinine rise >0.5 mg/dL (44 umol/L) above baseline or creatinine >2 mg/dL (> 177 umol/L)	1.Interrupt GSK2118436 2.If patient has fever (T ≥ 38.5ºC): treat pyrexia as per guidelines (please note NSAIDs can induce renal insufficiency, especially in patients with dehydration); consider IV hydration 3. Follow creatinine at least twice weekly (or consider hospitalization if creatinine cannot be monitored frequently) 4. Consider renal consultation 5. May restart study treatment if creatinine normalizes or with approval of medical monitor. Restart may be at the same dose, or reduced by one dose level at the investigator's discretion. 6. Consider renal biopsy if clinically indicated, for example: a. Renal insufficiency persists despite volume repletion b. Subject has new rash or signs of hypersensitivity (such as elevated eosinophil count) 7. Prior approval of Medical Monitor required to re-initiate therapy if a. Subject's creatinine has not returned to baseline b. There is evidence of thrombotic microangiopathy

Table F: Fever. GSK2118436 Dose Modification and Management Guidelines. BRF113683 Protocol.

Category	Definition	Management	Dose Adjustment of GSK2118436
Complicated fever (≥38.5° C or 101.3° F)	Grade ≥3 or any grade with signs and symptoms including; rigors, dehydration, hypotension, dizziness or weakness	• Subject must be evaluated in clinic • Labs: Obtain blood sample to assess ANC, serum creatinine and BUN if sample was not collected within 3 days of the fever. Additionally blood sample for cytokine testing must also be drawn at the time of complicated fever and sent to central laboratory. • Evaluate for signs and symptoms of infection and consider work up as clinically indicated. • If signs and symptoms of dehydration occur, consider intravenous hydration. • When restarting drug, administer acetaminophen 500 mg or ibuprofen 400 mg (or suitable alternative) prophylactically BID with study drug for 2-3 days.1 • Re-check ANC 1 week after the start of fever; encourage patient to take oral temperature daily for 4 weeks after restarting GSK2118436.	• Interrupt GSK2118436 immediately and hold until fever resolves to <38.0 ^{0}C or 100.4 ^{0}F and accompanying symptoms resolve • At rechallenge reduce dose of GSK2118436 by one dose level.

Category	Definition	Management	Dose Adjustment of GSK2118436
Uncomplicated Fever (≥38.5^{0}C or 101.3 ^{0}F)	Grade≤ 2 without signs and symptoms as described above	• Encourage oral hydration. • If patient is seen in the clinic: obtain blood sample to assess ANC, serum creatinine and BUN if sample was not collected within 3 days of the fever and obtain blood sample for cytokine testing (cytokine sample must be sent to central laboratory.) • Evaluate for signs and symptoms of infection and consider work up as clinically indicated. • If signs and symptoms of dehydration occur, follow algorithm for complicated fever. • When restarting drug, administer acetaminophen 500 mg or ibuprofen 400 mg (or suitable alternative) prophylactically BID with study drug for 2-3 days.[1] • Re-check ANC 1 week after the start of fever; encourage patient to take oral temperature daily for 4 weeks after restarting GSK2118436.	• Hold until fever resolves to <38.0 ^{0}C or 100.4 ^{0}F • GSK2118436 may be restarted at the original dose level or reduced one dose level as clinically indicated.

[1] If fever does not recur after 3 days, prophylactic antipyretics may be discontinued or tapered.

Table G: Neutropenia. GSK2118436 Dose Modification and Management Guidelines. BRF113683 Protocol.

Toxicity Grade	Management of Neutropenia	GSK2118436 Dose Adjustment
1	• Monitor per protocol time and events table	• Continue at current dose
2	• Re-check ANC in 1 week, if improvement to Grade 1, continue to monitor per protocol time and events table • Once stable at Grade 2, monitor every 2 weeks until resolution to Grade 1 or stable for 4 weeks.	• Continue at current dose
3	• Re-check ANC at least weekly during dose interruption • If resolved to Grade 1, recheck ANC 3 days after rechallenge with GSK2118436 and then 1 week later	• Interrupt dosing until return to Grade 1, the reduce one dose level • 1st recurrence: discontinue GSK2118436 or hold until return to Grade 1, then reduce one dose level • 2nd recurrence: discontinue GSK2118436
4	• Re-check ANC at least weekly • If resolved to Grade 1, recheck ANC 3 days after rechallenge with GSK2118436 and then 1 week later	• Discontinue or hold until return to Grade 1, then reduce GSK2118436 by one dose level • 1st recurrence: discontinue GSK2118436

Liver Chemistry Guidelines

The protocol specified immediate discontinuation of dabrafenib administration if a patient encountered any of the following liver chemistry abnormalities:

- ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) (or ALT≥3xULN and INR>1.5, if INR measured)

  NOTE: If serum bilirubin fractionation is not immediately available, study drug should be discontinued if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, record presence of detectable urinary bilirubin on dipstick, indicating direct bilirubin elevations and suggesting liver injury.

- ALT ≥ 8xULN
- ALT ≥ 5 x ULN but <8x ULN persists for ≥2 weeks
- ALT ≥ 3xULN if associated with the appearance or worsening of symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia.
- ALT ≥ 5xULN but <8 x ULN and cannot be monitored weekly for >2 weeks

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/s/

MARC R THEORET
05/15/2013

SUZANNE G DEMKO
05/15/2013
I have reviewed the contents of this document and agree with the contents and conclusions.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 202,806 **Applicant: GlaxoSmithKline** **Stamp Date: 07/30/2012**

Drug Name: (b) (4) (dabrafenib) **NDA/BLA Type: 505(b)(1), Original Application**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:	X			The attempt is appropriate based on the serious and life-threatening indication.
EFFICACY					

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: BREAK-3 Indication: advanced (unresectable Stage III) or metastatic BRAF ^{V600E} mutation-positive melanoma Pivotal Study #2 Indication:	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	There were no previous agreements regarding primary/secondary endpoints. (b) (4) [redacted]
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	BRF113683 was a multicenter, international study, which included U.S. study sites, conducted under IND 105032
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			

(b)

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			The assessment of the arrhythmogenic potential is adequate based on the serious and life-threatening indication. The applicant is planning to conduct a formal assessment of the arrhythmogenic potential of dabrafenib on the QT interval. GSK submitted the proposed QTc protocol (BRF113773) to FDA on 19APR12.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	A requisite number of patients was not provided to the applicant. The safety population for the ISS consists of 578 patients who received at least one dose of dabrafenib 150 mg BID. Of the safety population, 27% (n=157) were exposed to dabrafenib for >6 to 12 months and <1% (n=4) were exposed for > 12 months.
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			All trials included in the integrated summary of safety datasets used MedDRA v 14.1.

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			On 9/24/2012, GSK submitted the requested narratives for on-study patient deaths which were attributed to disease progression.
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			GSK is requesting waiver of pediatric studies for NDA 202806, (b) (4) (dabrafenib, formerly GSK2118436) Capsules for the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation. Dabrafenib received orphan designation on January 12, 2011, for treatment of BRAF V600 mutation positive Stage IIb through IV melanoma.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __YES_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Reviewing Medical Officer Date

Clinical Team Leader Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARC R THEORET
09/27/2012

SUZANNE G DEMKO
09/27/2012