CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

202806Orig1s002

Trade Name: **Tafinlar**

Generic Name: **dabrafenib**

Sponsor: **GlaxoSmithKline, LLC**

Approval Date: 01/09/2014

Indications: TAFINLAR is a kinase inhibitor indicated as a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.
TAFINLAR in combination with trametinib is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. The use in combination is based on the demonstration of durable response rate. Improvement in disease-related symptoms or overall survival has not been demonstrated for TAFINLAR in combination with trametinib.

CENTER FOR DRUG EVALUATION AND RESEARCH

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202806/S-002

ACCELERATED APPROVAL

GlaxoSmithKline, LLC
Attention: Eric Richards, M.S., M.P.H.
Director, Global Regulatory Affairs
1250 South Collegeville Road; UP4400
Collegeville, PA 19426

Dear Mr. Richards:

Please refer to your Supplemental New Drug Application (sNDA) dated July 8, 2013, received July 9, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Tafinlar (dabrafenib) capsules, 50 mg and 75 mg.

We acknowledge receipt of your amendment(s) dated August 28, 2013, September 12, 2013, September 24, 2013, October 4, 2013, October 14, 2013, October 18, 2013 (2), October 23, 2013, October 24, 2013, November 5, 2013 , November 6, 2013, November 7, 2013, November 8, 2013, November 20, 2013, November 22, 2013, December 13, 2013, January 7, 2014, and January 9, 2014.

This Prior Approval supplemental new drug application proposes to include a new indication for Tafinlar (dabrafenib), in combination with trametinib, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. This indication is based on the demonstration of durable response rate. Improvement in disease-related symptoms or overall survival has not been demonstrated for TAFINLAR in combination with trametinib

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes, and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 314.510, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such studies/clinical trials with due diligence. If the postmarketing trial described below fails to verify clinical benefit for Tafinlar (dabrafenib) capsules, 50 mg and 75 mg, or is not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 314.530, withdraw this approval.

Granting of this approval is contingent upon completion of a clinical trial to verify the clinical benefit of Tafinlar (dabrafenib) capsules, 50 mg and 75 mg. This postmarketing trial is subject to the reporting requirements of 21 CFR 314.81.

2115-1 To submit an efficacy supplement containing the final report, including summary analyses, datasets, and revised labeling based on the results of the ongoing MEK115306 trial, "A Phase III, Randomized, Double-Blinded Study, Comparing the Combination of the BRAF inhibitor, Dabrafenib and the MEK inhibitor, Trametinib to Dabrafenib and Placebo as First-Line Therapy in Subjects with unresectable

(Stage IIIC) or Metastatic (Stage IV) BRAF V600E/K Mutation-Positive Cutaneous Melanoma." Enrollment of approximately 340 patients is expected. The primary endpoint is progression-free survival. Overall survival is a key secondary endpoint.

The timetable you submitted on December 13, 2013, states that you will conduct this trial according to the following schedule:

Final Report Submission: August, 31, 2014

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2115-2 Complete and submit the final report, including datasets, for the ongoing MEK116513 trial, "A Phase III, Randomised, Open-Label Study Comparing the Combination of the BRAF Inhibitor Dabrafenib and the MEK Inhibitor Trametinib to the BRAF Inhibitor Vemurafenib in Subjects with Unresectable (Stage IIIC) or Metastatic (Stage IV) BRAF V600E/K Mutation-Positive Cutaneous Melanoma." Enrollment of approximately 694 patients is expected. The primary endpoint is overall survival.

The timetable you submitted on December 13, 2013, states that you will conduct this trial according to the following schedule:

Final Report Submission: June, 30, 2015

2115-3 Complete and submit a final report, including datasets, for Part C of trial BRF113220 that compares the combination of dabrafenib and trametinib to dabrafenib in patients with unresectable or metastatic BRAF V600E or V600K mutation-positive melanoma.

The timetable you submitted on December 13, 2013, states that you will conduct this trial according to the following schedule:

Final Report Submission: October, 31, 2014

Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Norma Griffin, Senior Regulatory Project Manager, at (301) 796-4255**.**

Sincerely,

{See appended electronic signature page}

Patricia Keegan, M.D.
Director
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S): Content of Labeling

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

/s/

PATRICIA KEEGAN
01/09/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202806Orig1s002

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TAFINLAR safely and effectively. See full prescribing information for TAFINLAR.

TAFINLAR (dabrafenib) capsules, for oral use
Initial U.S. Approval: 2013

RECENT MAJOR CHANGES

Indications and Usage (1.2)	01/2014
Dosage and Administration (2.1-2.3)	01/2014
Warnings and Precautions (5-5.9, 5.11)	01/2014

INDICATIONS AND USAGE

- TAFINLAR is a kinase inhibitor indicated as a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. (1.1, 2.1)
- TAFINLAR in combination with trametinib is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. The use in combination is based on the demonstration of durable response rate. Improvement in disease-related symptoms or overall survival has not been demonstrated for TAFINLAR in combination with trametinib. (1.2, 2.1, 14.2)

Limitation of Use: TAFINLAR is not indicated for treatment of patients with wild-type BRAF melanoma. (1.3, 5.2)

DOSAGE AND ADMINISTRATION

- Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with TAFINLAR as a single agent. Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to initiation of treatment with TAFINLAR in combination with trametinib. (2.1)
- The recommended dose of TAFINLAR is 150 mg orally twice daily as a single agent or in combination with trametinib 2 mg orally once daily. Take TAFINLAR at least 1 hour before or at least 2 hours after a meal. (2.2)

DOSAGE FORMS AND STRENGTHS

Capsules: 50 mg, 75 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- New primary malignancies, cutaneous and non-cutaneous, can occur when TAFINLAR is administered as a single agent or in combination with trametinib. Monitor patients for new malignancies prior to initiation of therapy, while on therapy, and following discontinuation of TAFINLAR or the combination therapy. (5.1, 2.3)
- Tumor Promotion in BRAF Wild-Type Melanoma: Increased cell proliferation can occur with BRAF inhibitors. (5.2)
- Hemorrhage: Major hemorrhagic events can occur in patients receiving TAFINLAR in combination with trametinib. Monitor for signs and symptoms of bleeding. (5.3)
- Venous Thromboembolism: Deep vein thrombosis and pulmonary embolism can occur in patients receiving TAFINLAR in combination with trametinib. (5.4, 2.3)
- Cardiomyopathy: Assess LVEF before treatment with TAFINLAR in combination with trametinib, after one month of treatment, then every 2 to 3 months thereafter. (5 5, 2.3)
- Ocular Toxicities: Perform ophthalmologic evaluation for any visual disturbances. (5.6, 2.3)
- Serious Febrile Reactions: Incidence and severity of pyrexia are increased with TAFINLAR in combination with trametinib. (5.7, 2 3)
- Serious Skin Toxicity: Monitor for skin toxicities and for secondary infections. Discontinue for intolerable Grade 2, or Grade 3 or 4 rash not improving within 3 weeks despite interruption of TAFINLAR. (5.8, 2.3)
- Hyperglycemia: Monitor serum glucose levels in patients with pre-existing diabetes or hyperglycemia. (5.9)
- Glucose-6-Phosphate Dehydrogenase Deficiency: Closely monitor for hemolytic anemia. (5.10)
- Embryofetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of potential risk to a fetus. TAFINLAR may render hormonal contraceptives less effective and an alternative method of contraception should be used. (5.11, 8.1)

ADVERSE REACTIONS

- Most common adverse reactions (≥20%) for TAFINLAR as a single agent are hyperkeratosis, headache, pyrexia, arthralgia, papilloma, alopecia, and palmar-plantar erythrodysesthesia syndrome. (6 1)
- Most common adverse reactions (≥20%) for TAFINLAR in combination with trametinib are pyrexia, chills, fatigue, rash, nausea, vomiting, diarrhea, abdominal pain, peripheral edema, cough, headache, arthralgia, night sweats, decreased appetite, constipation, and myalgia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Avoid concurrent administration of strong inhibitors of CYP3A4 or CYP2C8. (7.1)
- Avoid concurrent administration of strong inducers of CYP3A4 or CYP2C8. (7.1)
- Concomitant use with agents that are sensitive substrates of CYP3A4, CYP2C8, CYP2C9, CYP2C19, or CYP2B6 may result in loss of efficacy of these agents. (7.2)

USE IN SPECIFIC POPULATIONS

- Nursing Mothers: Discontinue drug or nursing. (8.3)
- Females and Males of Reproductive Potential: Advise female patients to use highly effective contraception during treatment and for 2 weeks following discontinuation of treatment. Advise male patients of potential risk for impaired spermatogenesis. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 01/2014

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*****Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 BRAF V600E Mutation-Positive Unresectable or Metastatic Melanoma

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

1.2 BRAF V600E or V600K Mutation-Positive Unresectable or Metastatic Melanoma

TAFINLAR, in combination with trametinib, is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test. This indication is based on the demonstration of durable response rate *[see Clinical Studies (14.2)]*. Improvement in disease-related symptoms or overall survival has not been demonstrated for TAFINLAR in combination with trametinib.

1.3 Limitation of Use

TAFINLAR is not indicated for treatment of patients with wild-type BRAF melanoma *[see Warnings and Precautions (5.2)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Confirm the presence of BRAF V600E mutation in tumor specimens prior to initiation of treatment with TAFINLAR as a single agent *[see Warnings and Precautions (5.2)]*. Confirm the presence of BRAF V600E or V600K mutation in tumor specimens prior to initiation of treatment with TAFINLAR in combination with trametinib. Information on FDA-approved tests for the detection of BRAF V600 mutations in melanoma is available at: http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosing

The recommended dosage regimens of TAFINLAR are:

- 150 mg orally taken twice daily, approximately 12 hours apart, as a single agent
- 150 mg orally taken twice daily, approximately 12 hours apart, in combination with trametinib 2 mg orally taken once daily

Continue treatment until disease progression or unacceptable toxicity occurs. Take TAFINLAR as a single agent, or TAFINLAR in combination with trametinib, at least 1 hour before or 2 hours after a meal *[see Clinical Pharmacology (12.3)]*. Do not take a missed dose of

TAFINLAR within 6 hours of the next dose of TAFINLAR. Do not open, crush, or break TAFINLAR capsule.

When administered in combination with trametinib, take the once-daily dose of trametinib at the same time each day with either the morning dose or the evening dose of TAFINLAR.

2.3 Dose Modifications

For New Primary Cutaneous Malignancies: No dose modifications are required.

For New Primary Non-Cutaneous Malignancies: Permanently discontinue TAFINLAR in patients who develop RAS mutation-positive non-cutaneous malignancies. If used in combination with trametinib, no dose modifications are required for trametinib in patients who develop non-cutaneous malignancies.

Table 1. Recommended Dose Reductions

Dose Reductions for TAFINLAR When Administered as a Single Agent or in Combination With Trametinib	
First Dose Reduction	100 mg orally twice daily
Second Dose Reduction	75 mg orally twice daily
Third Dose Reduction	50 mg orally twice daily
Subsequent Modification	Permanently discontinue TAFINLAR if unable to tolerate 50 mg orally twice daily
Dose Reductions for Trametinib When Administered in Combination With TAFINLAR	
First Dose Reduction	1.5 mg orally once daily
Second Dose Reduction	1 mg orally once daily
Subsequent Modification	Permanently discontinue if unable to tolerate trametinib 1 mg orally once daily

Table 2. Recommended Dose Modifications for TAFINLAR as a Single Agent and for TAFINLAR and Trametinib Administered in Combination

Severity of Adverse Reaction[a]	TAFINLAR[b]	Trametinib (When Used in Combination)[b,c]
Febrile drug reaction		
• Fever of 101.3°F to 104°F	Withhold TAFINLAR until fever resolves. Then resume at same or lower dose level.	Do not modify the dose of trametinib.
• Fever higher than 104°F • Fever complicated by rigors, hypotension, dehydration, or renal failure	• Withhold TAFINLAR until fever resolves. Then resume at a lower dose level. Or • Permanently discontinue TAFINLAR.	Withhold trametinib until fever resolves. Then resume trametinib at same or lower dose level.
Cutaneous		
• Intolerable Grade 2 skin toxicity • Grade 3 or 4 skin toxicity	Withhold TAFINLAR for up to 3 weeks. • If improved, resume at a lower dose level. • If not improved, permanently discontinue.	Withhold trametinib for up to 3 weeks. • If improved, resume at a lower dose level. • If not improved, permanently discontinue.
Cardiac		
• Asymptomatic, absolute decrease in LVEF of 10% or greater from baseline and is below institutional lower limits of normal (LLN) from pretreatment value	Do not modify the dose of TAFINLAR.	Withhold trametinib for up to 4 weeks. • If improved to normal LVEF value, resume at a lower dose level. • If not improved to normal LVEF value, permanently discontinue.
• Symptomatic congestive heart failure • Absolute decrease in LVEF of greater than 20% from baseline that is below LLN	Withhold TAFINLAR, if improved, then resume at the same dose.	Permanently discontinue trametinib.

Severity of Adverse Reaction[a]	TAFINLAR[b]	Trametinib (When Used in Combination)[b,c]
Venous Thromboembolism		
• Uncomplicated DVT or PE	Do not modify the dose of TAFINLAR.	Withhold trametinib for up to 3 weeks. • If improved to Grade 0-1, resume at a lower dose level. • If not improved, permanently discontinue.
• Life Threatening PE	Permanently discontinue TAFINLAR.	Permanently discontinue trametinib.
Ocular Toxicities		
• Grade 2-3 retinal pigment epithelial detachments (RPED)	Do not modify the dose of TAFINLAR.	Withhold trametinib for up to 3 weeks. • If improved to Grade 0-1, resume at a lower dose level. • If not improved, permanently discontinue.
• Retinal vein occlusion	Do not modify the dose of TAFINLAR.	Permanently discontinue trametinib.
• Uveitis and Iritis	Withhold TAFINLAR for up to 6 weeks. • If improved to Grade 0-1, then resume at the same dose. • If not improved, permanently discontinue.	Do not modify the dose of trametinib.

Severity of Adverse Reaction[a]	TAFINLAR[b]	Trametinib (When Used in Combination)[b,c]
Pulmonary		
• Interstitial lung disease/pneumonitis	Do not modify the dose of TAFINLAR.	Permanently discontinue trametinib.
Other		
• Intolerable Grade 2 adverse reactions • Any Grade 3 adverse reaction	Withhold TAFINLAR. • If improved to Grade 0-1, resume at a lower dose level. • If not improved, permanently discontinue.	Withhold trametinib for up to 3 weeks. • If improved to Grade 0-1, resume at a lower dose level. • If not improved, permanently discontinue.
• First occurrence of any Grade 4 adverse reaction	• Withhold TAFINLAR until adverse reaction improves to Grade 0-1. Then resume at a lower dose level. Or • Permanently discontinue TAFINLAR.	• Withhold trametinib until adverse reaction improves to Grade 0-1. Then resume at a lower dose level. Or • Permanently discontinue trametinib.
• Recurrent Grade 4 adverse reaction	Permanently discontinue TAFINLAR.	Permanently discontinue trametinib.

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.
[b] See Table 1 for recommended dose reductions of TAFINLAR and trametinib.
[c] Refer to Full Prescribing Information for trametinib.

3 DOSAGE FORMS AND STRENGTHS

50 mg Capsules: Dark red capsule imprinted with ‘GS TEW’ and ‘50 mg’.

75 mg Capsules: Dark pink capsule imprinted with ‘GS LHF’ and ‘75 mg’.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

Review the Full Prescribing Information for trametinib prior to initiation of TAFINLAR in combination with trametinib. The following serious adverse reactions of trametinib as a single agent, which may occur when TAFINLAR is used in combination with trametinib, are not described in the Full Prescribing Information for TAFINLAR:

- Retinal vein occlusion
- Interstitial lung disease

5.1 New Primary Malignancies

New primary malignancies, cutaneous and non-cutaneous, can occur when TAFINLAR is administered as a single agent or when used in combination with trametinib.

Cutaneous Malignancies:

TAFINLAR results in an increased incidence of cutaneous squamous cell carcinoma, keratoacanthoma, and melanoma. TAFINLAR when used in combination with trametinib results in an increased incidence of basal cell carcinoma.

In Trial 1, cutaneous squamous cell carcinomas and keratoacanthomas (cuSCC) occurred in 7% (14/187) of patients treated with TAFINLAR and in none of the patients treated with dacarbazine.

Across clinical trials of TAFINLAR (N = 586), the incidence of cuSCC was 11%. The median time to first cuSCC was 9 weeks (range: 1 to 53 weeks). Of those patients who developed new cuSCC, approximately 33% developed one or more cuSCC with continued administration of TAFINLAR. The median time between diagnosis of the first cuSCC and the second cuSCC was 6 weeks.

In Trial 1, the incidence of new primary malignant melanomas was 2% (3/187) for patients receiving TAFINLAR while no dacarbazine-treated patient was diagnosed with new primary malignant melanoma.

In Trial 2, the incidence of basal cell carcinoma was increased in patients receiving TAFINLAR in combination with trametinib: 9% (5/55) of patients receiving TAFINLAR in combination with trametinib compared with 2% (1/53) of patients receiving TAFINLAR as a single agent. The range of time to diagnosis of basal cell carcinoma was 28 to 249 days in patients receiving TAFINLAR in combination with trametinib and was 197 days for the patient receiving TAFINLAR as a single agent.

Cutaneous squamous cell carcinoma (SCC), including keratoacanthoma, occurred in 7% of patients receiving TAFINLAR in combination with trametinib and 19% of patients receiving TAFINLAR as a single agent. The range of time to diagnosis of cuSCC was 136 to197 days in the combination arm and was 9 to 197 days in the arm receiving TAFINLAR as a single agent.

New primary melanoma occurred in 2% (1/53) of patients receiving TAFINLAR as a single agent and in none of the 55 patients receiving TAFINLAR in combination with trametinib.

Perform dermatologic evaluations prior to initiation of TAFINLAR as a single agent or in combination with trametinib, every 2 months while on therapy, and for up to 6 months following discontinuation of TAFINLAR. No dose modifications of TAFINLAR or trametinib are required in patients who develop new primary cutaneous malignancies.

Non-cutaneous Malignancies:

Based on its mechanism of action, TAFINLAR may promote the growth and development of malignancies with activation of RAS through mutation or other mechanisms *[see Warnings and Precautions (5.2)]*. In patients receiving TAFINLAR in combination with trametinib four cases of non-cutaneous malignancies were identified: KRAS mutation-positive pancreatic adenocarcinoma (n = 1), recurrent NRAS mutation-positive colorectal carcinoma (n = 1), head and neck carcinoma (n = 1), and glioblastoma (n = 1). Monitor patients receiving the combination closely for signs or symptoms of non-cutaneous malignancies. Permanently discontinue TAFINLAR for RAS mutation-positive non-cutaneous malignancies. If used in combination with trametinib, no dose modification of trametinib is required for patients who develop non-cutaneous malignancies.

5.2 Tumor Promotion in BRAF Wild-Type Melanoma

In vitro experiments have demonstrated paradoxical activation of MAP-kinase signaling and increased cell proliferation in BRAF wild-type cells which are exposed to BRAF inhibitors. Confirm evidence of BRAF V600E or V600K mutation status prior to initiation of TAFINLAR as a single agent or combination therapy *[see Indications and Usage (1), Dosage and Administration (2.1)]*.

5.3 Hemorrhage

Hemorrhages, including major hemorrhages defined as symptomatic bleeding in a critical area or organ, can occur when TAFINLAR is used in combination with trametinib.

In Trial 2, treatment with TAFINLAR in combination with trametinib resulted in an increased incidence and severity of any hemorrhagic event: 16% (9/55) of patients treated with TAFINLAR in combination with trametinib compared with 2% (1/53) of patients treated with TAFINLAR as a single agent. The major hemorrhagic events of intracranial or gastric hemorrhage occurred in 5% (3/55) of patients treated with TAFINLAR in combination with trametinib compared with none of the 53 patients treated with TAFINLAR as a single agent. Intracranial hemorrhage was fatal in 4% (2/55) of patients receiving TAFINLAR in combination with trametinib.

Permanently discontinue TAFINLAR and trametinib for all Grade 4 hemorrhagic events and for any Grade 3 hemorrhagic events that do not improve. Withhold TAFINLAR for Grade 3

hemorrhagic events; if improved resume at a lower dose level. Withhold trametinib for up to 3 weeks for Grade 3 hemorrhagic events; if improved, resume at a lower dose level.

5.4 Venous Thromboembolism

Venous thromboembolism can occur when TAFINLAR is used in combination with trametinib.

In Trial 2, treatment with TAFINLAR in combination with trametinib resulted in an increased incidence of deep venous thrombosis (DVT) and pulmonary embolism (PE): 7% (4/55) of patients treated with TAFINLAR in combination with trametinib compared with none of the 53 patients treated with TAFINLAR as a single agent. Pulmonary embolism was fatal in 2% (1/55) of patients receiving TAFINLAR in combination with trametinib.

Advise patients to immediately seek medical care if they develop symptoms of DVT or PE, such as shortness of breath, chest pain, or arm or leg swelling. Permanently discontinue TAFINLAR and trametinib for life-threatening PE. Withhold trametinib and continue TAFINLAR at the same dose for uncomplicated DVT or PE; if improved within 3 weeks, trametinib may be resumed at a lower dose level *[see Dosage and Administration (2.3)]*.

5.5 Cardiomyopathy

Cardiomyopathy can occur when TAFINLAR is used in combination with trametinib and with trametinib as a single agent *[refer to Full Prescribing Information for trametinib]*.

In Trial 2, cardiomyopathy occurred in 9% (5/55) of patients treated with TAFINLAR in combination with trametinib and in none of patients treated with TAFINLAR as a single agent. The median time to onset of cardiomyopathy in patients treated with TAFINLAR in combination with trametinib was 86 days (range: 27 to 253 days). Cardiomyopathy was identified within the first month of treatment with TAFINLAR in combination with trametinib in two of five patients. Development of cardiomyopathy resolved in all five patients following dose reduction (4/55) and/or dose interruption (1/55).

Across clinical trials of TAFINLAR administered in combination with trametinib (N = 202), 8% of patients developed evidence of cardiomyopathy (decrease in LVEF below institutional lower limits of normal with an absolute decrease in LVEF ≥10% below baseline). Two percent demonstrated a decrease in LVEF below institutional lower limits of normal with an absolute decrease in LVEF of ≥20% below baseline.

Assess LVEF by echocardiogram or multigated acquisition (MUGA) scan before initiation of TAFINLAR in combination with trametinib, one month after initiation, and then at 2- to 3-month intervals while on treatment with the combination. Withhold treatment with trametinib and continue TAFINLAR at the same dose if absolute LVEF value decreases by 10% from pretreatment values and is less than the lower limit of normal. For symptomatic cardiomyopathy or persistent, asymptomatic LV dysfunction that does not resolve within 4 weeks, permanently discontinue trametinib and withhold TAFINLAR. Resume TAFINLAR at the same dose level upon recovery of cardiac function *[see Dosage and Administration (2.3)]*.

5.6 Ocular Toxicities

Retinal Pigment Epithelial Detachment (RPED):

Retinal pigment epithelial detachments (RPED) can occur when TAFINLAR is used in combination with trametinib and with trametinib as a single agent *[refer to Full Prescribing Information for trametinib]*. Retinal detachments resulting from trametinib are often bilateral and multifocal, occurring in the macular region of the retina.

In Trial 2, ophthalmologic examinations including retinal evaluation were performed pretreatment and at regular intervals during treatment. RPED occurred in 2% (1/55) of patients receiving TAFINLAR in combination with trametinib. Across clinical trials of TAFINLAR administered in combination with trametinib (N = 202), the incidence of RPED was 1% (2/202).

Perform ophthalmological evaluation at any time a patient reports visual disturbances and compare with baseline, if available. If TAFINLAR is used in combination with trametinib, do not modify the dose of TAFINLAR. Withhold trametinib if RPED is diagnosed. If resolution of the RPED is documented on repeat ophthalmological evaluation within 3 weeks, resume trametinib at a lower dose level. Discontinue trametinib if no improvement after 3 weeks *[see Dosage and Administration (2.3)]*.

Uveitis and Iritis:

Uveitis and iritis can occur when TAFINLAR is administered as a single agent or when used in combination with trametinib.

Uveitis (including iritis) occurred in 1% (6/586) of patients treated with TAFINLAR as a single agent and uveitis occurred in 1% (2/202) of patients treated with TAFINLAR in combination with trametinib. Symptomatic treatment employed in clinical trials included steroid and mydriatic ophthalmic drops. Monitor patients for visual signs and symptoms of uveitis (e.g., change in vision, photophobia, eye pain). If diagnosed, withhold TAFINLAR for up to 6 weeks until uveitis/iritis resolves to Grade 0-1. If TAFINLAR is used in combination with trametinib, do not modify the dose of trametinib.

5.7 Serious Febrile Reactions

Serious febrile reactions and fever of any severity complicated by hypotension, rigors or chills, dehydration, or renal failure, can occur when TAFINLAR is administered as a single agent or when used in combination with trametinib. The incidence and severity of pyrexia are increased when TAFINLAR is used in combination with trametinib compared with TAFINLAR as a single agent *[see Adverse Reactions (6.1)]*.

In Trial 1, the incidence of fever (serious and non-serious) was 28% in patients treated with TAFINLAR and 10% in patients treated with dacarbazine. In patients treated with TAFINLAR, the median time to initial onset of fever (any severity) was 11 days (range: 1 to 202 days) and the median duration of fever was 3 days (range: 1 to 129 days). Serious febrile reactions and fever of

any severity complicated by hypotension, rigors or chills occurred in 3.7% (7/187) of patients treated with TAFINLAR and in none of the 59 patients treated with dacarbazine.

In Trial 2, the incidence of fever (serious and non-serious) was 71% (39/55) in patients treated with TAFINLAR in combination with trametinib and 26% (14/53) in patients treated with TAFINLAR as a single agent. Serious febrile reactions and fever of any severity complicated by hypotension, rigors or chills occurred in 25% (14/55) of patients treated with TAFINLAR in combination with trametinib compared with 2% (1/53) of patients treated with TAFINLAR as a single agent. Fever was complicated with chills/rigors in 51% (28/55), dehydration in 9% (5/55), renal failure in 4% (2/55), and syncope in 4% (2/55) of patients in Trial 2.

In patients treated with TAFINLAR in combination with trametinib, the median time to initial onset of fever was 30 days compared with 19 days in patients treated with TAFINLAR as a single agent; the median duration of fever was 6 days with the combination compared with 4 days with TAFINLAR as a single agent.

Across clinical trials of TAFINLAR administered in combination with trametinib (N = 202), the incidence of pyrexia was 57% (116/202).

Withhold TAFINLAR for fever of 101.3ºF or higher. Withhold trametinib for any fever higher than 104ºF. Withhold TAFINLAR, and trametinib if used in combination, for any serious febrile reaction or fever complicated by hypotension, rigors or chills, dehydration, or renal failure and evaluate for signs and symptoms of infection. Refer to Table 2 for recommended dose modifications for adverse reactions *[see Dosage and Administration (2.3)]*. Prophylaxis with antipyretics may be required when resuming TAFINLAR or trametinib.

5.8 Serious Skin Toxicity

Serious skin toxicity can occur when TAFINLAR is used in combination with trametinib and with trametinib as a single agent *[refer to Full Prescribing Information for trametinib]*.

In Trial 2, the incidence of any skin toxicity was similar for patients receiving TAFINLAR in combination with trametinib (65% [36/55]) compared with patients receiving TAFINLAR as a single agent (68% [36/53]). The median time to onset of skin toxicity in patients treated with TAFINLAR in combination with trametinib was 37 days (range: 1 to 225 days) and median time to resolution of skin toxicity was 33 days (range: 3 to 421 days). No patient required dose reduction or permanent discontinuation of TAFINLAR or trametinib for skin toxicity.

Across clinical trials of TAFINLAR in combination with trametinib (N = 202), severe skin toxicity and secondary infections of the skin requiring hospitalization occurred in 2.5% (5/202) of patients treated with TAFINLAR in combination with trametinib.

Withhold TAFINLAR, and trametinib if used in combination, for intolerable or severe skin toxicity. TAFINLAR and trametinib may be resumed at lower dose levels in patients with improvement or recovery from skin toxicity within 3 weeks *[see Dosage and Administration (2.3)]*.

5.9 Hyperglycemia

Hyperglycemia can occur when TAFINLAR is administered as a single agent or when used in combination with trametinib.

In Trial 1, 5 of 12 patients with a history of diabetes required more intensive hypoglycemic therapy while taking TAFINLAR. The incidence of Grade 3 hyperglycemia based on laboratory values was 6% (12/187) in patients treated with TAFINLAR compared with none of the dacarbazine-treated patients.

In Trial 2, the incidence of Grade 3 hyperglycemia based on laboratory values was 5% (3/55) in patients treated with TAFINLAR in combination with trametinib compared with 2% (1/53) in patients treated with TAFINLAR as a single agent.

Monitor serum glucose levels as clinically appropriate when TAFINLAR is administered as a single agent or when used in combination with trametinib in patients with pre-existing diabetes or hyperglycemia. Advise patients to report symptoms of severe hyperglycemia such as excessive thirst or any increase in the volume or frequency of urination.

5.10 Glucose-6-Phosphate Dehydrogenase Deficiency

TAFINLAR, which contains a sulfonamide moiety, confers a potential risk of hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Closely observe patients with G6PD deficiency for signs of hemolytic anemia.

5.11 Embryofetal Toxicity

Based on its mechanism of action, TAFINLAR can cause fetal harm when administered to a pregnant woman. Dabrafenib was teratogenic and embryotoxic in rats at doses three times greater than the human exposure at the recommended clinical dose. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Use in Specific Populations (8.1)]*.

Advise female patients of reproductive potential to use a highly effective non-hormonal method of contraception since TAFINLAR can render hormonal contraceptives ineffective, during treatment and for at least 2 weeks after treatment with TAFINLAR or for 4 months after treatment with TAFINLAR in combination with trametinib. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking TAFINLAR *[see Drug Interactions (7.2), Use in Specific Populations (8.6)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in another section of the label:

- New Primary Malignancies *[see Warnings and Precautions (5.1)]*
- Tumor Promotion in BRAF Wild-Type Melanoma *[see Warnings and Precautions (5.2)]*
- Hemorrhage *[see Warnings and Precautions (5.3)]*
- Venous Thromboembolism *[see Warnings and Precautions (5.4)]*
- Cardiomyopathy *[see Warnings and Precautions (5.5)]*
- Ocular Toxicities *[see Warnings and Precautions (5.6)]*
- Serious Febrile Reactions *[see Warnings and Precautions (5.7)]*
- Serious Skin Toxicity *[see Warnings and Precautions (5.8)]*
- Hyperglycemia *[see Warnings and Precautions (5.9)]*
- Glucose-6-Phosphate Dehydrogenase Deficiency *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described in the Warnings and Precautions section and below reflect exposure to TAFINLAR as a single agent and in combination with trametinib.

<u>BRAF V600E Unresectable or Metastatic Melanoma:</u>

The safety of TAFINLAR as a single agent was evaluated in 586 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma, previously treated or untreated, who received TAFINLAR 150 mg orally twice daily until disease progression or unacceptable toxicity, including 181 patients treated for at least 6 months and 86 additional patients treated for more than 12 months. TAFINLAR was studied in open-label, single-arm trials and in an open-label, randomized, active-controlled trial. The median daily dose of TAFINLAR was 300 mg (range: 118 to 300 mg).

Table 3 and Table 4 present adverse drug reactions and laboratory abnormalities identified from analyses of Trial 1 *[see Clinical Studies (14.1)]*. Trial 1, a multicenter, international, open-label, randomized (3:1), controlled trial allocated 250 patients with unresectable or metastatic BRAF V600E mutation-positive melanoma to receive TAFINLAR 150 mg orally twice daily (n = 187) or dacarbazine 1,000 mg/m^2 intravenously every 3 weeks (n = 63). The trial excluded patients with abnormal left ventricular ejection fraction or cardiac valve morphology (≥Grade 2), corrected QT interval ≥480 milliseconds on electrocardiogram, or a known history of glucose-6-

phosphate dehydrogenase deficiency. The median duration on treatment was 4.9 months for patients treated with TAFINLAR and 2.8 months for dacarbazine-treated patients. The population exposed to TAFINLAR was 60% male, 99% white, and had a median age of 53 years.

The most commonly occurring adverse reactions (≥20%) in patients treated with TAFINLAR were, in order of decreasing frequency: hyperkeratosis, headache, pyrexia, arthralgia, papilloma, alopecia, and palmar-plantar erythrodysesthesia syndrome (PPES).

The incidence of adverse events resulting in permanent discontinuation of study medication in Trial 1 was 3% for patients treated with TAFINLAR and 3% for patients treated with dacarbazine. The most frequent (≥2%) adverse reactions leading to dose reduction of TAFINLAR were pyrexia (9%), PPES (3%), chills (3%), fatigue (2%), and headache (2%).

Table 3. Selected Common Adverse Reactions Occurring in ≥10% (All Grades) or ≥2% (Grades 3 or 4) of Patients Treated With TAFINLAR[a]

Primary System Organ Class Preferred Term	TAFINLAR N = 187		Dacarbazine N = 59	
	All Grades (%)	Grades 3 and 4[b] (%)	All Grades (%)	Grades 3 and 4 (%)
Skin and subcutaneous tissue disorders				
Hyperkeratosis	37	1	0	0
Alopecia	22	NA[f]	2	NA[f]
Palmar-plantar erythrodysesthesia syndrome	20	2	2	0
Rash	17	0	0	0
Nervous system disorders				
Headache	32	0	8	0
General disorders and administration site conditions				
Pyrexia	28	3	10	0
Musculoskeletal and connective tissue disorders				
Arthralgia	27	1	2	0
Back pain	12	3	7	0
Myalgia	11	0	0	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)				
Papilloma[c]	27	0	2	0
cuSCC[d, e]	7	4	0	0
Respiratory, thoracic, and mediastinal disorders				
Cough	12	0	5	0
Gastrointestinal disorders				
Constipation	11	2	14	0
Infections and infestations				
Nasopharyngitis	10	0	3	0

[a] Adverse drug reactions, reported using MedDRA and graded using CTCAE version 4.0 for assessment of toxicity.

[b] Grade 4 adverse reactions limited to hyperkeratosis (n = 1) and constipation (n = 1).

[c] Includes skin papilloma and papilloma.

[d] Includes squamous cell carcinoma of the skin and keratoacanthoma.

[e] Cases of cutaneous squamous cell carcinoma were required to be reported as Grade 3 per protocol.

[f] NA = not applicable.

Table 4. Incidence of Laboratory Abnormalities Increased From Baseline Occurring at a Higher Incidence in Patients Treated With TAFINLAR in Trial 1 [Between-Arm Difference of ≥5% (All Grades) or ≥2% (Grades 3 or 4)]

Test	TAFINLAR N = 187		DTIC N = 59	
	All Grades (%)	Grades 3 and 4 (%)	All Grades (%)	Grades 3 and 4 (%)
Hyperglycemia	50	6	43	0
Hypophosphatemia	37	6[a]	14	2
Increased alkaline phosphatase	19	0	14	2
Hyponatremia	8	2	3	0

[a] Grade 4 laboratory abnormality limited to hypophosphatemia (n = 1).

Other clinically important adverse reactions observed in <10% of patients (N = 586) treated with TAFINLAR were:

Gastrointestinal Disorders: Pancreatitis.

Immune System Disorders: Hypersensitivity manifesting as bullous rash.

Renal and Urinary Disorders: Interstitial nephritis.

BRAF V600E or V600K Unresectable or Metastatic Melanoma:

The safety of TAFINLAR in combination with trametinib was evaluated in Trial 2 and other trials consisting of a total of 202 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma who received TAFINLAR 150 mg orally twice daily in combination with trametinib 2 mg orally once daily until disease progression or unacceptable toxicity. Among these 202 patients, 66 (33%) were exposed to TAFINLAR and 68 (34%) were exposed to trametinib for greater than 6 to 12 months while 40 (20%) were exposed to TAFINLAR and 36 (18%) were exposed to trametinib for greater than one year. The median age was 54 years, 57% were male, and >99% were white.

Table 5 presents adverse reactions from Trial 2, a multicenter, open-label, randomized trial of 162 patients with BRAF V600E or V600K mutation-positive melanoma receiving TAFINLAR 150 mg twice daily in combination with trametinib 2 mg orally once daily (n = 55), TAFINLAR 150 mg orally twice daily in combination with trametinib 1 mg once daily (n = 54), and TAFINLAR as a single agent 150 mg orally twice daily (n = 53) *[see Clinical Studies (14.2)]*. Patients with abnormal LVEF, history of acute coronary syndrome within 6 months, current evidence of Class II or greater congestive heart failure (New York Heart Association), history RVO or RPED, QTc interval ≥480 msec, treatment refractory hypertension, uncontrolled arrhythmias, history of pneumonitis or interstitial lung disease, or a known history of G6PD deficiency were excluded. The median duration of treatment was 10.9 months for both

TAFINLAR and trametinib (2-mg orally once-daily treatment group) when used in combination, 10.6 months for both TAFINLAR and trametinib (1-mg orally once-daily treatment group) when used in combination, and 6.1 months for TAFINLAR as a single agent.

In Trial 2, 13% of patients receiving TAFINLAR in combination with trametinib experienced adverse reactions resulting in permanent discontinuation of trial medication(s). The most common adverse reaction resulting in permanent discontinuation was pyrexia (4%). Adverse reactions led to dose reductions in 49% and dose interruptions in 67% of patients treated with TAFINLAR in combination with trametinib. Pyrexia, chills, and nausea were the most common reasons cited for dose reductions and pyrexia, chills, and decreased ejection fraction were the most common reasons cited for dose interruptions of TAFINLAR and trametinib when used in combination.

Table 5. Common Adverse Drug Reactions Occurring in ≥10% at (All Grades) or ≥5% (Grades 3 or 4) of Patients Treated With TAFINLAR in Combination With Trametinib in Trial 2

Adverse Reactions	TAFINLAR plus Trametinib 2 mg N = 55		TAFINLAR plus Trametinib 1 mg N = 54		TAFINLAR N = 53	
	All Grades[a]	Grades 3 and 4	All Grades[a]	Grades 3 and 4	All Grades[a]	Grades 3 and 4
General disorders and administrative site conditions						
Pyrexia	71	5	69	9	26	0
Chills	58	2	50	2	17	0
Fatigue	53	4	57	2	40	6
Edema peripheral[b]	31	0	28	0	17	0
Skin and subcutaneous tissue disorders						
Rash[c]	45	0	43	2	53	0
Night Sweats	24	0	15	0	6	0
Dry skin	18	0	9	0	6	0
Dermatitis acneiform	16	0	11	0	4	0
Actinic keratosis	15	0	7	0	9	0
Erythema	15	0	6	0	2	0
Pruritus	11	0	11	0	13	0
Gastrointestinal disorders						
Nausea	44	2	46	6	21	0
Vomiting	40	2	43	4	15	0
Diarrhea	36	2	26	0	28	0
Abdominal pain[d]	33	2	24	2	21	2
Constipation	22	0	17	2	11	0
Dry mouth	11	0	11	0	6	0
Nervous system disorders						
Headache	29	0	37	2	28	0
Dizziness	16	0	13	0	9	0
Respiratory, thoracic, and mediastinal disorders						
Cough	29	0	11	0	21	0
Oropharyngeal pain	13	0	7	0	0	0

Adverse Reactions	TAFINLAR plus Trametinib 2 mg N = 55		TAFINLAR plus Trametinib 1 mg N = 54		TAFINLAR N = 53	
	All Grades[a]	Grades 3 and 4	All Grades[a]	Grades 3 and 4	All Grades[a]	Grades 3 and 4
Musculoskeletal, connective tissue, and bone disorders						
Arthralgia	27	0	44	0	34	0
Myalgia	22	2	24	0	23	2
Back pain	18	5	11	0	11	2
Muscle spasms	16	0	2	0	4	0
Pain in extremity	16	0	11	2	19	0
Metabolism and nutritional disorders						
Decreased appetite	22	0	30	0	19	0
Dehydration	11	0	6	2	2	0
Psychiatric Disorders						
Insomnia	18	0	11	0	8	2
Vascular disorders						
Hemorrhage[e]	16	5	11	0	2	0
Infections and infestations						
Urinary tract infection	13	2	6	0	9	2
Renal and urinary disorders						
Renal failure[f]	7	7	2	0	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.

[b] Includes the following terms: peripheral edema, edema, and lymphedema.

[c] Includes the following terms: rash, rash generalized, rash pruritic, rash erythematous, rash papular, rash vesicular, rash macular, and rash maculo-papular.

[d] Includes the following terms: abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort.

[e] Includes the following terms: brain stem hemorrhage, cerebral hemorrhage, gastric hemorrhage, epistaxis, gingival hemorrhage, hematuria, vaginal hemorrhage, hemorrhage intracranial, eye hemorrhage, and vitreous hemorrhage.

[f] Includes the following terms: renal failure and renal failure acute.

Other clinically important adverse reactions (N = 202) observed in <10% of patients treated with TAFINLAR in combination with trametinib were:

Eye Disorders: Vision blurred, transient blindness.

Gastrointestinal Disorders: Stomatitis, pancreatitis.

General Disorders and Administration Site Conditions: Asthenia.

Infections and Infestations: Cellulitis, folliculitis, paronychia, rash pustular.

Neoplasms Benign, Malignant, and Unspecified (including cysts and polyps): Skin papilloma.

Skin and Subcutaneous Tissue Disorders: Palmar-plantar erythrodysesthesia syndrome, hyperkeratosis, hyperhidrosis.

Vascular Disorders: Hypertension.

Table 6. Treatment-Emergent Laboratory Abnormalities Occurring at ≥10% (All Grades) or ≥2% (Grades 3 or 4)] of Patients Treated With TAFINLAR in Combination With Trametinib in Trial 2

Tests	TAFINLAR plus Trametinib 2 mg N = 55		TAFINLAR plus Trametinib 1 mg N = 54		TAFINLAR N = 53	
	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4[a]
Hematology						
Leukopenia	62	5	46	4	21	0
Lymphopenia	55	22	59	19	40	6
Neutropenia	55	13	37	2	9	2
Anemia	55	4	46	7	28	0
Thrombocytopenia	31	4	31	2	8	0
Liver Function Tests						
Increased AST	60	5	54	0	15	0
Increased alkaline phosphatase	60	2	67	6	26	2
Increased ALT	42	4	35	4	11	0
Hyperbilirubinemia	15	0	7	4	0	0
Chemistry						
Hyperglycemia	58	5	67	6	49	2
Increased GGT	56	11	54	17	38	2
Hyponatremia	55	11	48	15	36	2
Hypoalbuminemia	53	0	43	2	23	0
Hypophosphatemia	47	5	41	11	40	0
Hypokalemia	29	2	15	2	23	6
Increased creatinine	24	5	20	2	9	0
Hypomagnesemia	18	2	2	0	6	0
Hyperkalemia	18	0	22	0	15	4
Hypercalcemia	15	0	19	2	4	0
Hypocalcemia	13	0	20	0	9	0

[a] No Grade 4 events were reported in patients receiving TAFINLAR as a single agent.

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; GGT = Gamma glutamyltransferase.

QT Prolongation: In Trial 2, QTcF prolongation to >500 msec occurred in 4% (2/55) of patients treated with TAFINLAR in combination with trametinib and in 2% (1/53) of patients treated with TAFINLAR as a single agent. The QTcF was increased more than 60 msec from baseline in 13% (7/55) of patients treated with TAFINLAR in combination with trametinib and 2% (1/53) of patients treated with TAFINLAR as a single agent.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on Dabrafenib

Dabrafenib is primarily metabolized by CYP2C8 and CYP3A4. Strong inhibitors of CYP3A4 or CYP2C8 may increase concentrations of dabrafenib and strong inducers of CYP3A4 or CYP2C8 may decrease concentrations of dabrafenib *[see Clinical Pharmacology (12.3)]*. Substitution of strong inhibitors or strong inducers of CYP3A4 or CYP2C8 is recommended during treatment with TAFINLAR. If concomitant use of strong inhibitors (e.g., ketoconazole, nefazodone, clarithromycin, gemfibrozil) or strong inducers (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, St John's wort) of CYP3A4 or CYP2C8 is unavoidable, monitor patients closely for adverse reactions when taking strong inhibitors or loss of efficacy when taking strong inducers.

7.2 Effects of Dabrafenib on Other Drugs

Dabrafenib induces CYP3A4 and CYP2C9. Dabrafenib decreased the systemic exposures of midazolam (a CYP3A4 substrate), S-warfarin (a CYP2C9 substrate), and R-warfarin (a CYP3A4/CYP1A2 substrate) *[see Clinical Pharmacology (12.3)]*. Monitor international normalized ratio (INR) levels more frequently in patients receiving warfarin during initiation or discontinuation of dabrafenib. Coadministration of TAFINLAR with other substrates of these enzymes, including dexamethasone or hormonal contraceptives, can result in decreased concentrations and loss of efficacy *[see Use in Specific Populations (8.1, 8.6)]*. Substitute for these medications or monitor patients for loss of efficacy if use of these medications is unavoidable.

7.3 Trametinib

Coadministration of TAFINLAR 150 mg twice daily and trametinib 2 mg once daily resulted in no clinically relevant pharmacokinetic drug interactions *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D.

Risk Summary: Based on its mechanism of action, TAFINLAR can cause fetal harm when administered to a pregnant woman. Dabrafenib was teratogenic and embryotoxic in rats at doses

three times greater than the human exposure at the recommended clinical dose of 150 mg twice daily based on AUC. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus *[see Warnings and Precautions (5.11)]*.

Animal Data: In a combined female fertility and embryofetal development study in rats, developmental toxicity consisted of embryo-lethality, ventricular septal defects, and variation in thymic shape at a dabrafenib dose of 300 mg/kg/day (approximately three times the human exposure at the recommended dose based on AUC). At doses of 20 mg/kg/day or greater (equivalent to the human exposure at the recommended dose based on AUC), rats demonstrated delays in skeletal development and reduced fetal body weight.

8.3 Nursing Mothers

It is not known whether this drug is present in human milk. Because many drugs are present in human milk and because of the potential for serious adverse reactions from TAFINLAR in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of TAFINLAR have not been established in pediatric patients.
In a repeat-dose toxicity study in juvenile rats, an increased incidence of kidney cysts and tubular deposits were noted at doses as low as 0.2 times the human exposure at the recommended adult dose based on AUC. Additionally, forestomach hyperplasia, decreased bone length, and early vaginal opening were noted at doses as low as 0.8 times the human exposure at the recommended adult dose based on AUC.

8.5 Geriatric Use

One hundred and twenty-six (22%) of 586 patients in clinical trials of TAFINLAR administered as a single agent and 40 (21%) of the 187 patients receiving TAFINLAR in Trial 1 were ≥65 years of age. No overall differences in the effectiveness or safety of TAFINLAR were observed in the elderly in Trial 1.

Across all clinical trials of TAFINLAR administered in combination with trametinib, there was an insufficient number of patients aged 65 years and over to determine whether they respond differently from younger patients. In Trial 2, 11 patients (20%) were 65 years of age and older, and 2 patients (4%) were 75 years of age and older.

8.6 Females and Males of Reproductive Potential

Contraception: *Females:* Advise female patients of reproductive potential to use highly effective contraception during treatment and for at least 2 weeks after the last dose of TAFINLAR or at least 4 months after the last dose of TAFINLAR taken in combination with trametinib. Counsel patients to use a non-hormonal method of contraception since TAFINLAR

can render hormonal contraceptives ineffective. Advise patients to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking TAFINLAR *[see Warnings and Precautions (5.11), Drug Interactions (7.1), Use in Specific Populations (8.1)]*.

Infertility:

Females: Increased follicular cysts and decreased corpora lutea were observed in female rats treated with trametinib. Advise female patients of reproductive potential that TAFINLAR taken in combination with trametinib may impair fertility in female patients.

Males: Effects on spermatogenesis have been observed in animals. Advise male patients of the potential risk for impaired spermatogenesis, and to seek counseling on fertility and family planning options prior to starting treatment with TAFINLAR *[see Nonclinical Toxicology (13.1)]*.

8.7 Hepatic Impairment

No formal pharmacokinetic trial in patients with hepatic impairment has been conducted. Dose adjustment is not recommended for patients with mild hepatic impairment based on the results of the population pharmacokinetic analysis. As hepatic metabolism and biliary secretion are the primary routes of elimination of dabrafenib and its metabolites, patients with moderate to severe hepatic impairment may have increased exposure. An appropriate dose has not been established for patients with moderate to severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.8 Renal Impairment

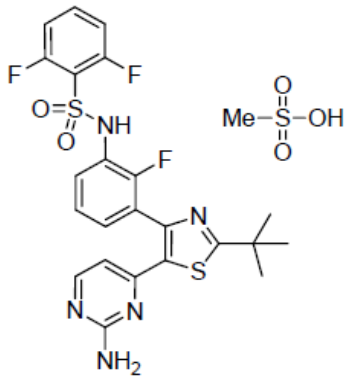
No formal pharmacokinetic trial in patients with renal impairment has been conducted. Dose adjustment is not recommended for patients with mild or moderate renal impairment based on the results of the population pharmacokinetic analysis. An appropriate dose has not been established for patients with severe renal impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

There is no information on overdosage of TAFINLAR. Since dabrafenib is highly bound to plasma proteins, hemodialysis is likely to be ineffective in the treatment of overdose with TAFINLAR.

11 DESCRIPTION

Dabrafenib mesylate is a kinase inhibitor. 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, methanesulfonate salt. It has the molecular formula $C_{23}H_{20}F_3N_5O_2S_2 \bullet CH_4O_3S$ and a molecular weight of 615.68. Dabrafenib mesylate has the following chemical structure:



Dabrafenib mesylate is a white to slightly colored solid with three pK_as: 6.6, 2.2, and -1.5. It is very slightly soluble at pH 1 and practically insoluble above pH 4 in aqueous media.

TAFINLAR (dabrafenib) capsules are supplied as 50-mg and 75-mg capsules for oral administration. Each 50-mg capsule contains 59.25 mg dabrafenib mesylate equivalent to 50 mg of dabrafenib free base. Each 75-mg capsule contains 88.88 mg dabrafenib mesylate equivalent to 75 mg of dabrafenib free base.

The inactive ingredients of TAFINLAR are colloidal silicon dioxide, magnesium stearate, and microcrystalline cellulose. Capsule shells contain hypromellose, red iron oxide (E172), and titanium dioxide (E171).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dabrafenib is an inhibitor of some mutated forms of BRAF kinases with in vitro IC_{50} values of 0.65, 0.5, and 1.84 nM for BRAF V600E, BRAF V600K, and BRAF V600D enzymes, respectively. Dabrafenib also inhibits wild-type BRAF and CRAF kinases with IC_{50} values of 3.2 and 5.0 nM, respectively, and other kinases such as SIK1, NEK11, and LIMK1 at higher concentrations. Some mutations in the BRAF gene, including those that result in BRAF V600E, can result in constitutively activated BRAF kinases that may stimulate tumor cell growth *[see Indications and Usage (1)]*. Dabrafenib inhibits BRAF V600 mutation-positive melanoma cell growth in vitro and in vivo.

Dabrafenib and trametinib target two different tyrosine kinases in the RAS/RAF/MEK/ERK pathway. Use of dabrafenib and trametinib in combination resulted in greater growth inhibition of BRAF V600 mutation-positive melanoma cell lines in vitro and prolonged inhibition of tumor growth in BRAF V600 mutation positive melanoma xenografts compared with either drug alone.

12.3 Pharmacokinetics

Absorption: After oral administration, median time to achieve peak plasma concentration (T_{max}) is 2 hours. Mean absolute bioavailability of oral dabrafenib is 95%. Following a single dose, dabrafenib exposure (C_{max} and AUC) increased in a dose-proportional manner across the dose

range of 12 to 300 mg, but the increase was less than dose-proportional after repeat twice-daily dosing. After repeat twice-daily dosing of 150 mg, the mean accumulation ratio was 0.73 and the inter-subject variability (CV%) of AUC at steady-state was 38%.

Administration of dabrafenib with a high-fat meal decreased C_{max} by 51%, decreased AUC by 31%, and delayed median T_{max} by 3.6 hours as compared with the fasted state *[see Dosage and Administration (2.2)]*.

Distribution: Dabrafenib is 99.7% bound to human plasma proteins. The apparent volume of distribution (V_c/F) is 70.3 L.

Metabolism: The metabolism of dabrafenib is primarily mediated by CYP2C8 and CYP3A4 to form hydroxy-dabrafenib. Hydroxy-dabrafenib is further oxidized via CYP3A4 to form carboxy-dabrafenib and subsequently excreted in bile and urine. Carboxy-dabrafenib is decarboxylated to form desmethyl-dabrafenib; desmethyl-dabrafenib may be reabsorbed from the gut. Desmethyl-dabrafenib is further metabolized by CYP3A4 to oxidative metabolites. Hydroxy-dabrafenib terminal half-life (10 hours) parallels that of dabrafenib while the carboxy- and desmethyl-dabrafenib metabolites exhibited longer half-lives (21 to 22 hours). Mean metabolite-to-parent AUC ratios following repeat-dose administration are 0.9, 11, and 0.7 for hydroxy-, carboxy-, and desmethyl-dabrafenib, respectively. Based on systemic exposure, relative potency, and pharmacokinetic properties, both hydroxy- and desmethyl-dabrafenib are likely to contribute to the clinical activity of dabrafenib.

Elimination: The mean terminal half-life of dabrafenib is 8 hours after oral administration. The apparent clearance of dabrafenib is 17.0 L/h after single dosing and 34.4 L/h after 2 weeks of twice-daily dosing.

Fecal excretion is the major route of elimination accounting for 71% of radioactive dose while urinary excretion accounted for 23% of total radioactivity as metabolites only.

Specific Populations:

Age, Body Weight, and Gender: Based on the population pharmacokinetics analysis, age has no effect on dabrafenib pharmacokinetics. Pharmacokinetic differences based on gender and on weight are not clinically relevant.

Pediatric: Pharmacokinetics of dabrafenib has not been studied in pediatric patients.

Renal: No formal pharmacokinetic trial in patients with renal impairment has been conducted. The pharmacokinetics of dabrafenib were evaluated using a population analysis in 233 patients with mild renal impairment (GFR 60 to 89 mL/min/1.73 m^2) and 30 patients with moderate renal impairment (GFR 30 to 59 mL/min/1.73 m^2) enrolled in clinical trials. Mild or moderate renal impairment has no effect on systemic exposure to dabrafenib and its metabolites. No data are available in patients with severe renal impairment.

Hepatic: No formal pharmacokinetic trial in patients with hepatic impairment has been conducted. The pharmacokinetics of dabrafenib was evaluated using a population analysis in 65 patients with mild hepatic impairment enrolled in clinical trials. Mild hepatic impairment has no effect on systemic exposure to dabrafenib and its metabolites. No data are available in patients with moderate to severe hepatic impairment.

Drug Interactions:

In vitro studies show that dabrafenib is a substrate of CYP3A4 and CYP2C8 while hydroxy-dabrafenib and desmethyl-dabrafenib are CYP3A4 substrates. Coadministration of dabrafenib 75 mg twice daily and ketoconazole 400 mg once daily (a strong CYP3A4 inhibitor) for 4 days increased dabrafenib AUC by 71%, hydroxy-dabrafenib AUC by 82%, and desmethyl-dabrafenib AUC by 68%. Coadministration of dabrafenib 75 mg twice daily and gemfibrozil 600 mg twice daily (a strong CYP2C8 inhibitor) for 4 days increased dabrafenib AUC by 47%, with no change in the AUC of dabrafenib metabolites. Dabrafenib is a substrate of human P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) in vitro.

In vitro data demonstrate that dabrafenib is an inducer of CYP3A4 and CYP2B6 via activation of the pregnane X receptor (PXR) and constitutive androstane receptor (CAR) nuclear receptors. Dabrafenib may also induce CYP2C enzymes via the same mechanism. Coadministration of dabrafenib 150 mg twice daily for 15 days and a single dose of midazolam 3 mg (a CYP3A4 substrate) decreased midazolam AUC by 74%. Coadministration of dabrafenib 150 mg twice daily for 15 days and a single dose of warfarin 15 mg decreased the AUC of S-warfarin (a CYP2C9 substrate) by 37% and the AUC of R-warfarin (a CYP3A4/CYP1A2 substrate) by 33% *[see Drug Interactions (7.2)]*.

Dabrafenib and its metabolites, hydroxy-dabrafenib, carboxy-dabrafenib, and desmethyl-dabrafenib, are inhibitors of human organic anion transporting polypeptide OATP1B1, OATP1B3 and organic anion transporter OAT1 and OAT3 in vitro. Dabrafenib and desmethyl-dabrafenib are inhibitors of BCRP in vitro.

Coadministration of trametinib 2 mg daily with dabrafenib 150 mg twice daily resulted in a 23% increase in AUC of dabrafenib, a 33% increase in AUC of desmethyl-dabrafenib, and no change in AUC of trametinib or hydroxy-dabrafenib as compared with administration of either drug alone.

Drugs that alter the pH of the upper GI tract (e.g., proton pump inhibitors, H_2-receptor antagonists, antacids) may alter the solubility of dabrafenib and reduce its bioavailability. However, no formal clinical trial has been conducted to evaluate the effect of gastric pH-altering agents on the systemic exposure of dabrafenib. When TAFINLAR is coadministered with a proton pump inhibitor, H_2-receptor antagonist, or antacid, systemic exposure of dabrafenib may be decreased and the effect on efficacy of TAFINLAR is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with dabrafenib have not been conducted. TAFINLAR increased the risk of cutaneous squamous cell carcinomas in patients in clinical trials.

Dabrafenib was not mutagenic in vitro in the bacterial reverse mutation assay (Ames test) or the mouse lymphoma assay, and was not clastogenic in an in vivo rat bone marrow micronucleus test.

In a combined female fertility and embryofetal development study in rats, a reduction in fertility was noted at doses greater than or equal to 20 mg/kg/day (equivalent to the human exposure at the recommended dose based on AUC). A reduction in the number of ovarian corpora lutea was noted in pregnant females at 300 mg/kg/day (which is approximately three times the human exposure at the recommended dose based on AUC).

Male fertility studies with dabrafenib have not been conducted; however, in repeat-dose studies, testicular degeneration/depletion was seen in rats and dogs at doses equivalent to and three times the human exposure at the recommended dose based on AUC, respectively.

13.2 Animal Toxicology and/or Pharmacology

Adverse cardiovascular effects were noted in dogs at dabrafenib doses of 50 mg/kg/day (approximately five times the human exposure at the recommended dose based on AUC) or greater, when administered for up to 4 weeks. Adverse effects consisted of coronary arterial degeneration/necrosis and hemorrhage, as well as cardiac atrioventricular valve hypertrophy/hemorrhage.

14 CLINICAL STUDIES

14.1 BRAF V600E Mutation-Positive Unresectable or Metastatic Melanoma

In Trial 1, the safety and efficacy of TAFINLAR as a single agent were demonstrated in an international, multicenter, randomized (3:1), open-label, active-controlled trial conducted in 250 patients with previously untreated BRAF V600E mutation-positive, unresectable or metastatic melanoma. Patients with any prior use of BRAF inhibitors or MEK inhibitors were excluded. Patients were randomized to receive TAFINLAR 150 mg orally twice daily (n = 187) or dacarbazine 1,000 mg/m^2 intravenously every 3 weeks (n = 63). Randomization was stratified by disease stage at baseline [unresectable stage III (regional nodal or in-transit metastases), M1a (distant skin, subcutaneous, or nodal metastases), or M1b (lung metastases) versus M1c melanoma (all other visceral metastases or elevated serum LDH)]. The main efficacy outcome measure was progression-free survival (PFS) as assessed by the investigator. In addition, an independent radiology review committee (IRRC) assessed the following efficacy outcome measures in pre-specified supportive analyses: PFS, confirmed objective response rate (ORR), and duration of response.

The median age of patients in Trial 1 was 52 years. The majority of the trial population was male (60%), white (99%), had an ECOG performance status of 0 (67%), M1c disease (66%), and normal LDH (62%). All patients had tumor tissue with mutations in BRAF V600E as determined by a clinical trial assay at a centralized testing site. Tumor samples from 243 patients (97%) were tested retrospectively, using an FDA-approved companion diagnostic test, THxID™-BRAF assay.

The median durations of follow-up prior to initiation of alternative treatment in patients randomized to receive TAFINLAR was 5.1 months and in the dacarbazine arm was 3.5 months. Twenty-eight (44%) patients crossed over from the dacarbazine arm at the time of disease progression to receive TAFINLAR.

Trial 1 demonstrated a statistically significant increase in progression-free survival in the patients treated with TAFINLAR. Table 7 and Figure 1 summarize the PFS results.

Table 7. Investigator-Assessed Progression-Free Survival and Confirmed Objective Response Results in Trial 1

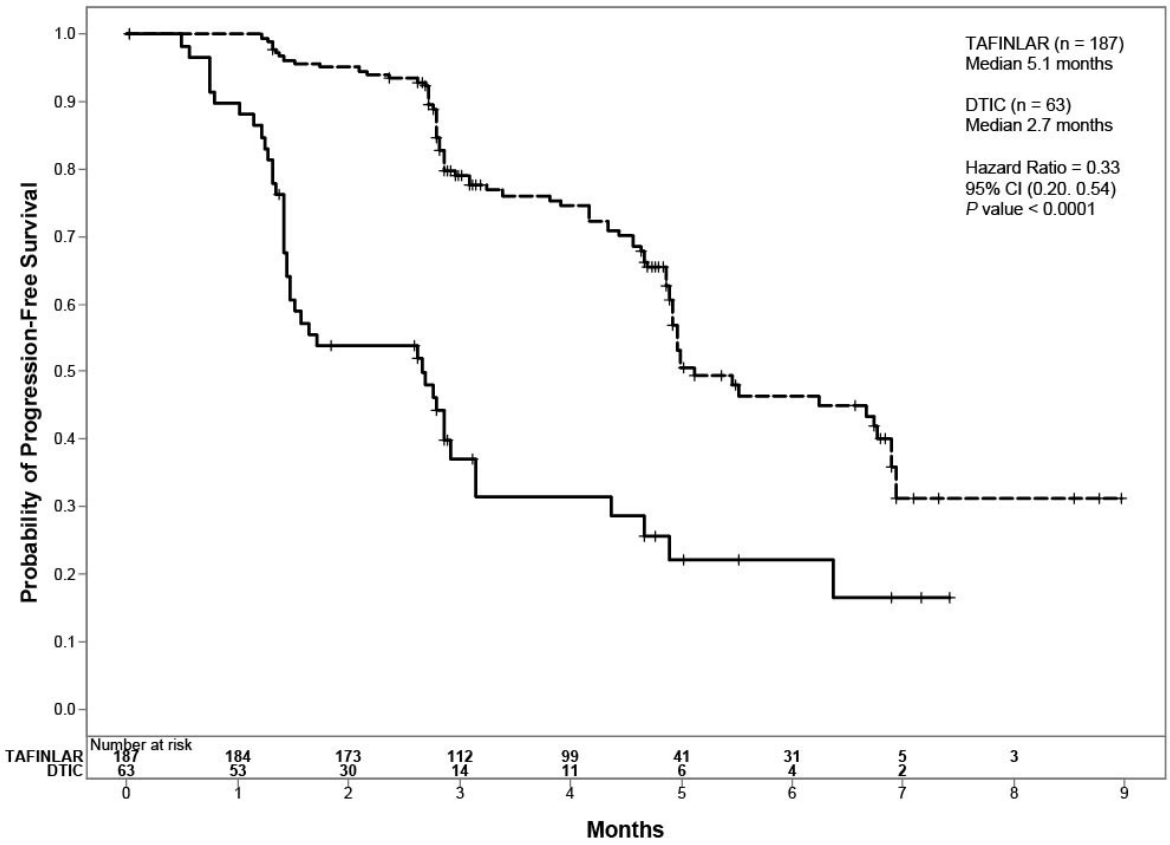
	TAFINLAR N = 187	**Dacarbazine N = 63**
Progression-free Survival		
Number of Events (%)	78 (42%)	41 (65%)
Progressive Disease	76	41
Death	2	0
Median, months (95% CI)	5.1 (4.9, 6.9)	2.7 (1.5, 3.2)
HR[a] (95% CI)	0.33 (0.20, 0.54)	
P-value[b]	*P* <0.0001	
Confirmed Tumor Responses		
Objective Response Rate	52%	17%
(95% CI)	(44, 59)	(9, 29)
CR, n (%)	6 (3%)	0
PR, n (%)	91 (48%)	11 (17%)
Duration of Response		
Median, months (95% CI)	5.6 (5.4, NR)	NR (5.0, NR)

[a] Pike estimator, stratified by disease state.

[b] Stratified log-rank test.

CI = Confidence interval; CR = Complete response; HR = Hazard ratio; NR = Not reached; PR = Partial response.

Figure 1. Kaplan-Meier Curves of Investigator-Assessed Progression-Free Survival



In supportive analyses based on IRRC assessment and in an exploratory subgroup analysis of patients with retrospectively confirmed V600E mutation-positive melanoma with the THxID™-BRAF assay, the PFS results were consistent with those of the primary efficacy analysis.

The activity of TAFINLAR for the treatment of BRAF V600E mutation-positive melanoma, metastatic to the brain was evaluated in a single-arm, open-label, two-cohort multi-center trial (Trial 3). All patients received TAFINLAR 150 mg twice daily. Patients in Cohort A (n = 74) had received no prior local therapy for brain metastases, while patients in Cohort B (n = 65) had received at least one local therapy for brain metastases, including, but not limited to, surgical resection, whole brain radiotherapy, or stereotactic radiosurgery such as gamma knife, linear-accelerated-based radiosurgery, charged particles, or CyberKnife. In addition, patients in Cohort B were required to have evidence of disease progression in a previously treated lesion or an untreated lesion. Additional eligibility criteria were at least one measurable lesion of 0.5 cm or greater in largest diameter on contrast-enhanced MRI, stable or decreasing corticosteroid dose, and no more than two prior systemic regimens for treatment of metastatic disease. The primary outcome measure was estimation of the overall intracranial response rate (OIRR) in each cohort.

The median age of patients in Cohort A was 50 years, 72% were male, 100% were white, 59% had a pre-treatment ECOG performance status of 0, and 57% had an elevated LDH value at baseline. The median age of patients in Cohort B was 51 years, 63% were male, 98% were white, 66% had a pre-treatment ECOG performance status of 0, and 54% had an elevated LDH value at baseline. Efficacy results as determined by an independent radiology review committee, masked to investigator response assessments, are provided in Table 8.

Table 8. Efficacy Results in Patients With BRAF V600E Melanoma Brain Metastases (Trial 3)

	IRRC Assessed Response	
Endpoint	**Cohort A** **N = 74**	**Cohort B** **N = 65**
Overall Intracranial Response Rate (OIRR) % (95% CI)	18 (9.7, 28.2)	18 (9.9, 30.0)
Duration of OIRR Median, months (95% CI)	(N = 13) 4.6 (2.8, NR)	(N = 12) 4.6 (1.9, 4.6)

IRRC = Independent radiology review committee; CI = Confidence interval; NR = Not reached.

14.2 BRAF V600E or V600K Unresectable or Metastatic Melanoma

Trial 2 was a multicenter, open-label, randomized (1:1:1) dose-ranging trial designed to evaluate the clinical activity and safety of TAFINLAR in combination with trametinib (at two different doses) and to compare the safety with TAFINLAR as a single agent in 162 patients with BRAF V600E or V600K mutation-positive, unresectable or metastatic melanoma. Patients were permitted to have had one prior chemotherapy regimen and prior aldesleukin; patients with prior exposure to BRAF or MEK inhibitors were ineligible. Patients were randomized to receive TAFINLAR 150 mg orally twice daily with trametinib 2 mg orally once daily (n = 54), TAFINLAR 150 mg orally twice daily with trametinib 1 mg orally twice daily (n = 54), or TAFINLAR 150 mg orally twice daily (n = 54). Treatment continued until disease progression or unacceptable toxicity. Patients randomized to TAFINLAR as a single agent were offered TAFINLAR 150 mg orally twice daily with trametinib 2 mg orally once daily at the time of investigator-assessed disease progression. The major efficacy outcome measure was investigator-assessed overall response rate (ORR). Additional efficacy outcome measures were investigator-assessed duration of response, independent radiology review committee (IRRC)-assessed ORR, and IRRC-assessed duration of response.

The median age of patients was 53 years, 57% were male, >99% were white, 66% of patients had a pre-treatment ECOG performance status of 0, 67% had M1c disease, 54% had a normal LDH at baseline, and 8% had history of brain metastases. Most patients (81%) had not received prior anti-cancer therapy for unresectable or metastatic disease. Based on local laboratory or centralized testing, 85% of patients' tumors had BRAF V600E mutations and 15% had BRAF V600K mutations.

The median duration of follow-up was 14 months. Efficacy outcomes for the trial arms receiving TAFINLAR in combination with trametinib 2 mg orally once daily and TAFINLAR as a single agent, are summarized in Table 9.

Table 9. Investigator-Assessed and Independent Review Committee-Assessed Response Rates and Response Duration in Trial 2

Endpoints	TAFINLAR plus Trametinib N = 54	TAFINLAR N = 54
Investigator Assessment		
Responders (ORR%) (95% CI)	41 (76%) (62%, 87%)	29 (54%) (40%, 67%)
Complete response	9%	4%
Partial response	67%	50%
Duration of Response (months)		
Median (95% CI)	10.5 (7, 15)	5.6 (5, 7)
Independent Radiology Review Committee Assessment		
Responders (ORR%) (95% CI)	31 (57%) (43%, 71%)	25 (46%) (33%, 60%)
Complete response	9%	7%
Partial response	48%	39%
Duration of Response (months)		
Median (95% CI)	7.6 (7, NR)	7.6 (6, NR)

CI = Confidence interval; ORR = Confirmed overall response rate; NR = Not reported.

The ORR results were similar in subgroups defined by BRAF mutation subtype, i.e., in the 85% of patients with V600E mutation-positive melanoma and in the 15% of patients with V600K mutation-positive melanoma. In exploratory subgroup analyses of the patients with retrospectively confirmed BRAF V600E or V600K mutation-positive melanoma using the THxID™-BRAF assay, the ORR results were also similar to the intent-to-treat analysis.

16 HOW SUPPLIED/STORAGE AND HANDLING

50 mg Capsules: Dark red capsule imprinted with ‘GS TEW’ and ‘50 mg’ available in bottles of 120 (NDC 0173-0846-08). Each bottle contains a silica gel desiccant.

75 mg Capsules: Dark pink capsule imprinted with ‘GS LHF’ and ‘75 mg’ available in bottles of 120 (NDC 0173-0847-08). Each bottle contains a silica gel desiccant.

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Inform patients of the following:

- Evidence of BRAF V600E mutation in the tumor specimen is necessary to identify patients for whom treatment with TAFINLAR as a single agent is indicated and evidence of BRAF V600E or V600K mutation in tumor specimens is necessary to identify patients for whom treatment with TAFINLAR in combination with trametinib is indicated *[see Dosage and Administration (2.1)]*.
- TAFINLAR increases the risk of developing new primary cutaneous and non-cutaneous malignancies. Advise patients to contact their doctor immediately for any new lesions, changes to existing lesions on their skin, or signs and symptoms of other malignancies *[see Warnings and Precautions (5.1)]*.
- TAFINLAR administered in combination with trametinib increases the risk of intracranial and gastrointestinal hemorrhage. Advise patients to contact their healthcare provider to seek immediate medical attention for signs or symptoms of unusual bleeding or hemorrhage *[see Warnings and Precautions (5.3)]*.
- TAFINLAR administered in combination with trametinib increases the risks of pulmonary embolism and deep venous thrombosis. Advise patients to seek immediate medical attention for sudden onset of difficulty breathing, leg pain, or swelling *[see Warnings and Precautions (5.4)]*.
- TAFINLAR administered in combination with trametinib can cause cardiomyopathy. Advise patients to immediately report any signs or symptoms of heart failure to their healthcare provider *[see Warnings and Precautions (5.5)]*.
- TAFINLAR can cause visual disturbances; TAFINLAR administered in combination with trametinib can lead to blindness. Advise patients to contact their healthcare provider if they experience any changes in their vision *[see Warnings and Precautions (5.6)]*.
- TAFINLAR, administered as a single agent and in combination with trametinib can cause pyrexia including serious febrile reactions. Inform patients that the incidence and severity of

pyrexia are increased when TAFINLAR is given in combination with trametinib. Instruct patients to contact their doctor if they develop fever while taking TAFINLAR *[see Warnings and Precautions (5.7)]*.

- TAFINLAR in combination with trametinib can cause serious skin toxicities which may require hospitalization. Advise patients to contact their healthcare provider for progressive or intolerable rash *[see Warnings and Precautions (5.8)]*.
- TAFINLAR can impair glucose control in diabetic patients resulting in the need for more intensive hypoglycemic treatment. Advise patients to contact their doctor to report symptoms of severe hyperglycemia *[see Warnings and Precautions (5.9)]*.
- TAFINLAR may cause hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Advise patients with known G6PD deficiency to contact their doctor to report signs or symptoms of anemia or hemolysis *[see Warnings and Precautions (5.10)]*.
- TAFINLAR can cause fetal harm if taken during pregnancy. Instruct female patients to use non-hormonal, highly effective contraception during treatment and for 2 weeks after discontinuation of treatment with TAFINLAR as a single agent, or for 4 months after discontinuation of treatment with TAFINLAR in combination with trametinib. Advise patients to contact their doctor if they become pregnant, or if pregnancy is suspected, while taking TAFINLAR *[see Warnings and Precautions (5.11), Use in Specific Populations (8.1)]*.
- Nursing infants may experience serious adverse reactions if the mother is taking TAFINLAR during breastfeeding. Advise breastfeeding mothers to discontinue nursing while taking TAFINLAR *[see Use in Specific Populations (8.3)]*.
- Male patients are at an increased risk for impaired spermatogenesis *[see Use in Specific Populations (8.6)]*.
- TAFINLAR should be taken either at least 1 hour before or at least 2 hours after a meal *[see Dosage and Administration (2.1)]*.

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THxID™ is a trademark of bioMérieux.

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Research Triangle Park, NC 27709
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TFR:XPI

MEDICATION GUIDE
TAFINLAR® (TAFF-in-lar)
(dabrafenib)
capsules

If your healthcare provider prescribes TAFINLAR for you in combination with trametinib, also read the Patient Information leaflet that comes with trametinib.

What is the most important information I should know about TAFINLAR?

TAFINLAR may cause serious side effects, including the risk of new cancers:

- **TAFINLAR, when used alone or in combination with trametinib, may cause a type of skin cancer, called cutaneous squamous cell carcinoma (cuSCC). New melanoma lesions have also occurred in people who take TAFINLAR.**
- **TAFINLAR, in combination with trametinib, may cause new cancers including basal cell carcinoma.**

Talk with your healthcare provider about your risk for these cancers.

Check your skin and tell your healthcare provider right away about any skin changes including a:

- new wart
- skin sore or reddish bump that bleeds or does not heal
- change in size or color of a mole

Your healthcare provider should check your skin before you start taking TAFINLAR, and every two months while taking TAFINLAR, to look for any new skin cancers. Your healthcare provider may continue to check your skin for six months after you stop taking TAFINLAR.

Your healthcare provider should also check for cancers that may not occur on the skin. Tell your healthcare provider about any new symptoms that have developed while taking TAFINLAR in combination with trametinib.

See "What are the possible side effects of TAFINLAR?" for more information about side effects.

What is TAFINLAR?

TAFINLAR is a prescription medicine used alone or in combination with trametinib to treat people with a type of skin cancer called melanoma:

- that has spread to other parts of the body or cannot be removed by surgery, and

- that has a certain type of abnormal “BRAF” gene.

Your healthcare provider will perform a test to make sure that TAFINLAR is right for you.

TAFINLAR (alone or in combination with trametinib) is not used to treat people with a type of skin cancer called wild-type BRAF melanoma.

It is not known if TAFINLAR is safe and effective in children.

What should I tell my healthcare provider before taking TAFINLAR?

Before you take TAFINLAR, tell your healthcare provider if you:

- have had bleeding problems or blood clots
- have heart problems
- have eye problems
- have liver or kidney problems
- have diabetes
- plan to have surgery, dental, or other medical procedures
- have a deficiency of the glucose-6-phosphate dehydrogenase (G6PD) enzyme
- have any other medical conditions
- are pregnant or plan to become pregnant. TAFINLAR can harm your unborn baby.
    - Females who are able to become pregnant should use birth control (contraception) during treatment with TAFINLAR and for 2 weeks after stopping treatment with TAFINLAR alone, or for 4 months when taking TAFINLAR in combination with trametinib.
    - Birth control using hormones (such as birth control pills, injections, or patches) may not work as well while you are taking TAFINLAR alone or in combination with trametinib. You should use another effective method of birth control while taking TAFINLAR alone or in combination with trametinib.
    - Talk to your healthcare provider about birth control methods that may be right for you during this time.
    - Tell your healthcare provider right away if you become pregnant during treatment with TAFINLAR alone or in combination with trametinib.
- are breastfeeding or plan to breastfeed. It is not known if TAFINLAR passes into your breast milk. You and your healthcare provider should decide if you will take TAFINLAR or breastfeed. You should not do both.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. TAFINLAR and certain other medicines can affect each other, causing side effects. TAFINLAR may affect the way other medicines work, and other medicines may affect how TAFINLAR works. You can ask your pharmacist for a list of medicines that may interact with TAFINLAR.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I take TAFINLAR?

- Take TAFINLAR exactly as your healthcare provider tells you. Do not change your dose or stop TAFINLAR unless your healthcare provider tells you.
- Take TAFINLAR 2 times a day, about 12 hours apart.
- If you take TAFINLAR in combination with trametinib, take the first dose of TAFINLAR in the morning, and take the second dose of TAFINLAR in the evening, about 12 hours apart. Take trametinib 1 time a day at the same time each day, either with the morning or the evening dose of TAFINLAR.
- Take TAFINLAR at least 1 hour before or 2 hours after a meal.
- Do not open, crush, or break TAFINLAR capsules.
- If you miss a dose of TAFINLAR, take it as soon as you remember. But, if it is within 6 hours of your next scheduled dose, just take your next dose at your regular time. Do not make up for the missed dose.
- If you are taking TAFINLAR in combination with trametinib and you miss a dose of trametinib, take it as soon as you remember. But, if it is within 12 hours of your next scheduled dose of trametinib, just take your next dose at your regular time. Do not make up for the missed dose.
- If you take too much TAFINLAR, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible side effects of TAFINLAR?

TAFINLAR may cause serious side effects, including:

- **See "What is the most important information I should know about TAFINLAR?"**
- **bleeding problems.** TAFINLAR, in combination with trametinib, can cause serious bleeding problems,especially in your brain or stomach, and can lead to death. Call your healthcare provider and get medical help right away if you have any unusual signs of bleeding, including:

  - headaches, dizziness, or feeling weak
  - cough up blood or blood clots
  - vomit blood or your vomit looks like “coffee grounds”
  - red or black stools that look like tar
- **blood clots.** TAFINLAR, in combination with trametinib, can cause blood clots in your arms or legs, which can travel to your lungs and can lead to death. Get medical help right away if you have the following symptoms:
  - chest pain
  - sudden shortness of breath or trouble breathing
  - pain in your legs with or without swelling
  - swelling in your arms or legs
  - a cool or pale arm or leg
- **heart problems, including heart failure.** Your healthcare provider should check your heart function before you start taking TAFINLAR in combination with trametinib and during treatment. Call your healthcare provider right away if you have any of the following signs and symptoms of a heart problem:
  - feeling like your heart is pounding or racing
  - shortness of breath
  - swelling of your ankles and feet
  - feeling lightheaded
- **eye problems.** TAFINLAR alone, or in combination with trametinib, can cause severe eye problems that can lead to blindness. Call your healthcare provider right away if you get these symptoms of eye problems:
  - blurred vision, loss of vision, or other vision changes
  - see color dots
  - halo (seeing blurred outline around objects)
  - eye pain, swelling, or redness
- **fever.** TAFINLAR alone or in combination with trametinib can cause fever which may be serious. When taking TAFINLAR, in combination with trametinib, fever may happen more often or may be more severe. In some cases, chills or shaking chills, too much fluid loss (dehydration), low blood pressure, dizziness, or kidney problems may happen with the fever. Call your healthcare provider right away if you get a fever while taking TAFINLAR.

- **skin reactions.** Rash is a common side effect of TAFINLAR alone, or when used in combination with trametinib. TAFINLAR alone, or in combination with trametinib, can also cause other skin reactions. In some cases these rashes and other skin reactions can be severe, and may need to be treated in a hospital. Call your healthcare provider if you get any of the following symptoms:
  - skin rash that bothers you or does not go away
  - acne
  - redness, swelling, peeling, or tenderness of hands or feet
  - skin redness
- **increased blood sugar (hyperglycemia).** Some people may develop high blood sugar or worsening diabetes during treatment with TAFINLAR, alone or in combination with trametinib. If you are diabetic, your healthcare provider should check your blood sugar levels closely during treatment with TAFINLAR alone or in combination with trametinib. Your diabetes medicine may need to be changed. Tell your healthcare provider if you have any of the following symptoms of severe high blood sugar:
  - increased thirst
  - urinating more often than normal, or urinating an increased amount of urine
- **TAFINLAR may cause healthy red blood cells to break down too early in people with G6PD deficiency.** This may lead to a type of anemia called hemolytic anemia where the body does not have enough healthy red blood cells. Tell your healthcare provider if you have any of the following signs or symptoms of anemia or breakdown of red blood cells:
  - yellow skin (jaundice)
  - weakness or dizziness
  - shortness of breath

The most common side effects of TAFINLAR when used alone include:

- thickening of the outer layers of the skin
- headache
- joint aches
- warts
- hair loss
- redness, swelling, peeling, or tenderness of hands or feet

Common side effects of TAFINLAR when used in combination with trametinib include:

- tiredness
- nausea or vomiting
- stomach-area (abdominal) pain
- diarrhea
- cough
- swelling of the face, arms, or legs
- headache
- night sweats
- decreased appetite
- constipation
- muscle or joint aches

TAFINLAR, in combination with trametinib, may cause fertility problems in females. This could affect your ability to become pregnant. Talk to your healthcare provider if this is a concern for you.

TAFINLAR may cause lower sperm counts in males. This could affect the ability to father a child. Talk to your healthcare provider if this is a concern for you.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of TAFINLAR. For more information about side effects, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to GlaxoSmithKline at 1-888-825-5249.

How should I store TAFINLAR?

Store TAFINLAR at room temperature, between 68°F to 77°F (20°C to 25°C).

Keep TAFINLAR and all medicine out of the reach of children.

General information about TAFINLAR

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use TAFINLAR for a condition for which it was not

prescribed. Do not give TAFINLAR to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about TAFINLAR that is written for health professionals.

For more information, call GlaxoSmithKline at 1-888-825-5249 or go to www.TAFINLAR.com.

What are the ingredients in TAFINLAR?

Active ingredient: dabrafenib

Inactive ingredients: colloidal silicon dioxide, magnesium stearate, microcrystalline cellulose

Capsule shells: hypromellose, red iron oxide (E172), titanium dioxide (E171).

This Medication Guide has been approved by the U.S. Food and Drug Administration.

GlaxoSmithKline
Research Triangle Park, NC 27709
Revised: January 2014
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TFR:XMG

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202806Orig1s002

SUMMARY REVIEW

Division Director Summary Review

Date	January 9, 2013
From	Patricia Keegan
Subject	Division Director Summary Review
NDASupplement #	202806/S-002
Applicant Name	GlaxoSmithKline
Date of Submission	July 8, 2013
PDUFA Goal Date	January 8, 2014
Proprietary Name / Established (USAN) Name	Taflinar/ dabrafenib capsules
Dosage Forms / Strength	capsules for oral administration/ 75mg and 50 mg
Proposed Indication(s)	TAFINLAR in combination with trametinib is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. The indication for use of TAFINLAR in combination with trametinib is based on the demonstration of durable response rate. (b) (4)
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager Review	Norma Griffin
Medical Officer Review	Maitreyee Hazarika
Statistical Review	Weishi (Vivian) Yuan
Pharmacology Toxicology Review	Alexander Putman
Quality Review	Sue Ching Lin
Clinical Pharmacology Review	Ruby Leong
OPDP	Quynh-Van Tran
OSI	Lauren Iacono-Connors
Patient Labeling Team Review	Nathan Caulk
Maternal Health Team Review	Carrie Ceresa

OND=Office of New Drugs
OSI=Office of Scientific Integrity
OPDP=Office of Prescription Drug Promotion

Reference ID: 3434259

Division Directory Summary Review

1. Introduction

Tafinlar (dabrafenib; GlaxoSmithKline) is an inhibitor of certain (BRAF V600E, BRAF V600K, and BRAF V600D) mutated forms of the BRAF kinase, a component of the mitogen-activated protein kinase (MAPK) pathway, in signaling leads through activation of the RAS/RAF/MEK/ERK cascade. For approximately 50% of patients with metastatic melanoma, the melanoma cells contain BRAF V600E mutation of the BRAF gene. In nonclinical studies, this mutation results in constitutively activated BRAF kinases that may stimulate tumor cell growth. Dabrafenib inhibits BRAF V600 mutation-positive melanoma cell growth in vitro and in vivo. The rationale development supporting this drug development program was based on the knowledge that dabrafenib and trametinib target different tyrosine kinases in the MAPK pathway and that, when used in combination, dabrafenib and trametinib resulted in greater growth inhibition of BRAF V600 mutation-positive melanoma cell lines in vitro and prolonged inhibition of tumor growth in BRAF V600 mutation positive melanoma xenografts compared with either drug alone.

On May 29, 2013, dafenib received accelerated approval for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation, as detected by an FDA-approved test. Approval was based primarily on the results of a single, randomized, open-label, multicenter trial (Protocol BRF113683) which compared the safety and efficacy of dabrafenib to dacarbazine in patients with previously untreated, unresectable locally advanced or metastatic cutaneous melanoma with BRAF V600E mutations as detected by a clinical trial assay. This trial demonstrated a statistically robust and clinically important improvement in progression-free survival (HR 0.33 $p<0.001$; median PFS of 5.4 months vs. 2.7 months) and a higher response rate (52% vs. 17%) for patients with previously untreated, metastatic or unresectable, BRAF V600E, cutaneous melanoma who were randomized to dabrafenib as compared to those randomized to dacarbazine.

This efficacy supplement will be approved for the following indication

> TAFINLAR, in combination with trametinib, is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test. This indication is based on the demonstration of durable response rate *[see Clinical Studies (14.2)]*. Improvement in disease-related symptoms or overall survival has not been demonstrated for TAFINLAR in combination with trametinib.

Approval is based on the results of a clinical substudy (Part C) within a larger, multi-stage protocol, Study BRF113220. Part C of the protocol was an open-label, three-arm, randomized trial that enrolled 162 patients with BRAF V600E or V600K mutation-positive, unresectable

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or metastatic melanoma. Patients were permitted to have had one prior chemotherapy regimen and prior aldesleukin; patients with prior exposure to BRAF or MEK inhibitors were ineligible. Patients were randomized (1:1:1) to the following treatment arms:

- dabrafenib at the approved dose (150 mg twice daily (BID)
- trametinib 1 mg daily plus dabrafenib 150 mg BID, or
- trametinib at the approved dose (2 mg daily) plus dabrafenib 150 mg BID.

Consistent with the approved labeling, treatment continued until unacceptable toxicity or investigator-assessed disease progression. Patients randomized to dabrafenib as a single agent were offered trametinib 2 mg plus dabrafenib 150 mg BID at the time of investigator-assessed disease progression.

The initial objective of this substudy was to demonstrate that the addition of trametinib to dabrafenib resulted in a reduction or abrogation of the development of dabrafenib-induced squamous cell cancers of the skin or keratoacanothoma. The protocol was subsequently revised, with the new primary objective of investigator-assessed overall response rate (ORR). Since this change occurred during the course of the trial, determination of alpha allocation was challenging and thus data are provided without test statistics. Secondary endpoints included the incidence of new primary skin cancers, investigator-assessed duration of response, independent radiology review committee (IRRC)-assessed ORR, and IRRC-assessed duration of response.

Of the 162 patients enrolled in this trial, most (67%) had M1c disease, 46% had a elevanted LDH at baseline, and 8% had a history of brain metastases. Most patients (81%) had not received prior anti-cancer therapy for unresectable or metastatic disease. All patients had tumor containing BRAF V600E or V600K mutations as determined by local laboratory or centralized testing, 85% with BRAF V600E mutations and 15% with BRAF V600K mutations.

The trial demonstrated a higher overall investigator-assessed response rate (76% vs. 54%) for patients randomized to receive trametinib at 2 mg po daily plus dabrafenib 150 mg BID as compared those randomized to receive dabrafenib 150 mg BID. The median durations of response by investigator assessment were 10.5 and 5.6 months, respectively. These response assessment and duration of response data were subsequently reviewed by an IRRC, which yielded qualitatively similar results (ORR 57% vs. 46%) and median durations of responses of 7.6 months in both arms. The common and serious adverse reactions of each single agent were generally observed in patients receiving the combination, however the incidence and severity of serious febrile reactions was higher with the combination and the incidence of cutaneous skin cancers was lower with the combination that with dabrafenib alone. In addition, two new safety signals were identified in the combination arm; the incidence of hemorrhage was 16% for the combination compared with 2% for dabrafenib alone and the incidence of venous thromboembolism was 4% for the combination compared with none in the dabrafenib alone arm.

The major issues considered during the review of this efficacy supplement were (1) whether the results of this study, which isolated the contribution of trametinib, should be included in

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the dabrafenib label and (2) the extent to which information relating to dabrafenib should be included in product labeling. The applicant, GlaxoSmithKline, proposed inclusion of dosing (particularly dose modifications) (b) (4) in the Tafinlar product labeling. The rationale for inclusion of these data in product labeling is discussed in Sections 7 and 8 of this review, respectively.

2. Background

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

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

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

On March 25, 2011, FDA approved ipilimumab (Yervoy, Bristol Myers Squibb) for the treatment of unresectable or metastatic melanoma. Ipilimumab is a fully human IgG1 kappa monoclonal antibody that is directed against the human cytotoxic lymphocyte antigen-4 (CTLA-4) present on activated T-cells. The approval of ipilimumab was based on the results of a single, randomized trial which demonstrated a statistically significant improvement in overall survival for patients receiving ipilimumab in combination with a peptide vaccine (gp100 peptides) compared to those receiving peptide vaccine alone [HR 0.66 (95% CI: 0.55,

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

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0.85), p=0.0004] with median survival times of 9.95 months and 6.44 months in the combination and gp100 monotherapy arms, respectively. The application was also supported by the high level results of Protocol CA 184024, a randomized trial of dacarbazine with or without ipilimumab, in which the high level results also demonstrated an improvement in overall survival [HR 0.85 (95% CI: 0.76, 0.93)] with a nominal p-value of 0.001, stratified log-rank test.

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

On May 29, 2013, trametinib was approved for XXXXX. Approval was based on Protocol MEK114267, a randomized (2:1), open-label, active-controlled, multinational comparing trametinib to single agent chemotherapy (dacarbazine or paclitaxel). A total of 322 patients were randomized to trametinib (n=214) at a dose or 2 mg orally once daily or one of two chemotherapy regimens (n=108), selected at the discretion of the investigator and consisting of dacarbazine 1000 mg/m^2 or paclitaxel 175 mg/m^2 by intravenous infusion every 21 days. The trial demonstrated a statistically significant improvement in the PFS for the trametinib arm compared with chemotherapy [HR 0.47 (95% confidence intervals (CI): 0.34, 0.65)] with an increase in median PFS from 1.5 months in the chemotherapy arm to a median PFS of 4.8 months for the trametinib arm.

On May 29, 2013, dabrafenib was approved for the the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation, as detected by an FDA-approved test. The basis for approval is discussed under in the next subsection on the regulatory history of NDA 202806.

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

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Regulatory History for NDA 202806

May 29, 2013: NDA 202806 was approved for Tafinlar (dabrafenib) capsules for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation, as detected by an FDA-approved test. Approval was based on the results of a single, randomized, open-label, multicenter trial (Protocol BRF113683) which compared the safety and efficacy of dabrafenib to dacarbazine in patients with previously untreated, unresectable locally advanced or metastatic cutaneous melanoma with BRAF V600E mutations as detected by a clinical trials assay and was supported by evidence of clinical activity (objective tumor responses) in two non-comparative trials of single agent dabrafenib in patients with previously untreated or previously treated, BRAF V600E or V600K mutation-positive, metastatic melanoma (BREAK –2 and BREAK-MB trials), (b) (4) for patients with unresectable locally advanced or metastatic cutaneous melanoma with BRAF V600K mutations and for treatment of CNS metastases from BRAF V600E primary melanomas, respectively.

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

Regulatory History of N202806/S-002

Clinical development was initiated for single agent dabrafenib and trametinib were initiated under IND 102175 and IND 105032, respectively. The clinical development for the combination of dabrafenib and trametinib, including conduct of the ongoing on-going Phase 1/2 trial of the combination, Study BRF113220 was continued under IND 113557.

October 7, 2010: A Type A meeting was held to discuss the revised development program for the combination of dabrafenib and trametinib for treatment of BRAF mutation-positive melanoma. FDA recommended a three-arm randomized study of trametinib vs. dabrafenib vs. the combination. FDA stated approval of both agents in combination would be considered if the combination arm is markedly superior.

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February 24, 2011: An end-of-Phase 1/pre-Phase 3 meeting was held to discuss the development program for treatment of patients with BRAF V600E, V660K (b) (4) mutation-positive, advanced or metastatic melanoma based primarily on the results of a three-arm, double-blind, randomized trial, Study MEK115306, comparing the combination of dabrafenib 150 mg twice daily and trametinib 2 mg daily to single agent dabrafenib 150 mg twice daily plus placebo and to single agent trametinib 2 mg daily plus placebo in patients with BRAF V600 mutation-positive, advanced or metastatic melanoma. The trial would be powered to demonstrate superior overall and progression-free survival for the combination to dabrafenib alone and superior progression-free survival for the combination to trametinib alone. Key agreements and advice communicated were

- GSK would conduct further development under a new IND and provide supportive information (final results of overall response rate from the single arm trial, BRF113370, of dabrafenib) to the new IND.
- Stdy BRF113370 would need to show a durable response rate of at least 50% to support single agent activity of dabrafenib.
- Overall survival should be the sole primary endpoint for the comparison of the dabrafenib to the combination of dabrafenib and trametinib in Study MEK115306. GSK agreed to revise the protocol for this comparison; since OS was the primary endpoint an IRC would not be required for tumor-based endpoints for this comparison
- For the comparison of trametinib to the combination of dabrafenib and trametinib in Study MEK115306, an improvement in PFS for the combination would provide supportive data for the combination arm (i.e., in addition to the pairwise comparison described in the bullet above.
- Study MEK115306 was not adequate in design to support approval of dabrafenib or trametinib as a single agent.
- A dedicated drug-interaction study would not be required if PK analyses in Studies BRF113220 and MEK115306 adequately evaluate for these interactions

January 27, 2012: A preIND meeting (pIND 113557) was held to discuss the continued development of the combination of dabrafenib and trametinib, consisting of the ongoing randomized activity-estimating trial (BRF113220) and two proposed randomized trials (MEK115306 and MEK116513). The MEK115306 trial was discussed during February 24, 2011 meeting. The MEK116513 trial was a randomized (1: 1), open-label study comparing the combination of the dabrafenib and trametinib to single agent vemurafenib as first-line treatment in 640 patients with unresectable (Stage IIIc) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma. Patients randomized to the experimental arm were to receive dabrafenib 150 mg orally twice daily and trametinib 2 mg orally once daily. Patients randomized to the control arm were to receive vemurafenib 960 mg orally twice daily. There were no provisions for crossover to the non-randomized treatment after progression. The primary endpoint of this trial was OS, and secondary endpoints included PFS, ORR and DoR. During this meeting, GSK proposed submission of the mature results of Study BRF113220, relying primarily on the randomized comparisons in Part C of that trial. GSK also proposed that

- GSK has maintained all scans and therefore a blinded independent central review (i.e. IRC review) of the scans can occur.

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- Patients for BRF 113220 were screened using local testing, not the RGI or the bioMerieux IUO assay. To address this issue, GSK intends to test all patient samples retrospectively with the bioMerieux IUO assay. GSK now possesses approximately 75% of the samples from this study (60% tissue and 15% DNA) and is in the process of obtaining the majority of samples.
- BRF113220 was conducted using the gelatin capsule of dabrafenib, not the intended to-be-marketed HPMC capsule dosage form. As noted during the May 5, 2011 teleconference with FDA and summarized in Appendix 1 Section 1.3 .3, the HPMC encapsulation resulted in higher exposure compared to the gelatin capsule (LS mean ratios (90% CIs) for AUC(O-∞) of 1.80 (1.32, 2.46)). Results from Part D of Study BRF113220 using HPMC capsules will be used to guide the dose selection for the proposed MEK115306 and MEK116513 trials.
- GSK planned to conduct final PFS analysis of BRF113220 when 70% events have occurred with approximately 15 months of median follow-up time (approximately June 2012).

Key agreements and advice during this meeting included:

- That GSK would request another meeting when the BRF113220 results were mature
- That the approach described above to address changes in intent of BRF113220 were generally acceptable; safety and efficacy data with dabrafenib HPMC capsules should include clinical data from all relevant studies; data from ongoing combination studies should be used to characterize drug interactions and justify rationale for not conducted a dedicated DDI study
- FDA agreed to rely on all available data sources to establish treatment effects of trametinib and would not require a trametinib monotherapy arm in future Phase 3 trials. FDA stated that cross-study comparisons would not suffice and that non-clinical data should also be submitted to support the contribution of trametinib to the combination.
- FDA agreed [redacted] (b) (4) based primarily on the results of MEK115306 with demonstration of a robust effect on PFS of sufficient magnitude to permit a positive risk-benefit determination in the event that BRF113220 was not sufficient robust to support approval. Under this scenario, MEK115306 should be adequately powered to rule out a clinically important, detrimental effect on survival and an interim analysis of survival should be provided in the application for assessment of safety. Whether the minimally-detectable, statistically significant PFS difference of two months as proposed for this trial constitutes clinical benefit would be a review issue.
- FDA agreed that the completed and ongoing non-clinical studies appeared adequate to support the proposed Phase 3 trial, and may be adequate to support the [redacted] (b) (4)
- In ongoing trials, GSK agreed that new cutaneous skin cancers (cuSCC) would be identified as serious adverse events; targeted monitoring for secondary cancers would be incorporated in the trials, and targeted collected of information for such events would be collected

June 29, 2012: FDA granted fast track designation for the development program for trametinib (GSK1120212) and dabrafenib (GSK2118436) for the treatment of patients with

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BRAF V600E or BRAF V600K mutation-positive, unresectable or metastatic melanoma to demonstrate improved overall response rates, progression-free survival, and overall survival.

September 12, 2012: Pre-NDA meeting to discuss the mature results from Part C of Study BRF113220, based on a data cut-off date of May 31, 2012, and to gain agreement on the contents (b) (4) for the use of these two agents used in combination. Key agreements and advice included

- (b) (4) FDA stated that an application should be submitted for the combination under a request for accelerated approval based on (1) compelling scientific rationale for the interactions between dabrafenib plus trametini (b) (4) (2), the nominal increase in overall response rate for the combination of dabrafenib plus trametinib over dabrafenib monotherapy; and (3) (b) (4)
- The application should include a discussion, based on clinical trial data, as to why dabrafenib/trametinib treatment administered sequentially is ineffective.
- FDA stated that the BRF113220 trial is likely to be evaluated as three single-arm trials rather than rely on comparison between arms to establish efficacy.
- GSK confirmed that efficacy will be verified in ongoing trials MEK115306 and MEK116513 and confirmed previous statements that the accelerated approval for the combination therapy will be withdrawn voluntarily if the confirmatory trials do not verify clinical benefit.
- Data from Part D of Study BRF113220 should be provided to support the safety and efficacy of the dabrafenib HPMC capsule dosage form; a follow-up teleconference would be scheduled on the formal bioequivalence trial between the dabrafenib two dosage forms.
- Formal agreement on the content of (b) (4) was not reached because insufficient information was provided in the meeting briefing package.

September 26, 2012: Teleconference held to continue discussion with Clinical Pharmacology discipline on Question 2 of September 12, 2012 pre-NDA meeting. Key agreements and advice included:

- GSK acknowledged that the to-be-marketed HPMC capsules are not bioequivalent to gelatin capsules, with higher exposure observed in a bioequivalence study. As discussed during the 9/12/2012 meeting, the clinical impact of the higher exposure with HPMC capsules on safety parameters needs to be addressed.
- GSK agreed with FDA in that the data collected in the combination trials is not adequate to demonstrate bioequivalence between the to-be-marketed product and the clinical trial product. Therefore, FDA reiterated, and GSK agreed, to provide additional safety data for the to-be-marketed product given the higher exposure observed with this product.

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December 6, 2012: preNDA meeting to discuss the content and format of a [redacted] (b) (4), including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and to reach agreement with FDA on late submissions (no later than 30 days after the submission of the original application). Key agreements and advice included:

- Agreement on the contents of a complete applicationp
- FDA's recommendation that the application be provided in CDISC format
- Based on the briefing package, FDA agreed that a REMS should not be included in the NDA
- FDA agreed to accept a late submission (no later than 30 days after receipt of the original application) information supporting bridging studies for the investigational-use only (IUO) and to-be-marketed companion diagnostic test.

3. CMC/Device /Biopharmaceutics

I concur with the conclusions reached by the chemistry reviewer that there are no outstanding issues that preclude approval of this supplement. The supplement does not include new CMC information and does not propose changes to the approved carton and immediate container labeling or to the CMC information in the physician package insert labeling. changes.

The CMC reviewer reviewed and determined that the categorical exclusion from the preparation of an environmental assessment, requested under 21 CFR 25.31(b), was acceptable.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding nonclinical pharmacology or toxicology issues that preclude approval. The supplement contained pharmacology studies evaluating the combination of trametinib and dabrafenib; these studies demonstrated that the dabrafenib and trametinib combination results in greater growth inhibition of BRAFV600 mutation-positive cell lines *in vitro* and *in vivo* xenograft models than with either drug alone. These data have been included in the Clinical Pharmacology section, under Mechanism of Action.

In addition, the supplement contained chronic (4-week) toxicology studies of trametinib and dabrafenib, administered concomitantly and a toxicology study of dabrafenib in juvenile rats. The findings of the chronic toxicology study for the combination did not suggest novel signals (i.e., not observed in clinical trials) and therefore were not included in the NonClinical Toxicology section of product labeling. In the juvenile rat study, there was evidence of effects on growth development (kidney cysts and tubular deposits, decreased bone length, and forestomach hyperplasia). There was also evidence of early vaginal opening, an indicator of early sexual development, however GSK noted that other signs of early sexual maturation were not observed and have attributed this finding to cutaneous effects. [redacted] (b) (4)

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(b) (4) these data have been included in product labeling in the Use in Specific Populations, Pediatric Use subsection.

5. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval. Clinical pharmacology assessment of the combination was conducted in Protocol BRF113220, as follows

- Part A to assess the potential for drug interactions between dabrafenib and trametinib;
- Part B to assess the tolerable doses of dabrafenib and trametinib when administered in combination;
- Part C to assess population pharmacokinetic (popPK) and exposure-response (E-R) analyses using PK data from Part C of Study BRF113220 did not identify clinically important covariates influencing dabrafenib or trametinib PK. There appears to be an E-R relationship for efficacy (ORR) with trametinib, which is consistent with the higher ORR observed with the 2 mg versus 1 mg daily dose of trametinib in combination with 150 mg BID dabrafenib. There is evidence for a relationship between safety (pyrexia) and hydroxy-dabrafenib, supporting the proposed dose reduction for management of patients with pyrexia in product labeling; and
- Part D to assess differences in pharmacokinetics (PK) and safety with the marketed HPMC formulation and gelatin clinical trial formulation of dabrafenib.

Product labeling was updated to include the results of drug interaction assessments. Although trametinib increases dabrafenib exposure by 23%, this increase was not deemed to be clinical significant; no effects of dabrafenib on trametinib exposure were observed. As noted by the clinical pharmacologist, the population PK analysis did not identify clinically meaningful effects of body weight, age, gender, mild and moderate renal impairment, or mild hepatic impairment as covariates on clearance or volume of distribution of dabrafenib and trametinib when used in combination.

In addition, for consistency across product labeling, FDA requested and GSK agreed to shorten the duration of contraceptive use following the last dose of dabrafenib. The direction to continue highly effective contraceptive use for 2 weeks after the last dose of dabrafenib is based on 5-half lives for the active metabolites, which is longer than for the parent drug.

6. Clinical Microbiology

Not applicable for this efficacy supplement.

7. Clinical/Statistical-Efficacy

Protocol BRF 113220, titled “An Open-Label, Dose-Escalation, Phase I/II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of the BRAF Inhibitor

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GSK2118436 in Combination with the MEK Inhibitor GSK1120212 in Subjects with BRAF Mutant Metastatic Melanoma" was generated on November 30, 2009. Protocol BRF113220 was amended six times between August 2, 2010 and February 26, 2013.

August 2, 2010: BRF113220 was amended to modify safety assessments, include supportive care guidelines, and to add a plan for randomization to treatment arms in Part C.

December 8, 2010: BRF113220 was amended to revise secondary endpoints for Part C, update safety assessments and supportive care guidelines, and in Part C to 50 patients per arm.

June 20, 2011: BRF113220 was amended to add an evaluation of the pharmacokinetics of dabrafenib HPMC capsules in Part and provide additional details on the interim analyses of safety and efficacy in Part C.

December 16, 2011: BRF113220 was amended to include results obtained to date, to add overall survival as a secondary endpoint in Parts B, C, and D, to add a requirement for patient follow-up every 3 months for survival, and to enroll an additional 15 patients in cohort B to collect pharmacodynamic biomarkers (based on tumor biopsies and PDG-PET) in patients with BRAF mutant colorectal cancer; clarified dose modification guidelines for fever; management of renal toxicity; and modified exclusion criteria for MEK inhibitors and prior anti-cancer therapy.

March 30, 2012: Protocol BRF113220 was to clarify the secondary objectives for Part C; modify the PK sampling schedule; add monitoring and management of hypertension guidelines; clarify drug rechallenge following hepatotoxicity.

February 26, 2013: BRF113220 was amended to clarify secondary objectives for overall survival in Part C; allow dose escalation in Part D; revise prohibited and cautionary medications lists; modify hypertension management guidelines; clarify LVEF stopping criteria; and revised description of final analysis of overall survival.

Protocol Design

The study design, as specified in BRF113220, version 6, is an open-label, dose escalation trial designed to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of dabrafenib and trametinib administered in combination. This trial consists of four distinct parts (A-D)

- Part A was designed to evaluated the effect of multiple doses of trametinib on the pharmacokinetics of single dose of dabrafinib and will evaluate for drug interactions
- Part B was designed to determine the tolerable doses of dabrafenib and trametinib administered in combination.
- Part C was designed to evaluate the clinical activity of dabrafenib and trametinib in combination; population pharmacokinetics for both drugs will also be assessed.
- Part D was designed to evaluate the safety, tolerability, pharmacokinetics and clinical activity of dabrafenib HPMC administered alone and in combination with trametinib.

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In Part C of Study BRF113220, patients were randomized (1:1:1) to

- dabrafenib 150 mg twice daily (BID),
- trametinib 1 mg daily plus dabrafenib 150 mg BID, or
- trametinib 2 mg daily plus dabrafenib 150 mg BID.

Treatment was to continue until unacceptable toxicity or investigator-assessed disease progression. Patients randomized to dabrafenib as a single agent were offered trametinib 2 mg plus dabrafenib 150 mg BID at the time of investigator-assessed disease progression. Key eligibility criteria were BRAF V600E or V600K mutation-positive, unresectable or metastatic melanoma. Patients were permitted to have had one prior chemotherapy regimen and prior aldesleukin; patients with prior exposure to BRAF or MEK inhibitors were ineligible. . In the analysis plan, the primary efficacy endpoints were ORR and progression-free survival, with overall survival as a secondary endpoint. The final analysis of survival was to occur after events in 70% of the study population. As noted by the statistical reviewer (Dr. Yuan), the formal hypothesis testing was specified only for the safety endpoint of comparative incidence of new superficial skin cancers. A power analysis was not conducted for any efficacy endpoint and no adjustments for multiplicity or for interim analyses were proposed.Additional efficacy outcome measures were independent radiology review committee (IRRC)-assessed ORR and IRRC-assessed duration of response. The independent radiology review committee was constituted after the study was initiated, which led to discrepancies between investigators and the IRRC on whether all patients were evaluable for response at baseline. Patients deemed inevaluable by the IRRC were identified as non-responders in the IRRC-assessed determination of response rate and duration.

Bioresearch monitoring inspections were conducted at two clinical sites which were chosen based on Two clinical sites were chosen based on the number of patients enrolled at these sites (21 patients and 22 patients, respectively) and the high response rates reported. The inspectors concluded that the data from these sites were deemed reliable for determination of safety and efficacy.

Results

The trial enrolled 162 patients across at 16 sites; two sites were in Australia and 14 sites were in the US. The median age of patients in Part C of Study BRF113220 was 53 years, 57% were male, >99% were white, 66% of patients had a pretreatment ECOG performance status of 0, 67% had M1c disease, 54% had a normal LDH at baseline, and 8% had a history of brain metastases. Most patients (81%) had not received prior anti-cancer therapy for unresectable or metastatic disease. All patients had tumor containing BRAF V600E or V600K mutations as determined by local laboratory or centralized testing, 85% with BRAF V600E mutations and 15% with BRAF V600K mutations.

The median duration of follow-up was 14 months.

The efficacy results are summarized in the table below, abstracted from the package insert:

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Table (b) (4) Investigator-Assessed and Independent Review Committee-Assessed Response Rates and Response Durations in Trial 2

Endpoints	Trametinib plus Dabrafenib N = 54	Dabrafenib N = 54
Investigator Assessment		
Responders (ORR%) (95% CI)	41 (76%) (62%, 87%)	29 (54%) (40%, 67%)
Complete response	9%	4%
Partial response	67%	50%
Duration of Response (months)		
Median (95% CI)	10.5 (7, 15)	5.6 (5, 7)
Independent Radiology Review Committee Assessment		
Responders (ORR%) (95% CI)	31 (57%) (43%, 71%)	25 (46%) (33%, 60%)
Complete response	9%	7%
Partial response	48%	39%
Duration of Response (months)		
Median (95% CI)	7.6 (7, NR)	7.6 (6, NR)

CI=Confidence interval; ORR=Confirmed overall response rate; NR Not reported.

(b) (4)

At the time of the data cut-off, 117 patients had progressed or died based on the investigator assessment. The median PFS was 8.4 months in the dabrafenib plus trametinib 2 mg arm and 5.8 months in the dabrafenib alone; comparison of PFS demonstrated a HR of 0.39 (95% CI 0.25, 0.62), based on a Pike estimator stratified by disease stage. At the time of the data cut-off for the clinical study report, there were 33 deaths and the median survival times had not been reached. There was no difference in survival between the dabrafenib plus trametinib 2 mg arm and dabrafenib alone [HR 0.67 (95% CI: 0.34, 1.34].

The ORR results were similar in subgroups defined by BRAF mutation subtype, i.e., in the 85% of patients with V600E mutation-positive melanoma and in the 15% of patients with V600K mutation-positive melanoma. These results are provided in the table below, abstracted from Dr. Yuan's review.

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Endpoints	Trametinib plus Dabrafenib N = 47	Dabrafenib N = 45
Investigator Assessment		
BRAF V600E		
ORR (95% CI)	36 (77%) (62%, 88%)	26 (58%) (42%, 72%)
Median Duration of Response (months)	10.5	5.6
(95% CI)	(7, 15)	(4, 7)
	Trametinib plus Dabrafenib N = 7	**Dabrafenib N = 9**
BRAF V600E		
ORR (95% CI)	5 (71%) (29, 96)	3 (33%) (7, 70)
Median Duration of Response (months)	NE	5.5
(95% CI)	(7,NE)	(4, 6)

NE=not-estimable

In exploratory subgroup analyses of the patients with retrospectively confirmed BRAF V600E or V600K mutation-positive melanoma using the THxID™-BRAF assay, the ORR results were also similar to the intent-to-treat analysis.

A major issue considered by the Division and review team was whether the results of Part C of Study BRF113220 should be included in the dabrafenib labeling, given that the trial was designed only to establish that the addition of trametinib results in superior responses as compared to dabrafenib alone. In order to show that dabrafenib "adds value" to the combination requires a cross-study comparison of the combination to single agent trametinib. In comparing data from this trial to that used to support approval of trametinib (at the dose and schedule to be approved for the combination use), the differences in ORR are so great (22% for single agent trametinib vs. 76% for the combination in the new trial) that it is not credible that they result from differences in patient factors alone. In addition, dabrafenib and trametinib have a strong pharmacologic basis supporting combination use based on well-characterized inhibition at different points in the MAPK pathway; evidence of these pharmacologic interactions were confirmed in this trial with improved efficacy and, as predicted, improvement in certain risks, specifically the risk of new primary cutaneous malignancies.

This is consistent with the advice provided to GSK at the September 12, 2012 meeting, discussed in greater detail in Section 2 of this review, in which FDA stated (b) (4) FDA stated that an application should be submitted for the combination under a request for accelerated approval based on (1) compelling scientific rationale for the interactions between dabrafenib plus trametinib, (b) (4) (2), the nominal

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increase in overall response rate for the combination of dabrafenib plus trametinib over dabrafenib monotherapy; and (3) (b) (4)

Additional considerations supporting inclusion of these results in Tafinlar labeling were that the single-arm dabrafenib cohort provided compelling results of efficacy both for BRAF V600E and BRAF V600K mutation-positive melanoma because the endpoint of objective tumor shrinkage can be readily compared to historical controls. Use of time-to-event endpoint would have precluded an evaluation of efficacy in the single agent dabrafenib arm. Finally, the results of the study, including all relevant documentation, were available to the applicant for both drugs, since it is the same sponsor and evidence of an effect on a surrogate, resulting in accelerated approval, in the major subgroup of this patient population (patients with nor prior systemic therapy for BRAF V600E mutation-positive melanoma) has already been confirmed.

8. Safety

Size of the database,
The size of the safety database from in Part C of Study BRF113220 was not adequate to identify adverse reactions occurring at an incidence of up to 3% in patients receiving trametinib plus dabrafenib, however the inclusion of a control arm did increase the ability to identify adverse reactions occurring more frequently in the combination arm that with dabrafenib alone. The safety profile for combination use was supplemented with data from other clinical trials, with an integrated safety database of 202 patients receiving trametinib plus dabrafenib across clinical trials. In these 202 patients, 68 (34%) were exposed to trametinib and 66 (33%) were exposed to dabrafenib for greater than 6 to 12 months while 36 (18%) were exposed to trametinib and 40 (20%) were exposed to dabrafenib for greater than one year.

However, the adequacy of the safety database also relied on safety information from the prior approval of dabrafenib, in which safety was evaluated in 586 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma, previously treated or untreated, who received TAFINLAR 150 mg orally twice daily until disease progression or unacceptable toxicity, including 181 patients treated for at least 6 months and 86 additional patients treated for more than 12 months. TAFINLAR was studied in open-label, single-arm trials and in an open-label, randomized, active-controlled trial.

Major safety concerns related to labeling
Serious adverse reactions of dabrafenib previously identified during drug development were new primary malignancies, predominantly cutaneous, serious febrile drug reactions, hyperglycemia, and uveitis and iritis. These were also seen in patients receiving dabrafenib in combination with trametinib, however as discussed below, the incidence of new primary malignancies was lower with the combination than with dabrafenib alone.

There were two serious adverse reactions of trametinib that were not reported for patients receiving dabrafenib in combination with trametinib; these were interstitial lung disease and

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retinal vein occlusion. Given the small number of patients receiving both drugs in the two combination arms (109 patients; of whom 55 received trametinib 2 mg daily plus dabrafenib and 54 received trametinib 1 mg daily plus dabrafenib) as well as the low incidence of these events, it is unclear whether there is actually a difference in incidence when trametinib is administered with dabrafenib as compared to single agent trametinib. Because no events were reported, these risks were not included in Tafinlar labeling as doing so would be based only on events in patients receiving trametinib only. Tafinlar labeling will be updated to include such events if they are observed with the combination.

Among patients receiving dabrafenib in combination with trametinib, novel serious adverse reactions were identified; specifically hemorrhage and venous thromboembolism, which were not identified with either drug as a single agent in earlier studies. In Part C of Study BRF113220, the incidence and severity of hemorrhagic events were increased in patients receiving trametinib plus dabrafenib compared with dabrafenib alone (16% vs. 2%). Major hemorrhagic events of intracranial or gastric hemorrhage occurred in 5% (3/55) of patients treated with trametinib and dabrafenib compared with none of the 53 patients treated with dabrafenib alone. Intracranial hemorrhage was fatal in two (4%) patients receiving the combination.

In Part C of Study BRF113220, the incidence and severity of venous thromboembolism were increased in patients receiving trametinib plus dabrafenib compared with dabrafenib alone. The incidence of deep venous thrombosis or pulmonary embolism was 7% for the combination compared with no events in 53 patients who received dabrafenib alone. Pulmonary embolism was fatal in one (2%) patient receiving the combination.

In addition, the incidence and severity of febrile drug reactions, a common and sometimes serious adverse reaction of dabrafenib, were increased with the addition of trametinib. In Part C of Study BRF113220, the incidence of fever (serious and non-serious) was 71% (39/55) for patients receiving trametinib plus dabrafenib compared with 26% (14/53) in patients treated with dabrafenib alone. Serious febrile reactions and fever of any severity accompanied by hypotension, rigors or chills occurred in 25% (14/55) of patients treated with trametinib plus dabrafenib compared with 2% (1/53) of patients treated with dabrafenib alone.

As hypothesized, the addition of trametinib to dabrafenib resulted in a lower incidence of cutaneous squamous cell carcinomas and keratoacanthomas. The incidence of cutaneous squamous cell carcinomas or keratoacanthoma was lower in patients who received trametinib plus dabrafenib than in those receiving dabrafenib alone (7% vs. 19%). The incidence of new primary melanomas was similar in both groups, with 2% incidence (1/53) for patients receiving the combination and no cases in patients receiving dabrafenib alone.

However, the incidence of basal cell cancers may have been increased when trametinib was added to dabrafenib. , the incidence of basal cell carcinoma was increased in patients receiving trametinib plus dabrafenib compared to dabrafenib alone (9% vs. 2%). There were not enough cases of new primary, non-cutaneous, primary cancers to determine whether the addition of trametinib had any effect on the incidence of such events with dabrafenib alone.

With regard to general tolerability of the combination regimen, 13% of patients receiving dabrafenib in combination with trametinib (2 mg dose) in Part C of Study BRF113220 experienced adverse reactions resulting in permanent discontinuation of trial medication(s). The most common adverse reaction resulting in permanent discontinuation was pyrexia (4%).

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Adverse reactions led to dose reductions in 49% and dose interruptions in 67% of patients treated with trametinib plus dabrafenib. Pyrexia, chills, and nausea were the most common reasons cited for dose reductions, and pyrexia, chills, and decreased ejection fraction were the most common reasons cited for dose interruptions of trametinib plus dabrafenib.

The most common adverse reactions (with an incidence of ≥20%) in patients receiving trametinib plus dabrafenib were pyrexia, chills, fatigue, rash, nausea, vomiting, diarrhea, abdominal pain, peripheral edema, cough, headache, arthralgia, night sweats, decreased appetite, constipation, and myalgia.

A summary of the most common adverse reactions and of the most common laboratory abnormalities observed in Part C of Study BRF113220, by treatment arm, are presented in the following tables abstracted from the Tafinlar label.

Table 5. Common Adverse Drug Reactions Occurring in ≥10% at (All Grades) or ≥5% (Grades 3 or 4) of Patients Treated With TAFINLAR in Combination With Trametinib in Trial 2

	TAFINLAR plus Trametinib 2 mg N = 55		TAFINLAR plus Trametinib 1 mg N = 54		TAFINLAR N = 53	
Adverse Reactions	**All Grades[a]**	**Grades 3 and 4**	**All Grades[a]**	**Grades 3 and 4**	**All Grades[a]**	**Grades 3 and 4**
General disorders and administrative site conditions						
Pyrexia	71	5	69	9	26	0
Chills	58	2	50	2	17	0
Fatigue	53	4	57	2	40	6
Edema peripheral[b]	31	0	28	0	17	0
Skin and subcutaneous tissue disorders						
Rash[c]	45	0	43	2	53	0
Night Sweats	24	0	15	0	6	0
Dry skin	18	0	9	0	6	0
Dermatitis acneiform	16	0	11	0	4	0
Actinic keratosis	15	0	7	0	9	0
Erythema	15	0	6	0	2	0
Pruritus	11	0	11	0	13	0
Gastrointestinal disorders						
Nausea	44	2	46	6	21	0
Vomiting	40	2	43	4	15	0
Diarrhea	36	2	26	0	28	0
Abdominal pain[d]	33	2	24	2	21	2
Constipation	22	0	17	2	11	0
Dry mouth	11	0	11	0	6	0
Nervous system disorders						
Headache	29	0	37	2	28	0
Dizziness	16	0	13	0	9	0

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Adverse Reactions	TAFINLAR plus Trametinib 2 mg N = 55		TAFINLAR plus Trametinib 1 mg N = 54		TAFINLAR N = 53	
	All Grades[a]	Grades 3 and 4	All Grades[a]	Grades 3 and 4	All Grades[a]	Grades 3 and 4
Respiratory, thoracic, and mediastinal disorders						
Cough	29	0	11	0	21	0
Oropharyngeal pain	13	0	7	0	0	0
Musculoskeletal, connective tissue, and bone disorders						
Arthralgia	27	0	44	0	34	0
Myalgia	22	2	24	0	23	2
Back pain	18	5	11	0	11	2
Muscle spasms	16	0	2	0	4	0
Pain in extremity	16	0	11	2	19	0
Metabolism and nutritional disorders						
Decreased appetite	22	0	30	0	19	0
Dehydration	11	0	6	2	2	0
Psychiatric Disorders						
Insomnia	18	0	11	0	8	2
Vascular disorders						
Hemorrhage[e]	16	5	11	0	2	0
Infections and infestations						
Urinary tract infection	13	2	6	0	9	2
Renal and urinary disorders						
Renal failure[f]	7	7	2	0	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.
[b] Includes the following terms: peripheral edema, edema, and lymphedema.
[c] Includes the following terms: rash, rash generalized, rash pruritic, rash erythematous, rash papular, rash vesicular, rash macular, and rash maculo-papular.
[d] Includes the following terms: abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort.
[e] Includes the following terms: brain stem hemorrhage, cerebral hemorrhage, gastric hemorrhage, epistaxis, gingival hemorrhage, hematuria, vaginal hemorrhage, hemorrhage intracranial, eye hemorrhage, and vitreous hemorrhage.
[f] Includes the following terms: renal failure and renal failure acute.

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Table 6. Treatment-Emergent Laboratory Abnormalities Occurring at ≥10% (All Grades) or ≥2% (Grades 3 or 4)] of Patients Treated With TAFINLAR in Combination With Trametinib in Trial 2

Tests	TAFINLAR plus Trametinib 2 mg N = 55		TAFINLAR plus Trametinib 1 mg N = 54		TAFINLAR N = 53	
	All Grades	Grades 3 and 4[a]	All Grades	Grades 3 and 4	All Grades	Grades 3 and 4
Hematology						
Leukopenia	62	5	46	4	21	0
Lymphopenia	55	22	59	19	40	6
Neutropenia	55	13	37	2	9	2
Anemia	55	4	46	7	28	0
Thrombocytopenia	31	4	31	2	8	0
Liver Function Tests						
Increased AST	60	5	54	0	15	0
Increased alkaline phosphatase	60	2	67	6	26	2
Increased ALT	42	4	35	4	11	0
Hyperbilirubinemia	15	0	7	4	0	0
Chemistry						
Hyperglycemia	58	5	67	6	49	2
Increased GGT	56	11	54	17	38	2
Hyponatremia	55	11	48	15	36	2
Hypoalbuminemia	53	0	43	2	23	0
Hypophosphatemia	47	5	41	11	40	0
Hypokalemia	29	2	15	2	23	6
Increased creatinine	24	5	20	2	9	0
Hypomagnesemia	18	2	2	0	6	0
Hyperkalemia	18	0	22	0	15	4
Hypercalcemia	15	0	19	2	4	0
Hypocalcemia	13	0	20	0	9	0

(b) (4)

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; GGT = Gamma glutamyltransferase.

In Part C of Study BRF113220, the incidence of QTcF prolongation (>500msec) was similar in the two arms, occurring in 4% (2/55) of patients treated with trametinib plus dabrafenib and in 2% (1/53) of patients treated with dabrafenib alone. However, the proportion of patients with an increase in QTcF from baseline of > 60 msec was higher for patients receiving the combination as compared to dabrafenib alone (135 vs. 2%).

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Postmarketing data
There were no post-marketing data that provided substantial new safety signals beyond those identified in clinical trials.

Final labeling recommendations
The applicant proposed inclusion of information on trametinib in the following sections relating to product safety of the dabrafenib labeling

- Dosage and Administration section – this included dosing instructions and specific dose modification information for trametinib for febrile drug reactions, with references to the need to modify trametinib for [redacted] (b) (4) retinal vein occlusion [redacted] (b) (4)
- Warnings and Precautions – this included information from Part C of Study of BRF113220 in subsections on New Primary Cutaneous Malignancies, Serious Febrile Drug Reactions, Hyperglycemia, and Uveitis and Iritis.
- Adverse Reactions: Inclusion of data from all three study arms from Part C of Study of BRF113220, including the trametinib 1 mg combination arm, which will not be labeled for use and dose not inform the Tafinlar label.

While inclusion of adverse reaction information is typical, such data usually focus on the added toxicity of the new drug to the single agent in the combination. In this instance, because the two drugs have a strong pharmacologic basis of interaction and because the combination of the two drugs results in improved efficacy, it is anticipated that the future use of these two drugs will only be in combination, rather than as single agents is greater than with most drugs. In addition, given the variable outcomes of the pharmacologic interactions on risks, with lower risk of new skin cancers but higher risks of cutaneous toxicity and of serious febrile reactions, appropriate dose modification would be challenging without inclusion of directions for both agents.

The Division presented their proposal to take an unorthodox approach to product labeling, by inclusion of extensive safety data from both drugs in the product labeling of each, to the Office of Medical Policy (OMP). The OMP endorsed this approach, considering the unique pharmacologic interactions which are well-characterized on a molecular level.

REMS
I concur with the determination of the review team that a REMS is not required to ensure safe and effective use of this combination.

PMRs and PMCs
I concur with the determination of the review team that no new post-marketing requirements or commitments are needed to evaluate safety signals. I note that additional safety information will be provided in the trials required under the provisions of 21 CFR 314.510 which will further inform the safety profile of this combination.

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9. Advisory Committee Meeting

This efficacy supplement was not referred for review to the Oncologic Drugs Advisory Committee (ODAC) because this is not the original approval of dabrafenib, there were no issues related to the clinical trial design or primary endpoint used to support accelerated approval, and there were no novel issues identified that would benefit from the Advisory Committee's expertise.

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10. Pediatrics

Orphan drug designation was granted for the combination of dabrafenib and trametinib on September 20, 2012 for the treatment of Stage IIb through IV melanoma, therefore this supplement is not subject to the requirements of the Pediatric Research Equity Act (PREA).

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

Bioresearch monitoring inspections were conducted at two clinical sites; these sites were chosen for inspection based on enrollment of large numbers of study subjects and a high rate of objective response. Based on the interim classification, the Office of Scientific Integrity finds that the deviations not on FDA inspections can be addressed with voluntary action and that the data are reliable.

12. Labeling

- Proprietary name: Not applicable for this efficacy supplement.

- Physician labeling

  Please see Sections 7 and 8 of this review regarding the approach taken on inclusion of efficacy data from Part C of Study BRF113220 and of data on the safety of the concomitant use of dabrafenib and trametinib in product labeling.

  Dosage and Administration: This section was edited for brevity and clarity. Information on dabrafenib dose modifications were included in separate columns and directions for modification of dosing for each drug in the event of any serious or severe adverse reaction were included.

  Warnings and Precautions: information on all serious adverse reactions of either drug were included in product labeling with the exception of interstitial lung disease and retinal vein occlusion, since cases of other each serious adverse reactions of trametinib (i.e.,

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cardiomyopathy, retinal pigment epithelial detachment, and serious skin toxicity) were also observed in patients receiving dabrafenib and trametinib in combination in Part C of Study BRF113220. In addition, new subsections on Hemorrhage and Venous Thromboembolism were included based on results observed in this trial. In general, the description of these adverse reactions and management (primarily dose modifications) were harmonized between the two labels for description of this study.

Adverse Reactions: information on laboratory abnormalities was expanded to include information on QT assessments and clinical chemistries.

Drug Interactions: Information on the evaluation for interactions of drugs that affect gastric pH on dabrafenib pharmacokinetics was moved to the Clinical Pharmacology section as no clinically relevant changes were observed requiring dose modifications of dabrafenib or avoidance of drugs affecting gastric pH. As discussed above, information on the effects of dabrafenib on trametinib were included in this section, as proposed by the applicant.

Use in Specific Populations
Information on contraceptive use and on risks of infertility from both trametinib and dabrafenib were included to ensure adequate counseling on both agents when used in combination. Recommendations on the duration of contraceptive use after the last dose of dabrafenib were modified to conform to current practices of the Oncology Office (OHOP) to recommend dosing for up to 5 half-lives of the drug, if the potential for embryofetal toxicity exists. The half-life of the active metabolite rather than the parent drug was used, given the longer half-life of the former. Non-clinical study data added to pediatric use subsection (see discussion in section 4 of this review) and information geriatric use updated to include lack of adequate information for combination use.

Clinical pharmacology updated with information mechanism of action of the combination from non-clinical pharmacology studies; information on drug interactions on combination use added; information on dabrafenib interactions added.

Clinical Studies: Information on Part C of Study BRF113220 edited for brevity and for inclusion of information as discussed in FDA Guidance on this section of product labeling (e.g., inclusion of patient characteristics and study design elements). (b) (4) [redacted] Efficacy data were included for reasons discussed in Section 7 and also to support expansion of the indication to include treatment of patients with BRAF V600K mutation-positive melanoma when dabrafenib is administered in combination with trametinib. (b) (4) [redacted]

Patient Counseling modified to include counseling information on trametinib, when used in combination with dabrafenib.

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- Carton and immediate container labels: No modifications to approved carton and container labeling were recommended or incorporated under this efficacy supplement.

- Medication guide: The Medication Guide was modified to include information on the new indication and dosage regimen (in combination with trametinib), a description of serious and common side effects attributable to either drug in the combination (consistent with the approach taken for the physician package insert), and editorial changes for consistency with Patient Labeling guidance (e.g., patient-friendly language).

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval

- Risk Benefit Assessment
  BRAF V600 mutation positive melanoma is a serious disease with poor survival despite available therapies. In light of these serious risks of death from metastatic cancer, the benefits of a more effective therapeutic regimen (combination of trametinib and dabrafenib) outweigh the risks of this regimen.

  The results of the substudy (Part C) of Study BRF113220 demonstrate a clinically meaningful improvement in the overall response rate that are very durable (median duration of approximately 10 months) for a major subset (approximately 50%) of patients with metastatic melanoma. These results are supported by the demonstrated clinical activity of each drug as a single agent and the strong pharmacologic rationale for the combination. The most common risks of the combination (with an incidence of ≥20%) were pyrexia, chills, fatigue, rash, nausea, vomiting, diarrhea, abdominal pain, peripheral edema, cough, headache, arthralgia, night sweats, decreased appetite, constipation, and myalgia. These risks are considered acceptable given the potential for benefit. The incidence risks of overall and serious cutaneous toxicity and of serious febrile reactions were higher for the combination however the risk of new primary skin cancers (squamous cell cancers and keratoacanthoma) were lower for the combination than for single agent dabrafenib. The incidence of other serious risks (notably cardiomyopathy, ocular toxicities, and interstitial lung disease) appeared to be similar to the risks with single agent therapy, risks already deemed to be acceptable. Two novel signals were identified for the combination; hemorrhage and venous thromboembolism. The number of events observed was small and additional data will be needed to determine if these risks remain acceptable over time – such data will be obtained in the ongoing confirmatory trial and in other post-marketing commitments.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
  I concur with the recommendations of the clinical reviewer that a REMS is not required to ensure safe and effective use of this drug for the proposed indication.

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- Recommendation for other Postmarketing Requirements and Commitments
  A post-marketing trial is required to verify clinical benefit (as a condition of approval under 21 CFR 314.510). This trial is Study MEK115306, an ongoing, randomized, double-blind, trial comparing dabrafenib and trametinib in combination to dabrafenib alone for the first line treatment of patients with unresectable or metastatic BRAF V600E/K mutation-positive cutaneous melanoma. The planned enrollment is 340 patients and the primary endpoint for this study is progression-free survival and a key secondary endpoint is overall survival.

  In addition, the review team requested, and GSK agreed to provide, the following information as agreed-upon post-marketing commitments to provide additional data on long-term outcomes and survival.

  - To complete and submit the final study report for Study MEK116513, an ongoing, randomized, open-label, two-arm trial comparing dabrafenib and trametinib in combination with vemurafenib alone for the first-line treatment of patients with unresectable or metastatic BRAF V600E/K mutation-positive cutaneous melanoma. The planned enrollment of this study is 694 patients and the primary endpoint for this study is overall survival.

  - To complete and submit the final study report, including datasets, for Part C of trial BRF113220 that compares the combination of dabrafenib and trametinib to dabrafenib in patients with unresectable or metastatic BRAF V600E or V600K mutation-positive melanoma

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/s/

PATRICIA KEEGAN
01/09/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202806Orig1s002

OFFICER/EMPLOYEE LIST

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Officer/Employee List
Application: Efficacy Supplement sNDA 202806/S-002

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202806Orig1s002

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Efficacy Supplement
Application Number(s)	NDA 202806, NDA 204114
Priority or Standard	Priority
Submit Date(s)	07/08/2013, 07/08/2013
Received Date(s)	07/09/2013, 07/08/2013
PDUFA Goal Date(s)	01/09/2014, 01/08/2014
Division / Office	DOP2 / OHOP
Reviewer Name(s) Team Leader	Maitreyee Hazarika, MD Marc Theoret, MD
Review Completion Date	12/15/2013
Established Name	Dabrafenib, Trametinib
Trade Name	TAFINLAR, MEKINIST
Therapeutic Class	kinase inhibitor, kinase inhibitor
Applicant	GlaxoSmithKline
Formulation(s)	Dabrafenib capsules, Trametinib tablets for oral use
Dosing Regimen	Dabrafenib 150 mg orally BID, Trametinib 2 mg orally QD
Indication	Treatment of adult patients with BRAF V600E or V600K unresectable or metastatic melanoma
Intended Population	≥ 18 years of age

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The reviewer recommends accelerated approval [(Subpart H (21CFR314.510)] of the combination of dabrafenib and trametinib for use in the treatment of adults with BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma, for this supplemental new drug application (sNDA).

The clinical data presented in the sNDA demonstrate the efficacy of the combination of dabrafenib and trametinib in confirmed overall response rate (76%) which appears to be durable (median of 10.5 months). The Applicant has two ongoing randomized controlled trials designed to compare the efficacy of the combination dabrafenib and trametinib to a single-agent BRAF inhibitor and data from these trials could potentially be the basis for regular approval. The safety profile of the combination is acceptable, given the serious life-threatening nature of the disease.

1.2 Risk Benefit Assessment

The risk benefit assessment is favorable for the use of the combination of dabrafenib and trametinib in patients with BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma (See Table 1).

Table 1: Risk Benefit Assessment

Decision Factor	Evidence and Uncertainties	Conclusions and Recommendations
Analysis of Condition: BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma	The condition is an orphan indication that is considered serious and life threatening. Historically, the survival of patients with melanoma and distant metastatic disease has been 6 to 9 months. Approximately 50% of patients who are treated with BRAF or MEK inhibitors have disease progression within approximately five months after initiation of treatment. The expected long-term outcomes of BRAF V600 mutation-positive advanced melanoma is not well-defined with the rapidly evolving range of therapeutic options.	BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma is a serious and life threatening condition for which the combination of dabrafenib and trametinib demonstrated clinical activity in patients with both BRAF V600E and V600K mutations.
Unmet Medical Need	Recent FDA-approved available drugs for the condition are immunotherapy (IL-2, ipilimumab) and kinase inhibitors (BRAF inhibitors and MEK inhibitors). Both dabrafenib (BRAF inhibitor) and	There is a clear need for options for decreasing the emergence of resistance. In trial BRF113220, the confirmed overall response rate (ORR) was 76% and the

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Decision Factor	Evidence and Uncertainties	Conclusions and Recommendations
	trametinib (MEK inhibitor) received regular approval as single-agents. Patients who respond to initial therapy characteristically progress and require additional therapy. Resistance occurs commonly with BRAF-inhibitor therapy.	median duration of response (DOR) was 10.5 months for the combination of dabrafenib and trametinib compared to a confirmed ORR of 54% and median DOR of 5.6 months for the dabrafenib monotherapy treatment.
Clinical Benefit	The investigator-assessed confirmed ORR was 76% (95% CI: 62%, 87%) on the 150/2 combination treatment arm and 54% (95% CI: 40%, 67%) on the dabrafenib monotherapy arm. The median duration of response was 10.5 months (95% CI: 7, 15) for objective responders on the 150/2 combination arm and 5.6 months (95% CI: 4, 7) on the dabrafenib monotherapy arm; the treatment effect of the combination appeared consistent irrespective of BRAF V600 mutation subtype (V600E and V600K) The median PFS was 9.4 months for the 150/2 combination group and 5.8 months for the dabrafenib monotherapy group [HR 0.39, 95% CI (0.25, 0.62)]. After a median follow-up of 24 months, the median OS for the 150/2 mg combination was 23.8 months (95% CI: 17.5,NR), compared to 20.2 months (95% CI: 14.5, 25.9) for dabrafenib monotherapy [HR 0.73 (0.43, 1.24]. P-values were not calculated because formal statistical tests were not pre-specified for the endpoints. Uncertainties in the clinical benefit are based on the trial design in which the contribution of the effect of each single-agent to the effect on the combination is uncertain and which did not isolate the effect of dabrafenib in the combination. Uncertainties based on the endpoints include the uncertain relationship of ORR to outcomes of ultimate clinical benefit and uncertainly in the absolute magnitude of the effect and duration of the effect based on the discrepancy in ORR and duration of response between	Efficacy results from trial BRF113220 of ORR of 76% and median duration of 10.5 months indicate that the combination of dabrafenib 150 mg twice daily and trametinib 2 mg once daily has clinical activity. The evidence of substantial anti-tumor activity with the combination of dabrafenib and trametinib, and early evidence to suggest that the combination is not detrimental to survival, appears reasonably likely to predict an ultimate outcome of clinical benefit and supports accelerated approval.

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Decision Factor	Evidence and Uncertainties	Conclusions and Recommendations
	the investigator-assessment and independent assessment.	
Risks	The safety profile is notable for development of serious adverse events (SAEs) in more than half of the trial population (62%), dose interruptions due to adverse events of trametinib in 64% and dabrafenib in 62% of patients, dose reductions due to adverse events of trametinib in 22% and dabrafenib in 33% of patients, and permanent discontinuations in 9% of patients. Pyrexia accounted for the greatest number of SAEs. Pyrexia occurred at a higher incidence with the combination than with dabrafenib monotherapy. Other common AEs were generally consistent with single-agent dabrafenib or trametinib use . Unexpected AEs, such as thromboembolic events (8%) and major hemorrhagic events (6%) occurred at a higher incidence with the combination compared to dabrafenib monotherapy. Uncertainties in the risks exist based on the relatively small safety database for the combination and the two different formulations of dabrafenib used in Trial BRF113220.	According to review of the data in this application, the safety profile of dabrafenib in combination with trametinib is acceptable in the intended patient population. Pyrexia is manageable with the use of anti-pyretics and corticosteroids. Of note, secondary cutaneous squamous cell carcinoma and keratoacanthoma occurred less commonly in the 150/2 combination treatment arm (7%) compared to the dabrafenib monotherapy arm (19%). One confirmatory trial with approximately 340 patients and an additional randomized control trial with approximately 700 patients are ongoing and data from these trials better characterize the safety profile of dabrafenib and trametinib when used in combination.
Risk Management	The applicant has not proposed a risk evaluation and mitigation strategy (REMS).	A REMS is not recommended.

Recommendation for Accelerated Approval versus Regular Approval

21 CFR 314.510 of subpart H addresses marketing approval based on an effect on a clinical endpoint other than survival or irreversible morbidity. Accelerated approval is “subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome.” The recommendation for accelerated approval for the combination of dabrafenib and trametinib rather than regular approval, which was granted for single-agent dabrafenib (Tafinlar) and for single-agent trametinib (Mekinist) for treatment of patients with unresectable or metastatic melanoma with BRAF V600E or with BRAF V600E or V600K mutations, respectively, is based upon the following considerations:

- There is uncertainty as to the relation of ORR and DOR to ultimate outcomes indicative of clinical benefit, including overall survival (OS). In the BRF113220

trial, although the confirmed investigator-assessed ORR was 76% and the median DOR was 10.5 months, 57% of the patients experienced progressive disease or died.

- Whether the combination of dabrafenib and trametinib represents the most optimal use of these agents for the treatment of BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma is unknown. The Applicant's ongoing randomized controlled trials of the combination of dabrafenib and trametinib in patients with BRAF V600 mutation-positive unresectable or metastatic melanoma [Subpart H post marketing requirement (PMR)]) would allow for adequate evaluation of (1) time-to-event endpoints to assess clinical benefit, such as survival, and (2) the role of the combination treatment regimens, which is typically used for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma.
- The median DOR is based upon a small number of events with limited follow-up duration.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There are no safety issues identified at this time requiring Risk Evaluation and Mitigation Strategies (REMS).

1.4 Recommendations for Postmarket Requirements and Commitments

The following postmarketing requirements and commitments are recommended. PMR 1 is a confirmatory trial required to confirm clinical benefit for approvals based on a surrogate endpoint (21CFR314.510). The PMCs are for the MEK116513 trial data and for longer term follow-up of the results for the BRF113220 trial to further define efficacy.

PMR 1: Complete and submit the final results of the ongoing randomized, double-blind, placebo-controlled trial (MEK115306) comparing the combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib to dabrafenib and placebo as first-line therapy in subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E or V600K mutation-positive cutaneous melanoma. Enrollment of approximately 340 patients is expected. The primary endpoint is progression-free survival. Overall survival is a key secondary endpoint.

PMC 1: Complete and submit the final results for the ongoing randomized controlled trial MEK116513 comparing the combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib to the BRAF inhibitor vemurafenib in subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E or V600K mutation-positive cutaneous melanoma. Enrolment of approximately 694 patients is expected. The primary endpoint is overall survival.

PMC 2: Continue follow-up of patients (on treatment and in protocol defined post-treatment follow-up) and submit a final analysis report of Trial BRF113220 Part C, with a minimum follow-up of 24 months for each patient. If 24 months follow-up is not possible for certain patients, provide justification for each of these patient(s).

2 Introduction and Regulatory Background

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). The Surveillance Epidemiology and End Results (SEER) data collected between 2001 and 2007 show that 8% of patients are first diagnosed with stage III (regional metastasis) melanoma, and stage IV (distant metastasis) disease is initially detected in 4% of patients (Howlader, Noone, et al. 2013). Historically, the median survival of patients with melanoma who have distant metastases (American Joint Committee on Cancer stage IV) is less than 1 year. The annual age-adjusted mortality rate is 2.97 per 100,000 populations (Bristow, Casil et al. 2013).

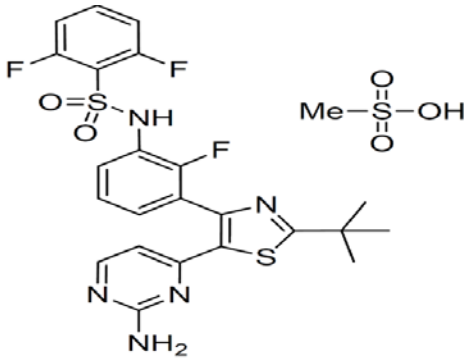
In 2002, investigators at the Sanger Institute discovered that mutations in the gene encoding the serine–threonine protein kinase BRAF occurred in more than 60% of melanomas initially tested (Davies, Bignell et al. 2002). The most common mutation results in a replacement of the valine with glutamate at amino acid 600 (V600E) through mutation of a single nucleotide (GTG to GAG). Another known mutation at this site involves two nucleotides (GTG to AAG), substituting lysine for valine (V600K). BRAF V600E accounts for 70-95% and BRAF V600K mutations account for 6-30% of the BRAF V600 mutations present in melanoma tumors (Rubinstein, Sznol et al. 2010). Melanomas carrying a BRAF V600E mutation constitutively activate the mitogen-activated protein kinase (MAPK) pathway, promoting cell proliferation and preventing apoptosis (Gray-Schopfer, Wellbrock et al. 2007). Suppression of an activating BRAF mutation in human melanoma cell lines inhibits the MAPK signaling pathway, leading to cell growth arrest and apoptosis, and abrogates the transformed phenotype (Hingorani, Jacobetz et al. 2003).

2.1 Product Information

Dabrafenib

Dabrafenib is an ATP-competitive inhibitor of BRAF, marketed in the U.S. under the trade name Tafinlar®. The drug product is an immediate release capsule dose form available in two strengths of 50 mg and 75 mg. Each 50 mg capsule contains 59.25 mg of dabrafenib mesylate equivalent to 50 mg of dabrafenib free base. Each 75 mg capsule contains 88.88 mg of dabrafenib mesylate equivalent to 75 mg of dabrafenib free base. The structural formula of dabrafenib is shown in Figure 1.

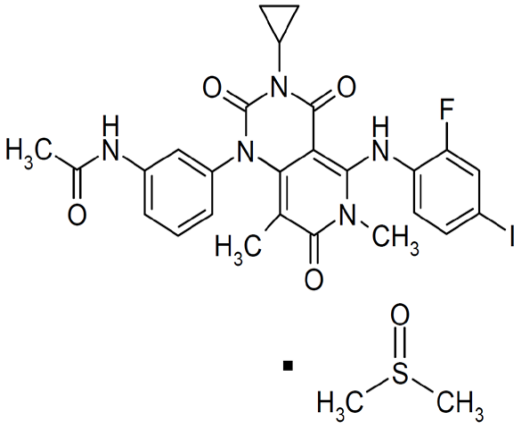
Figure 1: Structural Formula of Dabrafenib



Trametinib

Trametinib is an allosteric MEK inhibitor, marketed in the U.S. under the trade name Mekinist®. The drug product is an immediate release, film-coated tablet for oral administration containing trametinib dimethyl sulfoxide equivalent to 0.5 mg, 1 mg, and 2 mg of trametinib. The structural formula of trametinib is presented in Figure 2.

Figure 2: Structural Formula of Trametinib



2.2 Tables of Currently Available Treatments for Proposed Indications

Until 2011, standard FDA-approved treatment options for metastatic melanoma were limited to DTIC and interleukin-2 (aldesleukin). 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). 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 the demonstration of an improvement in OS in patients with unresectable or metastatic melanoma.

On March 25, 2011, FDA approved ipilimumab, 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, pruritus, rash, and colitis.

On August 17, 2011, FDA approved vemurafenib, 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 unresectable or metastatic melanoma to receive vemurafenib 960 mg orally twice daily (n=337) or DTIC 1000 mg/m2 IV on Day 1 every 3 weeks (n=338) (Zelboraf USPI). 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%).

On May 29, 2013, two more products were approved by the FDA for use in unresectable or metastatic melanoma, based on an improvement in progression-free survival. Dabrafenib was approved for patients with BRAF V600E mutations and trametinib was approved for patients with both BRAF V600E and V600K mutations, detected by an FDA-approved test.

Dabrafenib is a small molecule ATP competitive inhibitor of BRAF and is therapy targeted to the melanomas that contain BRAF V600E mutations. The safety and efficacy of dabrafenib was demonstrated in an open-label, multi-center, randomized active-controlled trial conducted in 250 patients with previously untreated BRAF V600E mutation-positive, unresectable or metastatic melanoma. The trial demonstrated a statistically significant increase in progression-free survival in the patients treated with dabrafenib compared to dacarbazine [HR (95%CI) for PFS was 0.30 (0.18, 0.53; p-value < 0.0001)]. The most common AEs (>20%) were hyperkeratosis, headache, pyrexia, arthralgia, papilloma, alopecia and palmar-plantar erythrodysesthesia syndrome. New primary cutaneous malignancies, tumor promotion in BRAF wild-type melanoma, serious febrile drug reactions, hyperglycemia, uveitis, and iritis were noted as toxicities (Tafinlar USPI).

Trametinib is an allosteric inhibitor of MEK in the MAP kinase pathway. The safety and efficacy of trametinib was evaluated in an open-label, international, multi-center, randomized, active-controlled trial in 322 patients with BRAF V600E or V600K mutation-positive, unresectable or metastatic melanoma. The trial demonstrated a statistically significant increase in progression-free survival (PFS) in the patients treated with trametinib [HR (95%CI) for PFS was 0.45 (0.33, 0.63; p-value < 0.0001)] (Mekinist USPI). The common AEs (>20%) were hypertension, rash, diarrhea, peripheral edema, fatigue, and dermatitis acneiform. Cardiomyopathy, retinal pigment epithelial detachment, retinal vein occlusion, and serious skin toxicity were noted as toxicities.

Table 2 lists the FDA-approved therapies for metastatic melanoma with details on clinical benefit/activity outcomes for each drug.

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Table 2: 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	**<u>Ipi vs. gp100:</u>** 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 **<u>Ipi+gp100 vs. gp100:</u>** OS: HR 0.68 (95% CI: 0.55, 0.85) median 10 vs. 6 months BORR: 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	**<u>Vemurafenib vs. DTIC</u>** 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) cORR: Vemurafenib: 48.4% (95% CI: 41.6%, 55.2%) CR 0.9% PR 47.4% DTIC: 5.5% (95% CI: 2.8%, 9.3%) PR: 5.5%
Tafinlar[3] (dabrafenib)	2013	Randomized, open-label active-controlled, two-arm	PFS ORR	**<u>Dabrafenib vs. Dacarbazine</u>** mPFS: 5.1 vs. 2.7 months HR: 0.33 (95% CI: 0.20, 0.54) cORR: Dabrafenib: 52% (95% CI: 44%, 59%) CR 3% PR 48% Dacarbazine: 17% (95% CI: 9%, 29%) CR 0% PR 17%

FDA Approved Drug[1]	Approval Year	Trial Design	Endpoint(s)	Clinical Benefit/Effect
Mekinist[4] (trametinib)	2013	Randomized, open-label active-controlled, two arm	PFS ORR	**Trametinib vs. Chemotherapy** mPFS: 4.8 vs. 1.5 months HR: 0.47 (95% CI: 0.34, 0.65) cORR: Trametinib: 22% (95% CI: 17%, 28%) CR 2% PR 20% Chemotherapy: 8% (95% CI: 4%, 15%) CR 0% PR 9%

Source: Proleukin (USPI); Yervoy (USPI); Zelboraf (USPI); Dacarbazine (USPI; Huncharek, Caubet, et al. 2001); Tafinlar (USPI); Mekinist (USPI).
Abbreviations in Table: BORR, best overall response rate; CR, complete response; cORR, confirmed objective response rate; DOR, duration of response; HR, hazard ratio; Ipi, ipilimumab; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; NR, not reached; ORR, objective response rate; OS, overall survival; PR, partial response; +, response is ongoing.
[1] Hydroxyurea is also FDA-approved for treatment of melanoma but is of historical interest.
[2] BRAF V600 mutation status unknown.
[3] Patient selection based on BRAF V600E mutation-positive tumors.
[4] Patient selection based on BRAF V600E or V600K mutation-positive tumors

2.3 Availability of Proposed Active Ingredient in the United States

Dabrafenib and trametinib have both been approved as monotherapy in the United States.

Tafinlar® is currently marketed in the U.S. for the following approved indication: treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.

Mekinist® is currently marketed in the U.S. for the following approved indication: treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.

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), non-cutaneous SCC, melanomas, basal cell carcinoma, and other malignancies

- Tumor promotion in BRAF wild-type melanoma
- Serious hypersensitivity reactions
- Severe dermatologic reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis
- QT prolongation
- Hepatotoxicity
- Photosensitivity
- Uveitis

Dabrafenib is a small molecule ATP competitive inhibitor of BRAF and 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 dabrafenib include the following:

- New primary cutaneous malignancies, including cutaneous squamous cell carcinomas (cuSCC) and melanomas
- Serious febrile drug reactions
- Tumor promotion in BRAF wild-type melanoma
- Hypersensitivity reactions
- Dermatologic toxicities
- Hyperglycemia
- Uveitis and iritis
- Glucose-6-phosphate dehydrogenase deficiency

Trametinib is an allosteric inhibitor of MEK in the MAP kinase pathway and is FDA-approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutation as detected by an FDA-approved test. Important safety issues with trametinib include the following:

- Cardiac disorders: LVEF decrease, syncope
- Ocular disorders: retinal pigment epithelial detachment (RPED), retinal vein occlusion (RVO), central serous retinopathy (CSR)
- Serious skin toxicity: rash (acneiform dermatitis, maculopapular rash)
- Interstitial lung disease
- General disorders and administration site conditions: edema (peripheral, facial)
- Vascular disorders: hypertension
- Gastrointestinal disorders: diarrhea, stomatitis
- Investigations: CK increase, ALT/AST increase
- Musculoskeletal and connective tissue disorders: muscular weakness

Reviewer's Comment:
The NDA approval for dabrafenib included PMRs to identify and characterize the risk of secondary malignancies, cardiac valve abnormalities, a pharmacokinetic (PK) study to evaluate hepatic impairment and renal impairment, and a study to evaluate the potential of prolongation of QT/QTc interval.

The NDA approval for trametinib included PMRs to identify and characterize the risk of cardiomyopathy, to identify and characterize the risk of retinal pigmented epithelial detachments, a PK study to evaluate hepatic impairment, and a study to evaluate the potential of prolongation of QT/QTc interval.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following summarizes the presubmission regulatory activity for the combination of dabrafenib and trametinib:

In a Type-A Revised Clinical Development Plan Meeting held October 7, 2010, regarding the development of GSK2118436 in BRAF mutation-positive melanoma; the FDA recommended a three arm randomized study of GSK1120212 vs. GSK2118436 vs. the combination. At this time, the FDA stated it would consider approval of both agents in combination if the combination arm is markedly superior.

On February 24, 2011, a Type B EOP1/Pre-Phase 3 meeting was held with the Applicant to discuss the development program for the combination of dabrafenib and trametinib (BRAF and MEK inhibitors) indicated for the treatment of (b) (4) The Applicant proposed a three-arm, double-blind, randomized Phase 3 study (MEK115306) comparing the combination of GSK2118436 (dabrafenib) and GSK112012 (trametinib) to single agent GSK2118436 plus placebo and single agent GSK1120212 + placebo in subjects with BRAF mutation-positive metastatic melanoma. The key agreements and issues communicated to the Applicant were:

- Agreement with the study design
- Recommendation that the Applicant must demonstrate the BRAF Inhibitor has high single-agent activity in other studies: The Applicant proposed to utilize study BRF113370, a Phase II, single-arm, open-label study to assess the efficacy, safety, and tolerability of GSK2118436 administered twice daily as a single agent in subjects with BRAF mutant metastatic melanoma which utilized the same dose of GSK2118436 as proposed for the phase III combination study. FDA stated that the Phase 2 study should show a response rate of at least 50%, but that the evaluation of the study and the required response rate will ultimately be a review issue.
- Recommendation that OS should be the sole primary endpoint with a clinically robust magnitude to support the approval of the combination of the two drugs.
- PFS and OS as co-primary endpoints would not be an acceptable endpoint.
- Agreement that if OS is the only primary endpoint, then no independent review committee is required.
- Recommendation to submit the protocol for Special Protocol Assessment prior to study initiation

On January 27, 2012, a pre-IND / pre-phase 3 meeting was held to discuss the proposed development of the combination of two investigational products, dabrafenib (GSK2118436) and trametinib (GSK1120212), for the proposed indication, “for the treatment of BRAF V600 E/K mutation positive unresectable or metastatic melanoma". The Applicant discussed an ongoing randomized activity-estimating trial (BRF113220) and proposed two randomized trials (MEK115306 and MEK116513). Study BRF113220 had four parts, A, B, C, and D. Part C was amended to an open-label, randomized, three-arm trial of dabrafenib (gelatin capsule formulation) administered at 150 mg BID alone or in combination with two different doses of trametinib (1 mg QD and 2 mg QD) in BRAF V600 E/K/D mutation-positive melanoma patients without prior exposure to BRAF or MEK inhibitors. One hundred and sixty-two patients were randomized to the three arms. The applicant stated their intention to file based on study BRF113220. The key agreement and issues discussed at this meeting were as follows:

- FDA advised the Applicant that potential sources of bias in the design, conduct, analysis and interpretation of the results of study BRF113220 would need to be identified and adequately addressed at the time of NDA submission to provide evidence of a treatment effect as well as an estimate of the size of a treatment effect for the combination.
- FDA stated that interpretation of the results from Part C of study BRF113220 would pose difficulties due to the study’s open-label nature and lack of pre-specified statistical criteria around the efficacy endpoints.
- Applicant proposed to submit several sensitivity analyses for both PFS and overall best response as well as provide a blinded independent central review of scans should the Applicant submit BRF113220 as primary evidence (b) (4).
- Applicant proposed to provide efficacy and safety data with the two capsule (gelatin and HPMC) formulations of dabrafenib based on the use of both formulations in the BRF113220 trial and the higher exposure of dabrafenib with the commercial formulation (HPMC).
- FDA stated that the submission should contain information indicating that combination therapy is better than sequential therapy
- FDA noted that the Applicant should withdraw the indication if confirmatory trials are negative

On June 29, 2012, Fast Track designation was granted to the combination of trametinib and dabrafenib for the treatment of patients with BRAF V600E or BRAF V600K mutation-positive, unresectable or metastatic melanoma to demonstrate improved overall response rates, progression-free survival, and overall survival.

On July 23, 2012, Orphan Drug Designation was granted for use of the combination.

On September 12, 2012, a pre-NDA meeting was held to discuss and share the high-level, mature data from study BRF113220, and to gain agreement on the contents of an NDA for the use of trametinib (GSK1120212) and dabrafenib (GSK2118436) in

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combination for the treatment of [redacted] (b) (4) The key agreement and issues discussed were:

- Agreement that an application could be submitted under a request for accelerated approval.
- Recommendation that the application should also include a discussion, based on clinical trial data, as to why dabrafenib and trametinib administered sequentially is ineffective.
- Confirmation by the Applicant that efficacy will be verified in ongoing trials MEK115306 and MEK116513 and that the accelerated approval for the combination therapy would be withdrawn if not confirmed. Agreement by the Applicant to include available safety data from part D of study BRF113220, in which 25% of the 54 patients will have been exposed for up to 6 months, in the NDA at time of submission.
- Agreement by the Applicant to provide additional safety information in support of the proposed recommended dose for the HPMC capsule in the 120-day safety update consisting of:
    - Updated safety data from the 54 patients enrolled in part D of study BRF113220 to include safety data for at least 6 months of exposure in all 54 patients.
    - The interim, high level, blinded safety results from both treatment arms of the MEK115306 study, as generated by the independent safety monitoring committee during the next planned meeting.
- Confirmation by the Applicant that [redacted] (b) (4) will contain an ISS and ISE which provides a thoughtful discussion of the evidence establishing efficacy and safety. The ISS and ISE will also contain links to cross referenced material in other applications as appropriate.
- Agreement to provide a detailed description of the contents [redacted] (b) (4), including a listing of the complete study reports to be provided in module 5.3 and links to those study reports referenced in other NDA applications, specifically, the clinical study report for MEK113583.
- Agreement to provide complete data sets containing primary data, derived data, and all SAS programs used to generate derived data and analyses.
- Agreement to provide narratives for deaths on study in all treatment arms for all studies contributing information to the safety database.
- Agreement to provide case report forms (CRFs) for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events either directly or through crossing reference to other applications.
- Confirmation that the clinical report and all bridging data supporting the BRAF test kit will be submitted to the NDA.

On December 6, 2012, a pre-NDA meeting was held to discuss the content and format [redacted] (b) (4) including

preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. The key agreement and issues were:

- Recommendation that the format for data submission be in CDISC.
- Agreement to provide analyses of adverse events based on both pooled analyses and individual analyses of parts A through D of the trial. In addition, the datasets will include pooled datasets, including flags identifying patients from the individual parts of the trial, and individual datasets for parts A through D.
- Recommendation that the analyses of the safety profile for the combination drug product should include both GSK's proposed modified standardized medical queries, and additional narrow- and broad-based MedDRA SMQs.
- A preliminary discussion on the need for REMS was held and the Applicant stated that they do not believe there is need for a REMS.

2.6 Other Relevant Background Information

Ongoing Phase 3 Studies

This early submission of the combination is based on efficacy and safety data from Study BRF113220 (Phase 1/2). Two combination Phase 3 studies, MEK115306 (approximately 340 patients) and MEK116513 (approximately 694 patients), are ongoing to establish the efficacy and safety of dabrafenib in combination with trametinib as summarized in Table 3.

Table 3: Ongoing Phase 3 Dabrafenib/Trametinib Studies

	MEK115306	MEK116513
Study Design	Randomized, double-blind, placebo-controlled	Randomized, double-blind, placebo-controlled
Treatments	150 mb BID dabrafenib + 2 mg QD trametinib 150 mg BID dabrafenib + PBO	150 mb BID dabrafenib + 2 mg QD trametinib 960 mg BID vemurafenib
Planned enrollment	340	694
Stratification	LDH (>ULN v <=ULN) BRAF mutation (V600E v V600K)	LDH (>ULN v <=ULN) BRAF mutation (V600E v V600K)
Primary endpoint	PFS	OS

Source: Clinical Overview, Table 3.

MEK115306

The primary objective of this study is to compare the combination of dabrafenib and trametinib to dabrafenib and trametinib-placebo with respect to PFS for patients with advanced/metastatic BRAF V600E or V600K mutation-positive cutaneous melanoma.

The Applicant states that MEK115306 has met its enrollment target and it expects top-line results of the primary analysis early next year (Response to FDA Information Request, November 4, 2013).

MEK116513
The primary objective of this two-arm study is to compare the combination of dabrafenib and trametinib to vemurafenib with respect to OS for patients with advanced or metastatic BRAF V600E or V600K mutation-positive cutaneous melanoma. The Applicant projects that MEK116513 will complete enrolment in the third quarter of 2013 and it expects results of the primary analysis in the second quarter of 2014.

Reviewer Comments:

1. *Protocol MEK115306 initially had an agreement under a Special Protocol Assessment in 2012, which was subsequently rescinded by the FDA in 2013, when changes were made by the Applicant to the primary analysis of PFS events.*
2. *The reviewer recommends that the Applicant submit the data from Trials MEK115306 as a PMR and MEK116513 as a PMC.*

Companion Diagnostic Assay

The Applicant partnered with bioMerieux (bMx) in the co-development of a companion diagnostic (cDx) assay (THxID-BRAF kit) which received FDA approval (May, 2013) in the USA. The THxID-BRAF kit is an In Vitro Diagnostic device intended for the qualitative detection of the BRAF V600E and V600K mutations in DNA samples extracted from formalin-fixed paraffin-embedded (FFPE) human melanoma tissue. The THxID-BRAF kit is a real-time PCR test on the ABI 7500 Fast Dx system and is intended to be used as an aid in selecting melanoma patients whose tumors carry the BRAF V600E mutation for treatment with dabrafenib and as an aid in selecting melanoma patients whose tumors carry the BRAF V600E or V600K mutation for treatment with trametinib.

Reviewer Comment:
The results of these analyses are submitted in a clinical study report comparing the analytical concordance between local and investigational use only (IUO) assays and bioMerieux's (bMx) THxID-BRAF assay results and the clinical concordance between BRAF mutation-positive subjects based on results from the three assays (original BRAF mutation result from a local lab that was the basis for enrolment and randomization, IUO and the bMx THxID-BRAF kit). Refer to section 6.1.10. and CDRH Consult.

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3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

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

3.2 Compliance with Good Clinical Practices

The Applicant states that the study protocol, any amendments, the informed consent, and other information that required pre-approval were reviewed and approved by a national, regional, or investigational center ethics committee or institutional review board (IRB), in accordance with the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice (GCP) and applicable country-specific requirements, including US 21 Code of Federal Regulations (CFR) 312.3(b) for constitution of independent ethics committees. Based on the information provided in the submission, the study was conducted in accordance with ICH GCP and all applicable subject privacy requirements, and, the ethical principles that are outlined in the Declaration of Helsinki 2008.

Investigators were trained to conduct the study in accordance with GCP and the study protocol as defined in ICH E3, Section 9.6. Written commitments were obtained from investigators to comply with GCP and to conduct the study in accordance with the protocol. The study was monitored in accordance with ICH E6, Section 5.18.

The Division of Oncology Products 2 (DOP2) consulted the Office of Scientific Investigation (OSI) on August 7, 2013, 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 reviewer selected clinical sites for inspection based on enrollment characteristics, patterns of treatment responders, protocol violations reported for the sites, (b) (6)

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

Kevin Kim, M.D.
Center #072218

Assessment of data integrity: The data for Dr. Kim's site, associated with Study BRF1132 20, Part C, submitted to the Agency in support of NDA 202806 S-002 and NDA 204114 S-001, appear reliable based on available information.

Hamid Omid, M.D.
Center # 085394

Assessment of data integrity: The data for Dr. Omid's site, associated with Study BRF1132 20, Part C, submitted to the Agency in support of NDA 202806 S-002 and NDA 204114 S-001, appear reliable based on available information.

OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS
Based on the review of preliminary inspectional findings for clinical investigators Dr. Kevin Kim (Site 072218) and Dr. Hamid Omid (Site 085394) the Study BRF113220, Part C, data appear reliable based on available information.

The preliminary classification for Dr. Hamid Omid's site (085394) is No Action Indicated (NAI). One clinical site inspected, Dr. Kevin Kim (Site 072218) was issued a Form FDA 483 citing inspectional observations and preliminary classification for this inspection is Voluntary Action Indicated (VAI). Although regulatory violations were noted, they are unlikely to importantly impact primary safety and efficacy analyses. The overall data for Study BRF113220, Part C, in support of these applications may be considered reliable based on available information.

Reviewer's Comments:

1. *OSI issued an FDA Form 483 to Dr. Kim due to the following observations:*
   - *One patient had certain study related screening procedures conducted the day prior to actually signing the informed consent form*
   - *There were several occasions where SAEs were not reported within the required timeframe of 24 hours per protocol. However, all AEs appeared to be reported*
2. *The reviewer agrees with the OSI reviewer's assessment that the inspectional observations should not importantly impact data generated by the site and should not impact the overall integrity of the data used in the analyses of efficacy and safety in trial BRF113220.*

3.3 Financial Disclosures

In accordance with 21 CFR 54.2, the Applicant submitted a list of the BRF113220 study investigators attached to FDA form 3454 certifying that the clinical 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.

The Applicant relied upon investigator financial interest information provided by the investigators through questionnaires. No investigator had a financial interest in the company at the time they started their participation in the covered study. The appropriate due diligence process as per the Applicant's standard operating procedures, which is up to three documented attempts to collect, was carried out. It is the policy of the Applicant not to allow the participation of investigators in a clinical study

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if they, their spouse or dependent children have proprietary interest in the tested product, and not to compensate investigators in a way that the amount of compensation received could be affected by the outcome of the study.

Of 295 investigators (principal and sub-investigators) in the BRF113220 trial, 269 investigators had no disclosures, 25 investigators were listed by the Applicant on List (B) to Form 3454 and one investigator had received significant payments.

For the 25 investigators, the Applicant states that based on information available internally, none of the clinical investigators listed had disclosable interests of the type described in 21 CFR 54.2(a) (compensation potentially affected by the outcome of the study). In addition, based on whatever information may have been obtained at the threshold from some or all of the listed clinical investigators, no one listed had a disclosable interest of the type described in 21 CFR 54.2(b) (significant equity interest in the study sponsor) or 21 CFR 54.2(c) (proprietary interest in the tested product). However, the Applicant was unable to obtain timely information from them regarding updated equity interest, proprietary interest information and/or information about payments of other sorts.

One investigator, [redacted] (b) (6) was the Sub-Investigator for center [redacted] (b) (6), which recruited [redacted] (b) (6) subjects from a total of 422 Subjects, which was [redacted] (b) (6) of the total recruitment. This sub-investigator received a significant payment, i.e. > $25,000, consisting of grants to fund ongoing research ($65,632), honoraria ($1,750) and other ($263.61), resulting in a total payment of $67,645.61.

[redacted] (b) (6)

The Applicant conducted analyses of the BRF113220 trial excluding the data from study site [redacted] (b) (6) on disposition, the most frequent AEs and Kaplan-Meier estimates of investigator-assessed PFS, results of which were consistent with the intent-to-treat (ITT) population.

Reviewer Comment:
A concern with respect to possible bias arose from the significant payment to center [redacted] (b) (6) *which enrolled* [redacted] (b) (6) *patients of which* [redacted] (b) (6) *had a confirmed objective tumor response.* [redacted] (b) (6)

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The sNDA does not propose CMC changes. Refer to CMC Review for details.

(b) (4) a hydroxypropyl methylcellulose (HPMC) capsule shell of dabrafenib was selected as the commercial formulation, instead of the gelatin capsule shell used in the early clinical development program (i.e., the Phase 1 dabrafenib monotherapy trial and Parts A, B and C of trial BRF113220). Part D (N=110) was performed to assess the potential impact of this change in capsule shell on the PK and safety profile. In Parts A, B, and C of trial BRF113220, the dabrafenib formulation used was gelatin capsules, while Part D of Study BRF113220 used HPMC capsules.

The two ongoing Phase 3 studies, MEK115306, and MEK116513, utilize the recommended dosing regimen for the combination, and use the commercial formulation of dabrafenib (HPMC capsule).

Reviewer's Comment:
Although dabrafenib gelatin capsules were meant to be administered to patients in Part C, 104 out of the 162 patients (dabrafenib monotherapy 35; 50/1/ combination 33; 150/2 combination 36) received HPMC capsules for a median duration of 1.8 months in each treatment group (range: 0.1 to 3.7 months across treatment groups). The overall exposure to dabrafenib in each treatment group ranged from 6.1 months to 10.9 months. For details on the safety of AEs between formulations, refer to section 7.7.

4.2 Clinical Microbiology

The drug product is a non-sterile capsule for oral administration. There was no FDA Clinical Microbiology review for this sNDA.

4.3 Preclinical Pharmacology/Toxicology

Refer to the FDA Pharmacology/Toxicology Review for details. The following is excerpted from the review.

Pharmacology studies demonstrated that the dabrafenib and trametinib combination results in greater growth inhibition of BRAFV600 mutation-positive cell lines *in vitro* and *in vivo* xenograft models than with either drug alone. Specifically, in 9 of 11 BRAFV600E mutant positive melanoma cell lines, the dabrafenib and trametinib combination resulted in a synergistic enhancement of cell growth inhibition. In the BRAFV600K mutant positive melanoma lines, the dabrafenib and trametinib combination showed an approximately additive enhancement of cell growth inhibition. Using a BRAFV600E mutation positive melanoma xenograft model, female CD-1 nude mice were dosed orally with either dabrafenib, trametinib, or a combination of the two, for 90 days. All doses of dabrafenib, trametinib, and the combination, were tolerated

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and did not result in any significant effect on body weight. Administration of the 10/0.1 mg/kg/day combination of dabrafenib and trametinib resulted in 95% tumor growth inhibition, suggestive of an additive effect. Other groups administered the dabrafenib and trametinib combination showed 100% tumor growth inhibition. The most pronounced effect of the dabrafenib and trametinib combination was seen following the 30/0.3 mg/kg/day combination dose and consisted of prolonged inhibition of tumor growth until the end of the 90-day dosing period (Day 114 post-tumor implantation).

The toxicity of repeated oral dosing of the dabrafenib and trametinib combination was assessed by conducting a 4-week toxicity studies in dogs. Target organs of toxicity were the stomach (inflammation), thymus (decreased cellularity), and male reproductive organs (germ cell degeneration/oligospermia in epididymis and germinal epithelium degeneration in the testes).

4.4 Clinical Pharmacology

Refer to the Clinical Pharmacology 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.

Trametinib is an inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2 activation and of MEK1 and MEK2 kinase activity. MEK proteins are upstream regulators of the extracellular signal-related kinase (ERK) pathway, which promotes cellular proliferation. V600 BRAF mutations, including V600E, result in constitutive activation of the BRAF pathway which includes MEK1 and MEK2.

4.4.2 Pharmacodynamics

There appears to be an exposure-response relationship for overall response rate (ORR) with trametinib, which is consistent with the higher ORR observed with the 2 mg versus 1 mg daily dose of trametinib in combination with 150 mg BID dabrafenib.

There is evidence for a relationship between pyrexia and hydroxy-dabrafenib, a metabolite of dabrafenib.

4.4.3 Pharmacokinetics

After administration of dabrafenib 150 mg BID in combination with trametinib 2 mg QD, the exposure of dabrafenib increased by 23% for the parent drug and by 33% for its metabolite desmethyl-dabrafenib; trametinib exposures were similar as compared to previously reported trametinib single agent PK data.

The bioavailability of dabrafenib is higher following single dose administration as HPMC capsules as compared to gelatin capsules. A population PK analysis showed that dabrafenib AUC increased by 42% (single agent) and 33% (combination) following administration of dabrafenib as HPMC capsules.

The population PK analysis did not identify clinically meaningful effects of body weight, age, gender, mild and moderate renal impairment, or mild hepatic impairment as covariates on clearance or volume of distribution of dabrafenib and trametinib when used in combination.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The primary evidence to support the clinical efficacy of the combination of dabrafenib and trametinib for the treatment of BRAFV600E or V600K mutation-positive unresectable or metastatic melanoma came from data from the randomized Phase 2 component of the trial BRF113220, Part C. Supportive results came from BRF113220 Part D.

The safety data to support the combination of dabrafenib and trametinib are derived from pooled data from trial BRF113220, Parts A, B, C, and D.

Table 4 lists the parts and purpose of trial BRF113220 and the four components.

Table 4: Tabular Listing of Clinical Trial Components in sNDA Submission

Study	Purpose	Population[a]	Formulation[b]	Sites N	Countries	Subjects N
BRF113220, Part A	Drug-drug interaction, safety	No prior BRAF inhibitor therapy	Gelatin tablet	1	US	8
BRF113220, Part B	Dose escalation, safety/efficacy expansion	No prior BRAF or MEK inhibitor therapy Expansion cohort: previous BRAF inhibitor therapy	Gelatin tablet	1	US	135
BRF113220, Part C[c]	Randomized, open-label, efficacy/safety	No prior BRAF or MEK inhibitor therapy	Gelatin tablet[d]	16	United States, Australia	162
BRF113220, Part D	HPMC capsule, efficacy/safety	No prior BRAF inhibitor therapy	HPMC capsule	1	US	110

Abbreviations: HPMC, hydroxypropyl methylcellulose; PD, pharmacodynamic trial, PK, pharmacokinetic trial.
[a] All patients with BRAF V600 mutation-positive melanoma.
[b] gelatin tablet or HPMC capsule formulation.
[c] Primary randomized trial reviewed in the clinical review of efficacy and safety.
[d] 104/162 patients received both the gelatin and HPMC formulations.

Reviewer's Comment:
The principal evidence of safety and effectiveness is provided by one trial only.

5.2 Review Strategy

BRF113220 is an open-label study to assess the safety, pharmacokinetics (PK), and clinical activity of dabrafenib and trametinib combination therapy. The study consisted of four parts: Part A (drug-drug interaction), Part B (dose escalation and efficacy expansion), Part C (randomized phase 2), and Part D (PK and safety of HPMC capsules of dabrafenib in combination with trametinib). In Part C, 162 patients were randomized to dabrafenib monotherapy and two combination arms of dabrafenib and trametinib in a 1:1:1 randomization ratio.

The initiation date (FPFV) for BRF113220, Part C is 14 Dec 2010 and the completion date is 31 May 2012 (data cutoff date). The original clinical study report was amended (Amendment 01) on 10 June 2013 to replace source data tables and figures (using the Applicant's internal standard) with tables and figures prepared in the Clinical Data Interchange Standards Consortium (CDISC) format. The Applicant states that there was no impact on study findings as a result of this change.

The FDA primary analyses focused on the randomized phase of Part C of Trial BRF113220 since the proposed indication is primarily supported by the results of Part C. The following efficacy endpoints are analyzed in the ITT population: investigator-assessed confirmed ORR, duration of response and PFS, blinded independent central review assessment of confirmed ORR, duration of response and PFS, and OS.

The clinical review of efficacy focused on detailed review and analyses of data from the Part C of Trial BRF113220, the randomized component of trial BRF113220, in support of the efficacy of the combination of dabrafenib and trametinib (subsequently referred to as Part C in the Clinical Review), including the clinical study reports, CRFs, and datasets. The clinical review also included review and analyses of the trial designs, statistical and analytic plans (SAP), and results of the Part D of Trial BRF113220, mainly to evaluate whether Part D supports the results of Part C.

The clinical review of safety focused on safety data from Part C with additional analyses focused on clinically important AEs with the combination of dabrafenib and trametinib (e.g., deaths, non-fatal SAEs, AEs leading to treatment modifications, significant AEs) from the ISS safety database, the pooled ISS 150/2 combination database, and the 90-day safety update.

Reviewer Comment:
As requested by the FDA, the Applicant submitted the 4-month safety update as a 90-day safety update. Safety data from Part C, Part D (N=39, follow-up ≥ 6 months) and safety information from the ongoing phase 3 confirmatory trial MEK115306 (N=40) were reviewed in order to determine whether the proposed safety database will be sufficient to evaluate the clinical impact on tolerability of the dabrafenib HPMC capsule in combination with trametinib.

The clinical review included the following:

- Evaluation of the current literature on melanoma epidemiology, genetics, diagnosis, prognostic features, and treatment
- Review of Applicant submitted trial BRF113220, including clinical study reports, protocols, protocol amendments, and SAPs
- Review of supporting tables and data listings of various aspects of the trials, especially objective response rates and adverse events, for evaluation of Applicant's claims
- Review of datasets submitted as SAS transport files
- Review of patient narratives of serious adverse events and deaths;
- Review of meeting minutes conducted during drug development;
- Assessment of the Module 2 summaries including the Summary of Clinical Efficacy, and Summary of Clinical Safety, Integrated Summary of Efficacy, Integrated Summary of Safety, Risk Management Plan, and proposed labeling for dabrafenib and trametinib

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- Review of reviews conducted by other teams including Pharmacology/ Toxicology, Clinical Pharmacology, Biostatistics, and CMC
- Review of consultation reports of Office of Scientific Investigations
- Requests for additional information from the Applicant and review of Applicant responses
- Formulation of the benefit-risk analysis and recommendations
- Evaluation of proposed labeling

5.3 Discussion of Individual Studies/Clinical Trials

PROTOCOL ID: BRF113220

Reviewer Comment: The focus is primarily on Part C of protocol BRF113220 which is the open-label, randomized phase 2 portion of the study. BRF113220 protocol (Amendment 5) is summarized. 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

An Open-Label, Dose-Escalation, Phase 1/2 Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of the BRAF Inhibitor GSK2118436 in Combination with the MEK Inhibitor GSK1120212 in Subjects with BRAF Mutant Metastatic Melanoma

Study Sites

The Applicant conducted Part C in 16 centers in 2 countries in USA (14) and Australia (2).

Objectives

- **Primary**:
  - To determine clinical activity of GSK2118436 and GSK1120212 in subjects with BRAF mutant metastatic melanoma.
  - To determine the safety, tolerability and range of tolerated doses of GSK2118436 and GSK1120212 dosed orally in combination in subjects with BRAF mutant metastatic melanoma.
- **Secondary**:
  - To characterize the population PK parameters of GSK2118436 and GSK1120212 when administered daily in subjects with BRAF mutant metastatic melanoma.
  - To characterize the durability of response in subjects achieving clinical benefit.

Study Design

The randomized open-label Phase 2 component of trial BRF113220, Part C, was initiated after analysis of available safety data in Part B. Three dose levels were enrolled spanning the range of tolerable dose levels determined in Part B and approximately 50 patients were enrolled in each arm. Patients were assigned in a randomized fashion to allow for comparison of tolerability and safety as well as clinical activity. Cohorts were enrolled in Part C at dose levels of GSK2118436 (dabrafenib) and GSK1120212 (trametinib) as defined in Table 5. Doses were assigned through the () Registration and Medication Ordering System (RAMOS) interactive voice recognition system (IVRS) after the subject was approved to enroll in Part C.

Study Population *(verbatim from protocol)*

Inclusion criteria:
1. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the consent form.
2. Male or female age ≥ 18 years of age and able to swallow and retain oral medication.
3. Tumor type criteria:
BRAF mutation-positive melanoma (i.e., V600E, V600K or V600D) as determined via relevant genetic testing (in Parts A and B, other BRAF mutation positive tumor types may be enrolled with approval of the GSK Medical Monitor). Testing with the GSK BRAF mutation assay may be required for enrollment.
4. Part A: No archived tissue required, but must have known BRAF mutation (i.e., V600E, V600K or V600D);
Part B: Must have archived tissue requested, must have BRAF mutation (i.e., V600E, V600K or V600D); Subjects in BRAF mutant CRC-Pharmacodynamic cohort must be able to provide fresh tissue at screening and Day 15 of the study.
Part C: Archived tissue is required; need fresh biopsy if archived tissue is not available, must have BRAF mutation (must be V600E, V600K or V600D). Only melanoma subjects can be enrolled;
Part D: Archived tissue is required; need fresh biopsy if archived tissue is not available, must have documentation of BRAF mutation (must be V600E or V600K).
Only melanoma subjects can be enrolled.
5. Measurable disease per RECIST criteria (required for Part C and Part D enrollment).
6. ECOG Performance Status of 0 or 1.
7. Male subjects must agree to use one of the contraception methods listed in Section 7.1.2 of the protocol. This criterion must be followed from the time of the first dose of study medication until 4 weeks after the last dose of study medication. However, the Sponsor advises that contraception be used for a total of 16 weeks following the last dose (based on the lifecycle of sperm).
8. A female subject is eligible to participate if she is of:
• Non-childbearing potential defined as pre-menopausal females with a documented tubal ligation or hysterectomy; or postmenopausal defined as 12 months of

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spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) > 40 MIU/mL and estradiol < 40 pg/mL (<140 pmol/L) is confirmatory]. Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the contraception methods in Section 7.1.1 of the protocol if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrollment. For most forms of HRT, at least 2-4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their post-menopausal status, they can resume use of HRT during the study without use of a contraceptive method.
• Child-bearing potential and agrees to use one of the contraception methods listed in Section 7.1.1 of the protocol for an appropriate period of time (as determined by the product label or investigator) prior to the start of dosing to sufficiently minimize the risk of pregnancy at that point. Female subjects must agree to use contraception until 4 weeks after the last dose of study medication, and must have a negative serum pregnancy test within 14 days prior to the start of dosing.
Note: Oral contraceptives are not reliable due to potential drug-drug interaction.
9. Calcium phosphate product (CPP) ≤4.0mmol^2/L^2 (50mg^2/dL^2).
10. Adequate organ system function as defined: ANC ≥1.2 x 10^9/L, , Hb ≥ 9g/dL, platelet count ≥ 75 x 10^9/L, PT/INR and PTT ≤ 1.5 x upper limit of normal (ULN), serum albumin ≥ 2.5 g/dL, total bilirubin ≤ 1.5 x ULN, AST and ALT ≤ 2.5 x ULN, serum creatinine ≤ ULN or creatinine clearance using Cockcroft and Gault method ≥ 50 mL/min, and left ventricular ejection fraction (LVEF) ≥ lower limit of normal (LLN) by ECHO or MUGA (if not defined, ≥ 50%).

Exclusion criteria:

1. Currently receiving cancer therapy (chemotherapy, radiation therapy, immunotherapy, or biologic therapy).
2. Part A and Part B: Prior exposure to BRAF or MEK inhibitors unless approved by the GSK Medical Monitor.
3. Part C: Prior exposure to BRAF or MEK inhibitors. Prior anti-cancer therapy in the metastatic setting, with the exception of up to one regimen of chemotherapy and/or interleukin-2 (IL-2).
4. Part D: Prior exposure to BRAF inhibitors. A washout period of 6 weeks is required for ipilimumab.
5. Received an investigational anti-cancer drug within four weeks or five half-lives (whichever is shorter) of the first dose of study drug administration. At least 14 days must have passed between the last dose of the prior investigational agent and the first dose of study drug. This washout period is not required for prior GSK2118436 or prior GSK1120212 administration. One week of washout is required for PLX4032.
6. Current use of a prohibited medication or requires any of these medications during treatment with study drug.

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7. Known HIV, Hepatitis B or Hepatitis C infection. Subjects who have evidence of clearance of Hepatitis B infection can be enrolled with approval of the GSK Medical Monitor.
8. Current use of therapeutic warfarin. Low molecular weight heparin (LMWH) is permitted provided that subject's PT and PTT meet entry criteria. Subjects requiring therapeutic levels of LMWH must receive approval from GSK Medical Monitor and must be monitored appropriately as clinically indicated.
9. Any major surgery, radiotherapy, or immunotherapy within the last 4 weeks. Limited radiotherapy within the last 2 weeks.
10. Chemotherapy regimens with delayed toxicity within the last 3 weeks. Chemotherapy regimens given continuously or on a weekly basis with limited potential for delayed toxicity within the last 2 weeks.
11. Unresolved toxicity greater than NCI-CTCAE v4 Grade 1 from previous anti-cancer therapy except alopecia.
12. History of RVO or CSR, or predisposing factors to RVO or CSR (e.g. uncontrolled glaucoma or ocular hypertension, uncontrolled systemic disease such as hypertension, diabetes mellitus, or history of hyperviscosity or hypercoagulability syndromes).
13. Visible retinal pathology as assessed by ophthalmic exam that is considered a risk factor for RVO or CSR such as:
a. Evidence of new optic disc cupping
b. Evidence of new visual field defects
c. Intraocular pressure > 21 mm Hg as measured by tonography
14. Presence of active gastrointestinal disease or other condition that will interfere significantly with the absorption, distribution, metabolism, or excretion of drugs.
15. Subjects with brain metastases are excluded, unless
a. All known lesions must be previously treated with surgery or stereotactic radiosurgery, and
b. Brain lesion(s), if still present, must be confirmed stable (i.e. no increase in lesion size) for ≥90 days prior to first dose on study (must be documented with two consecutive MRI or CT scans using contrast), and
c. Asymptomatic with no corticosteroids requirement for ≥ 30 days prior to first dose on study, and
d. No enzyme-inducing anticonvulsants for ≥ 30 days prior to first dose on study.
In addition, even in cases of NED (no evidence of disease), confirmation on two consecutive scans prior to first dose on study will be required.
Enrollment of a subject with brain metastases who meet the above criteria requires approval of a GSK Medical Monitor.
16. Psychological, familial, sociological, or geographical conditions that do not permit compliance with the protocol.
17. Subjects with a history of pneumonitis or interstitial lung disease.
18. History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting within the past 6 months.
19. QTc interval ≥ 480 msec (≥ 500 msec for subjects with Bundle Branch Block).

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• Uncontrolled arrhythmias. Subjects with controlled atrial fibrillation for >1 month prior to study Day 1 were eligible.
20. Class II, III, or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system.
a. Abnormal cardiac valve morphology (subjects with minimal abnormalities, could be entered on study with approval from the GSK Medical Monitor).
21. Treatment refractory hypertension defined as a blood pressure of systolic> 140 mmHg and/or diastolic > 90 mm Hg which cannot be controlled by anti-hypertensive therapy
22. Patients with intra-cardiac defibrillators or permanent pacemakers
23. Cardiac metastases
24. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study drugs, or excipients.
25. Pregnant or lactating female.
26. Unwillingness or inability to follow the procedures required in the protocol.
27. Uncontrolled diabetes, hypertension or other medical conditions that may interfere with assessment of toxicity
28. Subjects with known glucose 6 phosphate dehydrogenase (G6PD) deficiency.

Treatment Plan

Part C investigated two dose levels of dabrafenib and trametinib dosing in combination, and dabrafenib administered as monotherapy (Table 5).

Treatment continued until progressive disease (PD), death, or unacceptable toxicity.

Table 5: Treatment Doses for Dabrafenib and Trametinib (Protocol BRF113220 Part C)

	GSK 2118436 (Dabrafenib)	**GSK1120212 (Trametinib)**
Combination dose level 1	150 mg orally twice daily	2 mg orally once daily
Combination dose level 2	150 mg orally twice daily	1 mg orally once daily
Monotherapy	150 mg orally twice daily	

Patients who progressed on the dabrafenib monotherapy arm had the opportunity to receive dabrafenib and trametinib in combination dosing upon disease progression (as assessed by investigator as determined by RECIST 1.1) with approval of the GSK Medical Monitor.

Dose Modification and Supportive Care Guidelines

The protocol specified the following dose levels for dabrafenib and trametinib (Table 6).

Table 6: Dose Levels of Dabrafenib and Trametinib (Protocol BRF113220 Part C)

Dose Level	Dabrafenib	Trametinib
0	150 mg BID	2 mg QD
-1	100 mg BID	1.5 mg QD
-2	75 mg BID	1 mg QD
-3	50 mg BID	n/a

Abbreviations: BID, twice daily; QD, once daily

Protocol BRF113220 provided general dose modification guidelines for dabrafenib (Table 7) as well as specific treatment modification guidelines (Refer to Appendix 9.5) for neutropenia, fever, skin rash, palmar-plantar erythrodysesthesia renal insufficiency, left-ventricular ejection fraction decrease, liver function testing abnormalities, and visual changes.

Table 7: Dose Modification Guidelines (Protocol BRF113220)

Non-hematologic and Hematologic Toxicity (Except Neutropenia and Fever)	Dose Modification Algorithms[a,b,d,e]
Grade 1	Continue GSK2118436 and GSK1120212 at full dose, monitor as clinically indicated.
Grade 2	**For Grade 2 Diarrhea with accompanying risk factors**[c] Hold GSK2118436 and GSK1120212 until return to ≤ Grade 1, provide supportive care. **All other toxicities:** Consider holding GSK2118436 and GSK1120212 until resolution to Grade 1 or baseline; provide supportive care as clinically indicated. Monitoring of laboratory values should occur as clinically indicated. **For Grade 2 or higher respiratory symptoms (i.e. cough, dyspnea, hypoxia etc.),** evaluation by a CT scan is recommended.
Grade 3	**For Grade 3 toxicity,** hold GSK2118436 and GSK1120212 until toxicity is Grade 1 or baseline then reduce dose of GSK2118436 by 1 dose level. The subject may be continued at the same dose if, **in the judgment of the investigator, the toxicity is considered to be unrelated to GSK2118436.** Continue to monitor as clinically indicated.

Non-hematologic and Hematologic Toxicity (Except Neutropenia and Fever)	Dose Modification Algorithms[a,b,d,e]
Grade 4	Discontinue GSK2118436 and GSK1120212. Continue to monitor as clinically indicated, and provide supportive care as needed If in the investigator's judgment the toxicity is unlikely to recur then, hold until toxicity is Grade 1 or baseline, then reduce dose of GSK2118436 and/or GSK1120212 by 1 dose level. If Grade 4 toxicity recurs after dose reduction, discuss continuation of study drug with the GSK Medical Monitor.

[a.] The minimum dose is 50mg BID. If a subject requires dose reduction below 50mg BID then the subject must be discontinued from study medication.
[b.] For adverse events of abdominal pain or suspected pancreatitis, amylase and lipase laboratory samples should be collected.
[c.] Risk factors for cancer treatment-induced diarrhea include: fever, orthostatic symptoms (i.e. dizziness), abdominal pain/cramping, or weakness.
[d.] If the subject has a Grade 3 or 4 laboratory abnormality that, in the judgment of the investigator, is not considered clinically significant, dose modification is not required.
[e.] For subjects who develop symptoms associated with uveitis including blurry vision, eye pain or erythema ophthalmologic consult is required.

Monitoring Plan

The monitoring plan and study scheduled tests and evaluations are summarized in Table 8.

Table 8: Time and Events Table (Protocol BRF113220 Part C)

	Screening[1]	First Treatment Period		Continuation Phase[2] (±7 days)	Follow-up[3]
		Day 1	Day 15 (± 2 days)		
Informed Consent	X				
Demographics	X				
Medical history/ Interim History	X	X[5]		Every 4 weeks	X
Archived or fresh tumor tissue [11]	X				
Concurrent Medications	X	X[5]	X	Every 4 weeks	X
Serum or urine pregnancy test (β-hCG; women)[4]	X			Every 8 weeks	X
Physical Examination[6]	X	X[5]	X	Every 4 weeks	X
Dermatological examination[7]	X			4 weeks then every 8 weeks More frequently if there are new or changing lesions	X
Height and weight	X			Weight: Every 4 weeks	X
Ophthalmic examination	X			As symptomatically warranted	X
ECOG Performance Status	X	X[5]	X	Every 4 weeks	X
Vital signs (BP, HR, Body Temperature)	X	X[5]	X	Every 4 weeks	X
12-lead ECG[8]	X	X[5]	X	At Week 4 then at Week 12, Week 24, and every 12 weeks thereafter	X
Hematology/Clinical Chemistry	X	X[5]	X	Every 4 weeks	X
ECHO	X			At Week 4 then at Week 12, Week 24, and every 12 weeks thereafter	X
Coagulation	X				
Pharmacokinetics collection: blood			X[10]	Every 8 weeks until Week 48[10]	
Tumor tissue biopsy (optional)	X		X[9]	X[12] (at progression)	
Circulating cell free DNA (cfDNA) PD blood collection	X			X (at progression)	
Tumor Biopsy and FDG-PET (mandatory for Colorectal Expansion Cohort of Part B ONLY)	X		X[13]		

Tumor Biopsy and FDG-PET (optional for Colorectal Expansion Cohort of Part B ONLY)				X[12] (at progression)	
Study Drug Dosing		CONTINUOUS daily dosing			
Urinalysis	X	X[5]			
AE assessment		CONTINUOUS			
Disease Assessment	X			Every 8 weeks	X[14]
Long-term survival follow-up					X[15]

1. All screening assessments must be completed within 14 days prior to first dose except ophthalmic exam, ECHO and Disease Assessment, which can occur within 35 days prior to the first dose.
2. Assessments throughout the study are calendar-based starting from the first day of dosing (Day 1) in the first treatment period. Dose interruptions should not alter the assessment schedule for any subsequent treatment period. Events in the continuation phase are allowed ±7 days from projected date.
3. Follow-up visit should be 14 days from last dose of study drugs (±7 days). If a subject is unable to return to the clinic due to hospitalization, site staff are encouraged to telephone the subject for assessment of AEs.
4. Serum pregnancy test should be performed at screening; all subsequent pregnancy tests may be either serum or urine.
5. If within 72 hours of Screening, this assessment does not need to be repeated on Day 1.
6. Physical examination must include integument and genitalia.
7. Baseline skin photography should be performed at Screening. Photographs should be taken of new skin lesions that occur, or skin lesions that change on therapy. Refer to Section 6.2.
8. Single ECGs will be collected.
9. Optional collection of on-treatment tumor biopsy for subjects with accessible tumors. On-treatment biopsy may be collected on Day 15 (±7 days). Biopsy should not be done on target lesions.
10. A single PK sample for GSK2118436 and GSK1120212 will be obtained pre-dose. Subjects with morning clinic visits will be instructed to withhold their morning dose, and blood samples will be collected prior to administration of study treatments. Subjects with afternoon clinic visits will take their morning dose as usual. The date and exact time of the blood sample collection and of the most recent dose of GSK2118436 and GSK1120212 will be recorded.
11. Collection of archived tumor tissue or fresh tumor biopsies and determination of the subject's BRAF genetic status is required for enrollment; collection of on-study optional tumor biopsy may occur at any point after subject signs consent. Additional tumor genetic markers related to the activity of GSK2118436 or GSK1120212 may be analyzed.
12. Optional tumor biopsy at tumor progression in all subjects (including subjects in the colorectal cancer cohort of Part B) who have had a response is highly encouraged. A single PK sample will be collected at the time of the post-dose tumor biopsy unless the post-dose biopsy occurs on the same day that the Day 15 serial PK samples are collected.
13. Tumor biopsy and FDG-PET on Day 15 (±7 days) in the first 4 weeks of treatment.
14. Follow-up disease assessment results for subjects who discontinue study medication for any other reason than progression or death.
15. Subjects will be followed for Overall Survival every 3 months after last dose of study drugs. Site staff are to contact subjects via telephone.

Source: Protocol BRF113220 (Amendment 5), 3.8 Part C Randomized Phase II Study Time and Events Table

The protocol specified testing of standard clinical and laboratory parameters at screening, during therapy, and at treatment discontinuation. Patients underwent disease assessments every 8 weeks. Patients were followed for overall survival every 3 months after last dose of study drugs.

Statistical and Analytical Plan

The primary goal in Part C of this study is to identify at least one combination dose of dabrafenib and trametinib with superior safety profile in terms of occurrence of squamous cell carcinoma (SCC) to 150 mg BID GSK2118436 administered alone. The study is designed to provide evidence that the incidence rate of SCC at a combination dose of GSK1120212 and GSK2118436 is 17% (in absolute value) less than 150 mg BID GSK2118436 administered alone.

With a sample size of 50 in each arm, the study will have 82% statistical power to detect an absolute 17% decrease in squamous cell carcinoma (SCC) in subjects who receive the combination dose of GSK1120212 and GSK2118436 (pC=3%) compared to subjects who receive 150 mg BID GSK2118436 administrated alone (pM=20%).

Fisher's exact test is utilized in these calculations, and a nominal type I error rate of 0.05 is assumed. For sensitivity analyses, with a sample size of 50 in each arm, the study will have 74% statistical power to detect an absolute 16% decrease in SCC in subjects who receive the combination dose of GSK1120212 and GSK2118436 (pC=4%) compared to subjects who receive 150 mg BID GSK2118436 administrated alone (pM=20%).

The incidence rate of SCC will be compared between different arms in Part C for the purpose of identifying at least one combination dose of GSK1120212 and GSK2118436 with superior safety profile to 150 mg BID GSK2118436 administrated alone with respect to SCC.

Tumor response data will be summarized by treatment arm and reviewed by the same Internal Data Review Committee in an interim analysis. The interim analysis will occur after approximately 75 subjects across all three treatment arms have completed at least three post-dose disease assessments (including Week 24 assessment). A second interim analysis of tumor response data may be conducted after all subjects across three treatment arms have completed at least three post-dose disease assessments; however, if the criteria for final analysis (~70% of progression or death events) are met, then only the final analysis will be conducted at that time.

For Part C, final analyses may be conducted when at least 70% subjects have either progressed or died for all three treatment arms combined.

The incidence rate of SCC and a composite measure of SCC plus precursor lesions will be summarized by treatment group. Comparisons between treatment arms in SCC rate will also be performed using Fisher's exact test. Approximate 95% confidence limits for the differences will be calculated using a normal approximation.
DLTs will be listed for each subject and summarized according to GSK International Data Standards Library (IDSL) standards.

For Part C, the overall response rate and duration of response will be summarized by treatment group. Comparisons between treatment arms in overall response will also be performed using Fisher's exact test. Approximate 95% confidence limits for the differences will be calculated. Censoring rules for duration of response will be outlined in detail in the reporting and analysis plan.

The primary analysis in Part C will evaluate the ITT population on PFS based on the investigator's assessment. PFS will be summarized using Kaplan-Meier methods, and treatment arms will be compared using a log-rank test. For the analysis of PFS, if the subject received subsequent anti-cancer therapy prior to the date of documented events, they will be censored at the last adequate assessment (e.g., assessment where visit level response is CR, PR, or SD) prior to the initiation of therapy. Otherwise, if the subject does not have a documented date of events, PFS and survival will be censored

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at the date of the last adequate assessment. Further details on rules for censoring will be provided in the RAP. Sensitivity analyses may be conducted to confirm the results of the primary analysis and details will be defined in the RAP if any sensitivity analyses.

Analysis Populations

The Intent-to-Treat (ITT) population will comprise all randomized subjects regardless of whether or not treatment was administered. This population will be based on the treatment to which the subject was randomized and will be the primary population for the analysis of efficacy data in Part C.

The All Treated Population will consist of all subjects that received at least one dose of investigational product. Safety and clinical activity data will be evaluated based on this population.

Protocol Amendments

The Applicant submitted six amendments to Protocol BRF113220. Key revisions in each amendment were:

- Amendment 1 (August 2, 2010): added randomization to expansion arms in Part C.
- Amendment 2 (December 8, 2010): increased enrollment from 20 to 50 subjects per expansion arm in Part C based on incidence of squamous cell carcinoma to determine safety; revised secondary endpoints for Part C, overall survival will be focus of secondary endpoints and has replaced clinical benefit response rate and response ≥ 4 months.
- Amendment 3 (June 20, 2011): added Part D for evaluation of PK of GSK2118436 HPMC capsules administered as monotherapy and in combination with GSK1120212; provided more details on Part C safety and efficacy interim analyses: response rates will be summarized by treatment arm and reviewed by the Internal Data Review Committee in two interim analyses, the first interim analysis after approximately 75 subjects across all three treatment arms have completed at least three post-dose disease assessments (including week 24 assessment), the second after all 150 subjects have completed at least three post-dose disease assessments (including week 24 assessment).
- Amendment 4 (December 16, 2011): revised sections of Part D of protocol.
- Amendment 5 (March 30, 2012): added language for monitoring and management of hypertension and drug rechallenge following liver events.
- Amendment 6 (February 26, 2013, amendment submitted after the data cutoff date): clarified secondary objective relating to the overall survival endpoint, objective is to characterize overall survival and not durability of response.

Part C was in initially designed as a non-randomized expansion cohorts based on doses identified in Part B. The protocol was amended (Amendment 1) prior to initiation of Part

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C to add randomization and a dabrafenib monotherapy arm, in order to facilitate a robust evaluation for the combination. A total of 20 patients per arm were planned in Amendment 1. The sample size was subsequently increased to 50 subjects per arm in Amendment 2, the justification based on having adequate power to demonstrate a reduction in the rate of cuSCC between combination therapy and dabrafenib monotherapy.

Dose levels for Part C were chosen based on emerging PK, pharmacodynamics and tolerability data from Parts A and B. Doses were assigned through the Registration and Medication Ordering System interactive voice recognition system (RAMOS IVRS).

Reviewer Comments:

1. *Trial BRF113220 was initially designed as an exploratory trial. The randomized Part C component was added in a later amendment with no pre-specified statistical criteria and no alpha allocated to primary efficacy endpoints (ORR, PFS). For a single randomized trial* (b) (4)*, the trial should be well designed, well conducted, internally consistent and provide statistically persuasive and clinically meaningful efficacy findings. The Applicant was requested to perform several sensitivity analyses to support the results at the pre-NDA meeting.*
2. *The trial was not powered for primary efficacy endpoints and the sample size was based on the safety endpoint of decreased cuSCC which was included at a later amendment.*
3. *Trial BRF113220 is not designed to assess comparative efficacy between monotherapy and combination. The Applicant was informed by the FDA that Part C would be assessed as a single-arm trial. However, the randomization and treatment arms allow evaluation of a comparison of efficacy and safety of the combination. Randomization is useful in minimizing bias. The use of a dabrafenib control arm allowed for comparison with a standard of care drug.*
4. *Trial BRF113220 Part C was an open-label trial with investigator assessments which can lead to bias. A blinded independent central review (BICR) was conducted retrospectively after the study was completed. A BICR is useful in minimizing bias when investigators are not blinded to study treatment.*
5. *Trial BRF 113220 Part C, designed as a multicenter and multi-investigator trial provides a better basis for the subsequent generalization of its findings.*
6. *The Applicant requests accelerated approval based on the magnitude and duration of objective tumor responses. ORR is not an established surrogate for survival in melanoma.*
7. *Trial BRF113220 Parts A, B and C were conducted with the gelatin capsule formulation. Part D was included in a later amendment to treat patients with the HPMC formulation which is the current commercial formulation for single-agent dabrafenib and the formulation to be used when administered with dabrafenib.*

6 Review of Efficacy

Efficacy Summary

The sNDA submission contained a single phase 1/2 trial, BRF113220. The review of efficacy focused on Part C, the randomized component of study BRF113220, in support of the proposed indication.

Part C was a multicenter, international, open-label, randomized (1:1:1), active-controlled dose-ranging trial in 162 patients comparing the combination of dabrafenib and trametinib treatment to dabrafenib monotherapy. Patients randomized to the monotherapy arm received dabrafenib 150 mg orally twice daily. The combination arms evaluated dabrafenib 150 mg orally twice daily with two different doses of trametinib administered orally once daily, 1 mg (150/1 combination arm) and 2 mg (150/2 combination arm). Patients had histologically confirmed BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma and were previously treated with up to one prior chemotherapy regimen.

In Part C, the investigator-assessed confirmed ORR was 76% (95% CI: 62%, 87%) on the 150/2 combination treatment arm and 54% (95% CI: 40%, 67%) on the dabrafenib monotherapy arm, which was statistically significant. The median duration of response was 10.5 months (95% CI: 7, 15) for objective responders on the 150/2 combination arm and 5.6 months (95% CI: 4, 7) on the dabrafenib monotherapy arm. Per investigator's assessment, the median PFS was 9.4 months for the 150/2 combination arm and 5.8 months for the dabrafenib monotherapy arm [HR 0.39, 95% CI (0.25, 0.62)]. P-values were not calculated because formal statistical tests were not pre-specified for PFS. In updated data provided after a median follow-up of 24 months, the median OS for the 150/2 combination arm was 23.8 months (95% CI: 17.5,NR), compared to 20.2 months (95% CI: 14.5, 25.9) for dabrafenib monotherapy arm[HR 0.73, 95% CI (0.43, 1.24), p=0.24)]. The blinded independent central review (BICR) assessed ORR was also higher in the 150/2 combination arm compared to the dabrafenib monotherapy arm.

In exploratory subgroup analyses based on BRAF V600 mutation subtype, the trial results demonstrated high investigator-assessed confirmed ORRs irrespective of mutation subtype: 71% of patients with BRAF V600K and 77% of patients with BRAF V600E experienced an objective response. The median duration of response in the BRAF V600E population was 10.5 months and was not reached in the V600K population. In the BRAF V600K patients, the response durations ranged from 2+ months to 13+ months. Consistent with the reported 5-30% proportion of BRAF V600K mutations within the population of BRAF V600 mutation-positive melanoma, there was a small proportion of patients (15%) with the BRAF V600K mutation subtype available for this analysis.

6.1 Indication

The Applicant proposes the following supplemental indication for the dabrafenib label:

TAFINLAR® in combination with dabrafenib is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test.

The Applicant proposes the following supplemental indication for the trametinib label:

MEKINIST® in combination with trametinib is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test.

6.1.1 Methods

The Applicant submitted data from one Phase 1/2 trial, BRF113220, which is described in detail in Section 5.3. The primary population for the efficacy data is based on the randomized phase of Part C of study BRF113220 (subsequently referred to as Part C in the Clinical Review of Efficacy).

The ITT population consisted of all randomized subjects regardless of whether or not treatment was administered and is the primary population for the study population and efficacy data. Classification of treatment arms was based on the treatment to which the patient was randomized. There were 162 patients in the ITT population. [Dabrafenib monotherapy (N=54), 150/1 combination arm (N=54), 150/2 combination arm (N=54)].

The All Treated Population consisted of all patients who received at least one dose of either dabrafenib or trametinib and is the primary population for analyses of safety data for all parts and efficacy data in Part B. Classification of treatment cohorts was based on the actual treatment the patient received. One patient [redacted] (b) (6) was randomized to receive dabrafenib monotherapy but instead received 150/2 combination therapy. [Dabrafenib monotherapy (N=53), 150/1 combination arm (N=54), 150/2 combination arm (N=55)]. The safety review is described in detail in Section 7.

The Applicant specified several additional analyses (including BICR) performed at the time of the final analysis in order to support Part C as a potential registration trial.

Tumor response assessments included imaging (e.g., CT, MRI, bone scan, plain radiograph) and physical examination (as indicated for palpable / superficial lesions).

Reviewer Comment:

> *One patient* [redacted] (b) (6) *was randomized to the 150/2 combination arm instead of the dabrafenib monotherapy arm. The patient had a PR, both by*

investigator and BICR assessments. A sensitivity analysis excluding this patient was not performed as it is not expected to affect the overall validity of the results.

6.1.2 Demographics

Overall, the demographics for the ITT population were well balanced between the three treatment arms (Table 9). The majority of the patients were male (63% in the 150/2 combination arm, 56% in the 150/1 combination arm and 54% in the dabrafenib monotherapy arm), younger than 65 years of age (80%, 85%, 78%), predominantly Caucasian (>99% in the three arms), and enrolled in the US (82%, 93%, 91%). At the time of enrollment, the majority of patients had an ECOG PS of 0 (65% in the 150/2 combination arm, 70% in the 150/1 combination arm, 63% in the dabrafenib monotherapy arm), BRAF V600E mutation subtype (87%, 83%, 83%), predominantly stage IV (>98% in the three arms), M1c disease (70%, 61%, 69%), no prior history of brain metastases (96%, 87%, 93%), and normal LDH (59%, 54%, 50%).

There were fewer female subjects enrolled in the 150/2 combination arm (37%) than in the other two arms of the trial: 44% in the 150/1 combination arm and 46% in the dabrafenib monotherapy arm. There were more patients with ≥ 3 disease sites at baseline in the dabrafenib monotherapy arm (63%) than in the combination arms (52% in the 150/2 combination arm, 50% in the 150/1 combination arm).

Table 9 summarizes the demographics and baseline characteristics of patients randomized in Part C of BRF113220 trial.

Table 9: Demographics and Baseline Characteristics (BRF113220 Part C, ITT Population)

	D N=54 n (%)	**D + T 1 mg N=54 n (%)**	**D + T 2 mg N=54 n (%)**
Gender			
Female	25 (46)	24 (44)	20 (37)
Male	29 (54)	30 (56)	34 (63)
Age			
<65	42 (78)	46 (85)	43 (80)
>=65	12 (22)	8 (15)	11 (20)
<75	51 (94)	51 (94)	52 (96)
>=75	3 (6)	3 (6)	2 (4)
ECOG PS			
0	34 (63)	38 (70)	35 (65)
1	20 (37)	16 (30)	19 (35)
BRAF Mutation Subtype			
V600E	45 (83)	45 (83)	47 (87)
V600K	9 (17)	9 (17)	7 (13)
LDH			

	D N=54 n (%)	D + T 1 mg N=54 n (%)	D + T 2 mg N=54 n (%)
≤ ULN	27 (50)	29 (54)	32 (59)
> ULN	27 (50)	25 (46)	22 (41)
Primary tumor type initial diagnosis			
Melanoma tumor	53 (98)	53 (98)	54 (100)
Unknown	1 (2)	1 (2)	0
Disease Stage			
IIIcM0, IVM1a, or IVM1b	17 (31)	21 (39)	16 (30)
IVM1c	37 (69)	33 (61)	38 (70)
Disease sites at baseline			
<3	20 (37)	27 (50)	26 (48)
>=3	34 (63)	27 (50)	28 (52)
Countries			
Australia	5 (9)	4 (7)	10 (19)
USA	49 (91)	50 (93)	44 (81)
Prior Advanced or Metastatic Regimens			
0	47 (87)	42 (78)	42 (78)
1	4 (7)	10 (19)	11 (20)
2	3 (6)	1 (2)	0
3	0	1 (2)	0
4	0	0	1 (2)
Chemotherapy regimens			
0	50 (93)	45 (83)	48 (89)
1	4 (7)	7 (13)	6 (11)
2	0	2 (4)	0

Source: DM.xpt, ADCTX.xpt
Abbreviations: D, dabrafenib; T, trametinib

Table 10 summarizes the prior anti-cancer therapy received by patients randomized in Part C. Most patients in all treatment arms had not received previous anti-cancer therapy in the advanced or metastatic setting. Prior anti-cancer therapy had been received by 13% (7/54) in the dabrafenib monotherapy arm, 23% (12/54) in the 150/1 combination arm, and 22% (12/54) in the 150/2 combination arm.

Table 10: Prior Anti-cancer Therapy (BRF113220 Part C ITT Population)

Prior Anti-cancer Therapy	**D N=54**	**D + T 1mg N=54**	**D + T 2mg N=54**
Prior anti-cancer therapy			
bevacizumab	0	1 (2)	1 (2)
carboplatin	0	0	2 (4)
carmustine	0	1 (2)	0
cisplatin	0	4 (7)	0
dacarbazine	1 (2)	4 (7)	1 (2)

Prior Anti-cancer Therapy	D N=54	D + T 1mg N=54	D + T 2mg N=54
gemcitabine	0	1 (2)	0
hydroxychloroquine	1 (2)	0	0
imiquimod	0	0	1 (2)
interferon	1 (2)	1 (2)	2 (4)
interferon alfa	1 (2)	0	1 (2)
interleukin-2	2 (4)	4 (7)	3 (6)
interleukins	0	1 (2)	0
investigational antineoplastic vaccines	0	1 (2)	0
investigational vaccines	0	0	1 (2)
paclitaxel	0	1 (2)	3 (6)
sargramostim	0	0	1 (2)
sch 900776	0	1 (2)	0
temozolomide	3 (6)	4 (7)	2 (4)
veliparib	0	1 (2)	0
vinblastine	0	1 (2)	0
vinblastine sulfate	0	2 (4)	0

Source: DM.xpt, ADCTX.xpt
Abbreviations: D, dabrafenib; T, trametinib

6.1.3 Subject Disposition

In the ITT population, a total of 162 patients were enrolled at 16 centers in 2 countries, 2 centers in Australia and 14 centers in the United States. The first patient received the first dose of study drug in Part C on December 14, 2010; the last patient received the first dose of study drug on July 7, 2011. The data cutoff date was May 31, 2012.

One patient [redacted] (b) (6) was randomized to the dabrafenib monotherapy group but received treatment with the 150/2 combination (150/2). This patient is included in the dabrafenib monotherapy arm within the ITT population for analyses of efficacy and in the 150/2 combination arm within the All Treated Population for analyses of safety.

The Applicant stated that at study start, the BRF113220 study team did not plan to capture data for screen failure patients within the eCRF database but had inadvertently entered CRF data for the following screen failure subjects: [redacted] (b) (6)

These represent a subset of all the screen failures for the BRF113220 study. In addition, the CRF for patient 434555 enrolled at Center 080478 is for a fictitious test subject and center created by the Applicant data management as a training exercise.

The Applicant provided details on screen failures based on FDA request for information (Response to FDA Information request, October 10, 2013). They stated that there were 90 screen failures from Part C of. The most common reasons for screen failure were new brain metastasis (n=28), negative for the BRAF mutation (n=25), and safety/toxicity exclusions (n=16). The Applicant clarified that screen failures were not recorded in the

eCRF for this study and these data have been assembled from site screening/enrollment logs.

Randomization to the three arms occurred within 28 days of disease assessment for most patients. Six patients were randomized > 28 days after the last disease assessment.

At the time of data cutoff, the proportion of patients with treatment ongoing was higher in the two combination arms (43%) compared with the dabrafenib monotherapy arm (6%). In addition, 43 patients randomized to dabrafenib monotherapy crossed over to receive 150/2 combination treatment. Four patients, all in the 150/1 combination arm, withdrew from the study by withdrawing consent. A total of 51 patients across the three treatment arms died at or prior to the time of the data cutoff. Progressive disease was the most common reason for treatment discontinuations in the three treatment arms [26/31 (84%) in the 150/1 combination arm, 24/31 (77%) in the 150/2 combination arm and 6/8 (77%) in the dabrafenib monotherapy arm]. Table 11 summarizes the treatment status and reasons for treatment discontinuations for patients in Part C.

Table 11: Summary of Treatment Status (ITT and Cross-over Populations)

	Randomized Phase			**Cross-over Phase**
	D N=54 n (%)	**D + T 1mg N=54 n (%)**	**D + T 2mg N=54 n (%)**	
Treatment status				
Ongoing	3 (6)	23 (43)	23 (43)	13(30)
Crossed-over	43 (81)	0	0	
Discontinued	8 (14)	31 (57)	31 (57)	30(70)
Primary reason for discontinuation[1]				
Lack of Efficacy (Progressive Disease)	6 (10)	26 (48)	24 (44)	28(65)
Adverse Event	1 (2)	3 (6)	7 (13)	1 (2)
Withdrawal by subject	1 (2)	2 (4)	0	0
Subject met LVEF stopping criteria	0	0	0	1(2)

Source: ADDS.xpt
[1] Patients had only one primary reason for treatment discontinuation
Abbreviations: D, dabrafenib; T, trametinib

The incidence of study withdrawal due to death was 26% in the 150/2 combination arm, 33% in the 150/1 combination arm and 35% in the dabrafenib monotherapy arm. Study withdrawal for other reasons was infrequent (Table 12).

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Table 12: Summary of Subject Disposition (ITT Population)

	Randomized Arms		
	D[1] N=54 n (%)	**D + T 1 mg N=54 n (%)**	**D + T 2 mg N=54 n (%)**
Subject status			
Died	19 (35)	18 (33)	14 (26)
Ongoing On study treatment In follow-up	35 (65) 16 (30) 19 (35)	32 (59) 23 (43) 9 (17)	40 (74) 23 (43) 17 (31)
Withdrawal by subject	0	4 (7)	0
Primary reason for study withdrawal[2]			
Withdrew consent	0	4 (7)	0

Source: ADDS.xpt
[1] Monotherapy group includes data from cross-over phase
[2] Patients had only one primary reason for treatment discontinuation
Abbreviations: D, dabrafenib; T, trametinib

Protocol deviations to the inclusion and exclusion criteria were identified in five patients, one in the dabrafenib monotherapy arm and two each in the 50/1 and 50/2 combination arms. Patients (b) (6) and (b) (6) did not have adequate tumor tissue to provide for analysis, one of the requirements of the informed consent form. One additional patient (b) (6) did not have archived tumor tissue for central laboratory testing and was also included under protocol deviations for not meeting eligibility criteria. Patient (b) (6) was on cyclosporine which was a prohibited medicine during the study.

In all treatment arms, ipilimumab and vemurafenib were the most common subsequent anti-cancer treatments.

Reviewer Comment:

1. *There was incomplete information regarding screen failures in the initial sNDA submission and complete information was requested from the Applicant.*
2. *None of the protocol deviations are expected to impact efficacy or safety conclusions.*

6.1.4 Analysis of Primary Endpoint(s)

Reviewer Comment:
In Part C, the primary endpoints were ORR, PFS, and duration of response, and a superior safety profile in terms of occurrence of cuSCC in the combination arm compared to dabrafenib monotherapy. The Applicant requested accelerated approval based on ORR as a surrogate endpoint. Thus, ORR and duration of response are reviewed in detail in section 6.1.4. PFS and OS are reviewed in Section 6.1.5.

Overall Response Rate and Duration of Response

Overall response rates (ORR) were determined by the investigator per protocol. The duration of response is defined for the subject or subjects with a confirmed CR or PR, as the time from the first documented evidence of a CR or PR until the first documented disease progression or death due to any cause. At a pre-NDA meeting, the Applicant agreed to include a determination of the overall response rate by a blinded independent central review committee (BICR) for Part C. The BICR review was a retrospective review conducted by [redacted] (b) (4) for the Applicant.

There was discordance between the investigator and BICR assessments of ORR of 15% in the dabrafenib monotherapy arm, 21% in the 150/1 combination arm, and 35% in the 150/2 combination arm (Table 13). Reasons for discordance were limited to the selection of different lesions as target lesions, lack of identification of baseline measurable disease, and identification of new lesions.

Table 13: Discordance between Investigator and Independent Assessments of ORR (BRF113220 Part C ITT Population)

Confirmed response	D N=54		D + T 1 mg N=54		D + T 2 mg N=54	
	Concordance	Discordance	Concordance	Discordance	Concordance	Discordance
CR	1 (2%)	1 (2%)	2 (4%)	1 (2%)	1 (2%)	4 (7%)
PR	20 (37%)	7 (13%)	14 (26%)	10 (19%)	21 (39%)	15 (28%)
Total	21 (39%)	8 (15%)	16(30%)	11(21%)	22 (41%)	19 (35%)

Source: TR.xpt
Abbreviations: D, dabrafenib; T, trametinib

Patients with discordant objective response determinations between FDA analysis and investigator-assessed ORR and BICR analysis are shown in Table 14. Per the Study Procedure Manual, patients without any measurable disease are non-evaluable. The discrepancies were due to the following reasons: there was no measurable disease identified at baseline by the BICR, PRs were allowed to be non-consecutive, and identification of new lesions by the independent radiologist which were later overruled by the independent oncologist.

Table 14: Patients with Discordant Objective Response Determinations Between FDA Analysis and Investigator / Independent Analysis (BRF113220 Part C ITT Population)

Patient ID	Arm	INV/BIRC Confirmed Response	FDA Reviewer Initial Response	FDA Reviewer Comments*
BRF113220-Part C- [redacted] (b) (6)	150/2	INV PR	u PR	Patient had a PR on subsequent non-consecutive scans. The Applicant clarified that there is no assessment of PD nor has any new anti-cancer therapy been initiated, hence the PR assessment is confirmed. Per

Patient ID	Arm	INV/BIRC Confirmed Response	FDA Reviewer Initial Response	FDA Reviewer Comments*
				RECIST 1.1, the response may be claimed only if the criteria are met at a subsequent time point specified in the protocol (generally 4 weeks later). The Applicant's standard algorithm allows PRs to be non-consecutive; but the algorithm does not factor in the number of non-PR observations between two PRs. The INV response will be considered a confirmed PR in the FDA analysis.
BRF113220-Part C- (b) (6)	150/2	BICR cCR	PD	The Applicant clarified that subsequent review by the independent oncologist overruled the new lesions identified by the independent radiologist. Therefore, the response was reverted to PR by BICR at that time point. The BICR response will be considered a CR in the FDA analysis.
BRF113220-Part C- (b) (6)	150/2	BICR CR	Not evaluable	The Applicant agrees that no measurable disease was identified by the BICR at baseline. The investigator identified two target lesions, right neck nodule measured at 20mm diameter with a 5mm slice thickness, and suprasternal nodule measured at 10mm with a 5mm slice thickness by CT scan. The BICR response will be considered not evaluable for response in the FDA analysis.
BRF113220-Part C- (b) (6)	150/2	BICR CR	cPR	The Applicant clarified that at Week 24 assessment, the BICRdetermined that the liver lesions were benign and did not contribute to the disease burden. Hence, the assessments starting from Week 24 are based on the lymph nodes only. At Week 32 and all subsequent assessment timepoints, both target lesion lymph nodes were <10mm and therefore, assessed as CR. The radiologist's comments/justifications for making the assessment of CR was provided. The BICR response will

Patient ID	Arm	INV/BIRC Confirmed Response	FDA Reviewer Initial Response	FDA Reviewer Comments*
				be considered a CR in the FDA analysis.
BRF113220-Part C- (b) (6)	150/2	BICR CR	cPR	The Applicant clarified that based on the Week 24 assessment, the BICR determined that the target and non-target liver lesions were benign and did not contribute to the disease burden. Hence, the assessments starting from Week 24 are based on the target and non-target lung lesions and the target pleura lesion only. At both Week 24 and Week 32, all of the lung and pleura lesions were assessed as absent. The radiologist's comments/justifications for making the assessment of CR was provided. The BICR response will be considered a CR in the FDA analysis.
BRF113220-Part C- (b) (6)	150/2	BICR CR	Not evaluable	The Applicant agrees that no measurable disease was identified by the BICR at baseline. The investigator identified one target lesion, subcutaneous tissue right upper back measured at 15mm diameter with a 5mm slice thickness via CT scan. The BICR response will be considered not evaluable for response in the FDA analysis.
BRF113220-Part C- (b) (6)	150/1	BICR CR	Not evaluable	The Applicant agrees that no measurable disease was identified by the BICR at baseline. The investigator identified one target lesion, common iliac lymph node measured at 16mm diameter with a 5mm slice thickness via CT scan. The BICR response will be considered not evaluable for response in the FDA analysis.
BRF113220-Part C- (b) (6)	150/1	BICR CR	cPR	The Applicant clarified that the BICR identified one target lesion (lymph node measured at 16.6mm) at baseline. Starting from Week 16 (7/15/2011) through Week 56 (5/2/2012), the lymph node measured < 10mm. At Week 16 (7/15/2011), the Applicant

Patient ID	Arm	INV/BIRC Confirmed Response	FDA Reviewer Initial Response	FDA Reviewer Comments*
				agrees that a new brain lesion was identified by the BICR but states that because this new brain lesion was assessed 'equivocal', it was not considered in the Week 16 visit-level response determination. At subsequent time points, the 'equivocal' brain lesion identified at Week 16 was assessed as 'not present'. Therefore, the CR assessment at Week 16 and beyond was considered as CR. The BICR response will be considered a CR in the FDA analysis.

*Applicant clarifications based on Response to FDA Information Request, October 31, 2013
Abbreviations: BICR, blinded independent central review assessment; cCR, confirmed complete response; cPR, confirmed partial response; INV, investigator assessed; PD, progressive disease; uPR, unconfirmed partial response

The following table summarizes the ORR results based on FDA reviewer assessment as discussed above. The investigator assessed confirmed ORR was 76% (95% CI: 62%, 87%) in the 150/2 combination arm and 54% (95% CI: 40%, 67%) in the dabrafenib monotherapy arm. The median duration of response was 10.5 months (95% CI: 7, 15) for objective responders on the 150/2 combination arm and 5.6 months (95% CI: 4, 7) in the dabrafenib monotherapy arm. The BICR-assessed ORR was higher in the 150/2 combination arm compared to the dabrafenib monotherapy arm and duration of response was similar in both arms.

Table 15: ORR Results Based on FDA Reviewer Analysis

Overall Response Rate	D	D + T 1 mg	D + T 2 mg
FDA_Investigator	N=54	N=54	N=54
CR+PR (%)	29 (54%)	27 (50%)	41 (76%)
95% CI	(39.6%, 67.4%)	(36.1%, 63.9%)	(62.4%, 86.5%)
CR	2 (4)	3 (6%)	5 (9%)
PR	27 (50%)	24 (44%)	36 (67%)
Median DoR (95% CI)	5.6 (4.1, 7.4)	9.5 (7.4, NE)	10.5 (7.4, 14.9)
FDA_BICR	N=54	N=54	N=54
CR+PR (%)	25 (46%)	20 (37%)	31 (57%)
95% CI	(32.6%, 60.4%)	(24.3%, 51.3%)	(43.2%, 70.8%)
CR	4 (7%)	3 (6%)	5 (9%)
PR	21 (39%)	17 (31%)	26 (48%)
Median DoR (95% CI)	7.6 (4.7, NE)	9.5 (5.6, NE)	7.6 (6.7, NE)

Source: FDA Statistical Review
Abbreviations: CI: confidence interval; CR, complete response; D, dabrafen b; DoR, duration of response; NE, not reached; PR, partial response; T, trametinib

The following table summarizes subgroup analyses of ORR by BRAF V600E and V600K mutation status by investigator assessment and BICR assessment based on FDA reviewer evaluation.

Table 16: ORR Results by BRAF V600 Mutation Status

Overall Response Rate	**D**	**D + T 1 mg**	**D + T 2 mg**
FDA_Investigator			
V600E	N=45	N=45	N=47
CR+PR (%)	26 (58%)	24 (53%)	36 (77%)
95% CI	(42.2%, 72.3%)	(37.9%, 68.3%)	(62.0%, 87.7%)
Median DoR (95% CI)	5.6 (4.1, 7.4)	9.2 (5.5, NE)	10.5 (7.4, 14.9)
V600K	N=9	N=9	N=7
CR+PR (%)	3 (33%)	3 (33%)	5 (71%)
95% CI	(7.5%, 70.1%)	(7.5%, 70.1%)	(29.0%, 96.3%)
Median DoR (95% CI)	5.5 (3.7, 5.8)	NE (9.5, NE)	NE (7.4, NE)
FDA_BICR			
V600E	N=45	N=45	N=47
CR+PR (%)	23 (51%)	18 (40%)	27 (57%)
95% CI	(35.8%, 66.3%)	(25.7%, 55.7%)	(42.2%, 71.7%)
Median DoR (95% CI)	7.6 (4.1, NE)	9.4 (5.6, NE)	7.6 (5.6, NE)
V600K	N=9	N=9	N=7
CR+PR (%)	2 (22%)	2 (22%)	4 (57%)
95% CI	(2.8%, 60.0%)	(2.8%, 60.0%)	(18.4%, 90.1%)
Median DoR (95% CI)	5.5 (NE, NE)	NE (9.5, NE)	NE (7.4, NE)

Source: FDA Statistical Review
Abbreviations: CI: confidence interval; CR, complete response; D, dabrafen b; DoR, duration of response; NE, not reached; PR, partial response; T, trametinib

The numbers of V600K patients in the 150/2 combination groups of Part B (n=2) and Part D (n=5) are small. In Part B, both patients with V600K had confirmed responses (1 CR and 1 PR). In Part D, the ORR was 60% (1 CR and 2 PRs). The response duration ranged from 2+ months to 17+ months.

The results of ORR and DOR based on the FDA reviewer evaluation are consistent with the results provided by the Applicant. Durable responses were consistent in the BRAF V600k population.

Reviewer Comments:

1. *ORR may not reliably predict a treatment effect that results in clinical benefit, but the positive effect on ORR appears to provide some meaningful advantage over available therapy.*
2. *Retrospective analysis of efficacy endpoints based on central imaging vendor assessment of tumor response endpoints when patient disposition is based on investigator-assessment of tumor response may introduce bias. The Applicant had provided sensitivity analyses to evaluate potential bias to support the robustness of the primary efficacy results. These results demonstrate consistent treatment effects of the combination of dabrafenib and trametinib.*
3. *The overall response rate and response duration observed in the 150/2 combination arm were greater than that in the dabrafenib monotherapy arm, presumably through dual blockade of MAP kinase signaling and delay in acquired resistance with the combination. The large magnitude of the confirmed ORR [76% (95% CI: 62%, 87%)] with a relatively prolonged response duration (10.5 months) provides evidence of the anti-tumor activity of the combination of dabrafenib and trametinib.*
4. *The combination of dabrafenib and trametinib appears to offer similar benefit in both mutation subtypes, BRAF V600E and V600K. Dabrafenib as a single-agent is FDA-approved only for the BRAF V600E mutation subtype of 52%. However, response rate for dabrafenib as a single-agent in BRAF V600K mutations based on earlier reports is < 20%. Addition of trametinib to dabrafenib as a combination approach appears to extend the clinical activity of this therapeutic approach to patients with BRAF V600K mutation-positive melanoma as well.*
5. *The protocol defined primary analysis of ORR was based on investigator assessments. Blinded IRC- assessment is generally considered the primary assessment method of ORR for the purposes of analysis of ORR as a primary endpoint to support a regulatory action. Since trial BRF113220 is an open-label study with potential for investigator bias in determining the disease response and progression, and due to the discordance seen between investigator- and IRC-determined tumor response assessments, both investigator and IRC assessed ORR may be included in the product labeling.*

6.1.5 Analysis of Secondary Endpoints(s)

Progression Free Survival

In the Part C, PFS is defined as the interval of time between the date of randomization and the earlier of date of disease progression or date of death due to any cause. Per protocol, for the analysis of PFS, if the patient received subsequent anti-cancer therapy prior to the date of documented PFS event, they were censored at the last adequate assessment (e.g., assessment where visit level response is CR, PR, or SD) prior to the

initiation of therapy. Otherwise, if the subject did not have a documented date of a PFS event, PFS and survival was censored at the date of the last adequate assessment.

There was discordance between investigator and independent assessments of PFS, likely due to informative censoring. The investigator identified 47 PFS events in the dabrafenib monotherapy arm, 39 in the 150/1 combination arm, and 31 in the 150/2 combination arm. Of these investigator-determined PFS events, the independent assessment censored 19 in the dabrafenib monotherapy arm, 9 in the 150/1 combination arm, and 8 in the 150/2 combination arm.

Table 17 summarizes the results of the PFS analyses by investigator and BICR assessment. PFS in the combination arms was longer than that in the dabrafenib monotherapy arm. Per investigator's assessment, the median PFS was 5.8 months for the dabrafenib monotherapy arm, 9.2 months for the 150/1 combination arm and 9.4 months for the 150/2 combination arm. The estimated HR was 0.39 with 95% CI (0.25, 0.62) between the 150/2 combination arm and the dabrafenib monotherapy arm based on a Pike estimator stratified by disease staging at randomization. The results by the BICR were similar.

Table 17: PFS Analyses (ITT Population)

	Treatment Groups		
	D	D + T 1 mg	D + T 2 mg
Investigator	N=54	N=54	N=54
Number of Events (%)	47 (87.0%)	39 (72.2%)	31 (57.4%)
Progression	47	38	27
Death	0	1	4
Median PFS (95% CI)	5.8 (4.3, 7.4)	9.2 (5.7, 11.0)	9.4 (7.6, 16.7)
HR (95% CI) by Pike		0.56 (0.37, 0.87)	0.39 (0.25, 0.62)
HR (95% CI) by Cox		0.54 (0.35, 0.84)	0.37 (0.23, 0.60)
BICR	N=54	N=54	N=54
Number of Events (%)	32 (59.3%)	36 (66.7%)	28 (51.9%)
Progression	32	35	25
Death	0	1	3
Median PFS (95% CI)	7.3 (5.5, 9.4)	8.3 (5.6, 11.1)	9.2 (7.4, NE)
HR (95% CI) by Pike		0.73 (0.45, 1.19)	0.54 (0.32, 0.91)
HR (95% CI) by Cox		0.70 (0.43, 1.14)	0.53 (0.31, 0.88)

Source: FDA Statistical Review
Abbreviations: CI: confidence interval; CR, complete response; D, dabrafen b; DoR, duration of response; NE, not reached; PFS, progression-free survival; PR, partial response; T, trametinib

Figure 3 shows the estimated Kaplan-Meier curves for the distribution of PFS assessed by investigator.

Figure 3: Plots of Kaplan-Meier Estimates for Progression-Free Survival by Investigator (ITT Population)

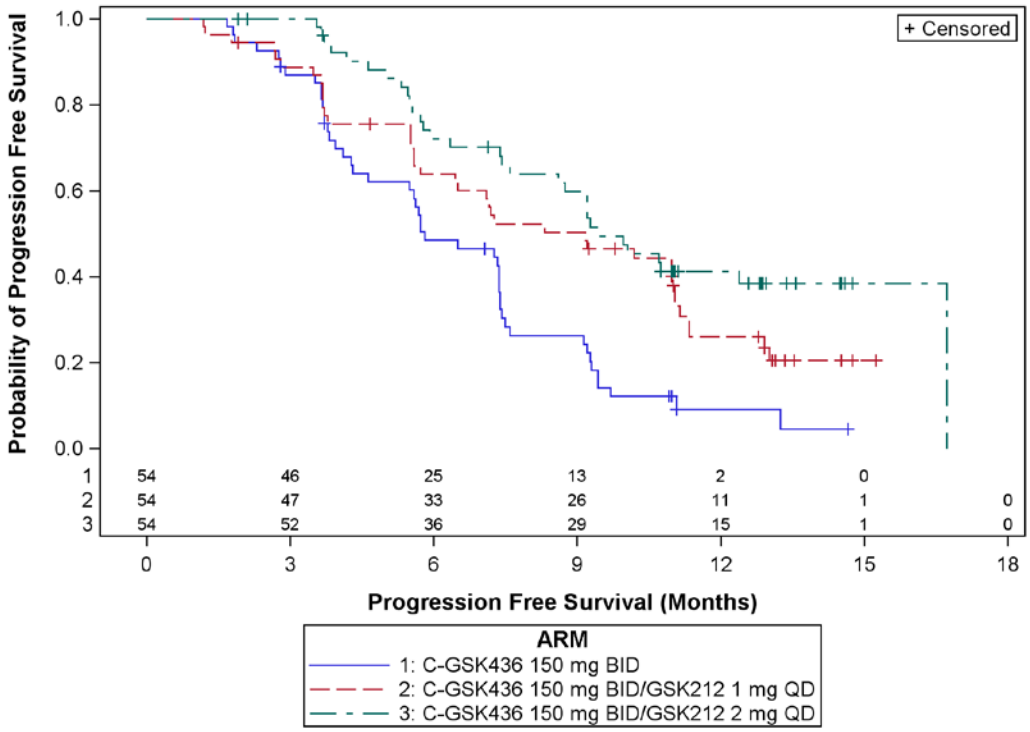
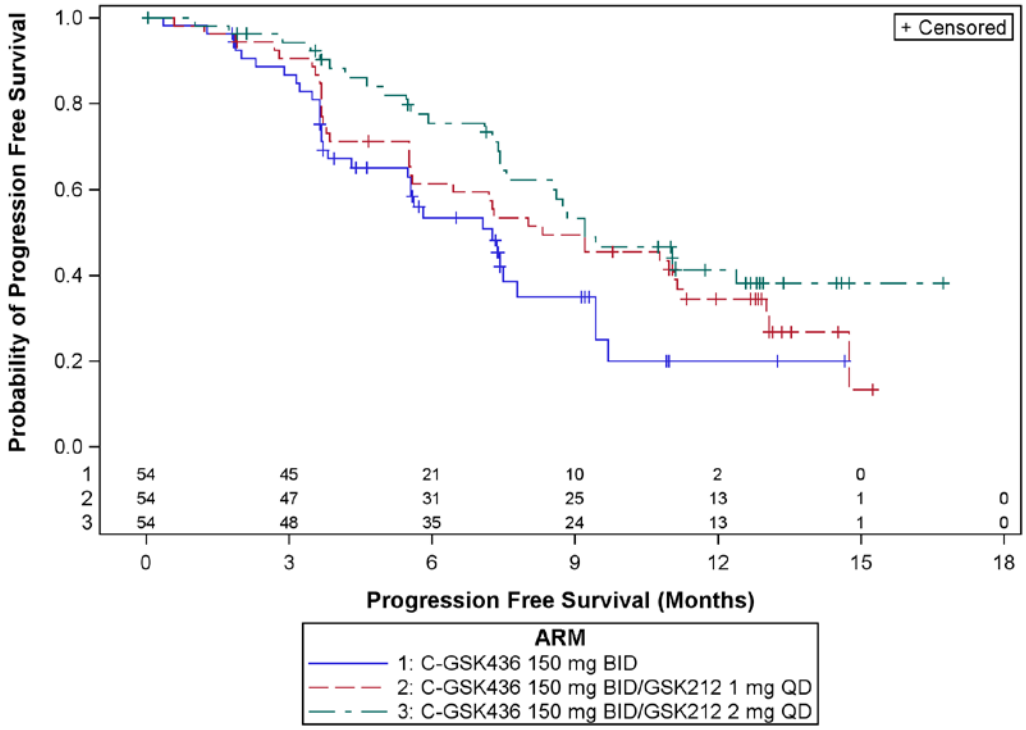


Figure 4 shows the estimated Kaplan-Meier curves for the distribution of PFS assessed by BICR.

Figure 4: Plots of Kaplan-Meier Estimates for Progression-Free Survival by BICR (ITT Population)



Source: FDA Statistical Review

Reviewer Comments:

1. *Retrospective analysis of efficacy endpoints based on central imaging vendor assessment of tumor response endpoints when patient disposition is based on investigator-assessment of tumor response may introduce bias. In addition, the allowance of continued randomized treatment beyond investigator-assessed PD, but crossover to a different treatment in only one arm, may result in an imbalance in tumor-imaging assessments performed after investigator-assessed PD which would be available to the BICR in the assessment of PFS for the randomized phase of the trial. The Applicant had provided sensitivity analyses to address these potential biases to support the robustness of the efficacy results.*
2. *P-values were not calculated by the FDA Statistical Reviewer because formal statistical tests were not pre-specified for PFS* [redacted] (b) (4)

Overall Survival

The definition of OS included all death events, including those which occurred following the date of crossover from the dabrafenib monotherapy treatment to the 150/2 combination treatment.

Table 18 summarizes the results from the OS analysis. There were a total of 51 patients who had died at time of the primary analysis, of which 19 were in the dabrafenib monotherapy arm, 18 were in the 150/1 combination arm and 14 in the 150/2 combination arm. Median OS was not estimable for any of the treatment arms because the OS data are not mature.

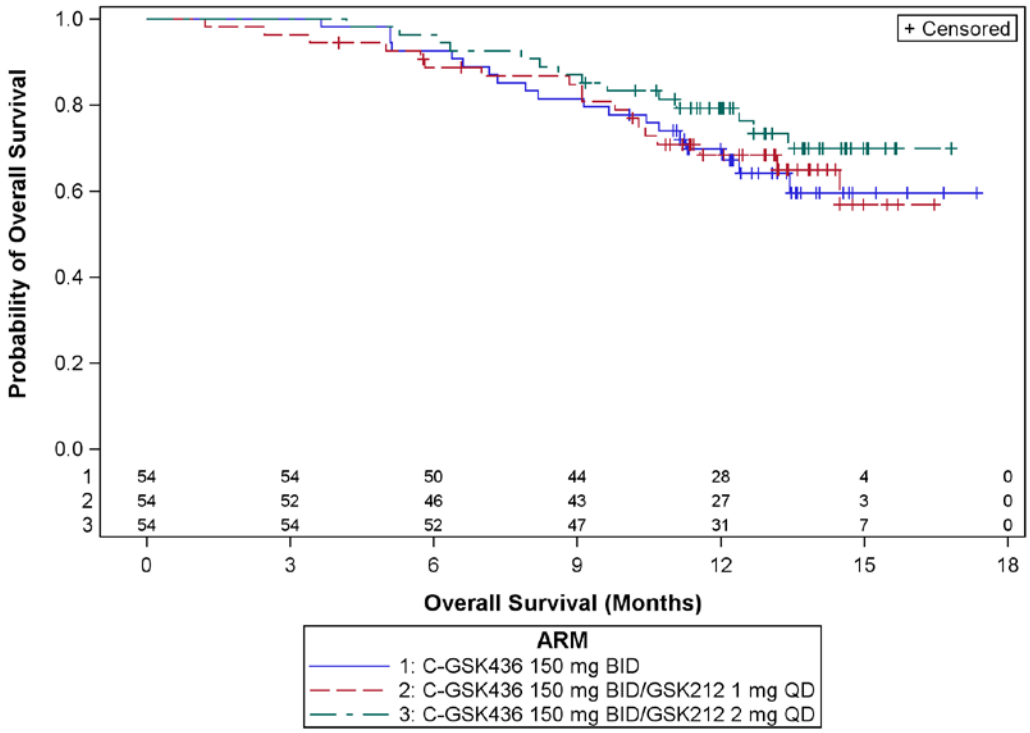
Table 18: Analysis on Overall Survival by Treatment Arm (ITT Population)

	D	**D + T 1 mg**	**D + T 2 mg**
	N=54	N=54	N=54
Number of Deaths (%)	19 (35.2%)	18 (33.3%)	14 (25.9%)
Median OS (95% CI)	NE (12.4, NE)	NE (13.2, NE)	NE (NE, NE)
HR (95% CI) by Pike		0.98 (0.51, 1.87)	0.67 (0.34, 1.34)
HR (95% CI) by Cox		0.97 (0.51, 1.86)	0.67 (0.34, 1.34)

Source: FDA Statistical Review
Abbreviations: CI: confidence interval; CR, complete response; D, dabrafen b; DoR, duration of response; NE, not reached; PR, partial response; T, trametinib

Figure 5 shows the estimated Kaplan-Meier plots for the distribution of OS.

Figure 5: Plots of Kaplan-Meier Estimates for Overall Survival (ITT Population)



Source: FDA Statistical Review

In the 90-day safety data submission, the Applicant also provided an updated overall survival analysis based on data from 10 additional months after the original sNDA data cutoff date with a median 24 months of follow up of overall survival based on the 29 March 2013 data cutoff for trial BRF113220. At the initial data cutoff, 31% of patients (51/162) had died across all three arms. The median follow-up was 14 months for the combination arms. In the updated analysis, 51% of patients had died (83/162) across all three arms and the median follow-up was 24 months. The more mature overall survival estimates are summarized in Table 19 and the Kaplan-Meier plots are presented Figure 6.

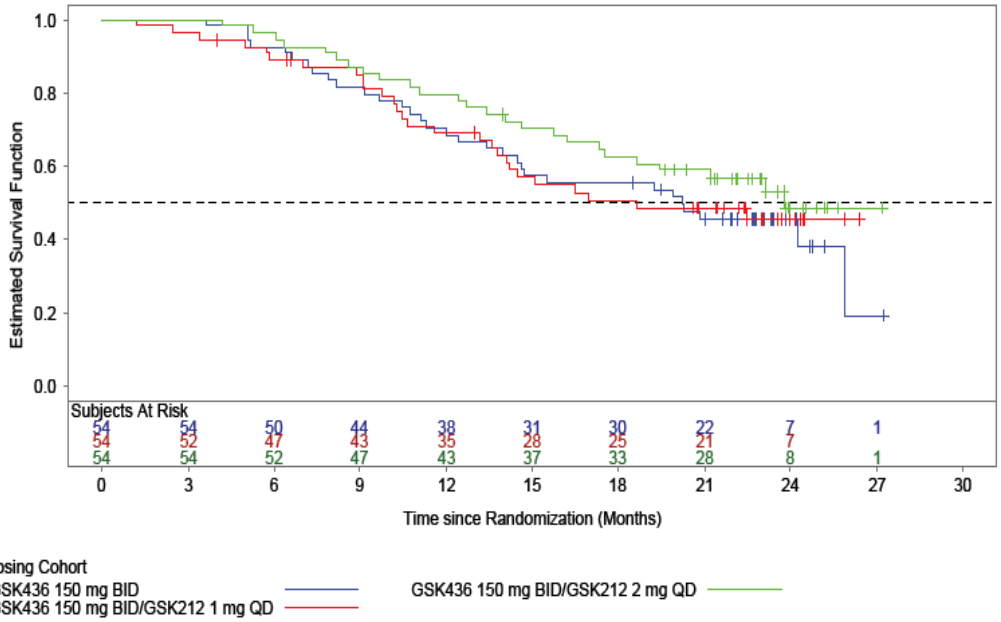
The median OS (95% CI) observed for the 150/2 combination arm was 23.8 months (17.5,NR), compared to 20.2 months (14.5, 25.9) for the dabrafenib monotherapy arm and 18.7 months (13.7, NR) for the 150/1 combination arm. For the comparison to dabrafenib monotherapy, this represents a HR of 0.73 (0.43, 1.24; p=0.24) which was not statistically significant.

Table 19: Survival Data Summaries from the Primary and Post-hoc Analyses

Cutoff dates	Treatment	Number of deaths (%)	Median months	Hazard Ratio (95% CI)
May 31, 2012	Dabrafenib	19 (35)	NR (13.4.4, NR)	
	150/1 Combination	18 (33)	NR (14.5, NR)	0.98 (0.51, 1.87)
	150/2 Combination	14 (26)	NR (NR, NR)	0.67 (0.34, 1.34)
March 29, 2013	Dabrafenib	31 (57)	20.2 (14.5, 25.9)	
	150/1 Combination	27 (50)	18.7 (13.7, NR)	0.96 (0.57,1.60)
	150/2 Combination	25 (46)	23.8 (17.5, NR)	0.73 (0.43,1.24)

Source: OS Table 2, 90-Day Safety Update

Figure 6: Updated Plots of Kaplan-Meier Estimates for Overall Survival



Source: OS Figure 1, 90-Day Safety Update

The Applicant states that the final analysis for OS will be conducted when 75% of deaths or loss to follow-up have been observed, which is currently projected to occur in June 2014.

Reviewer Comment:
The protocol allowed patients on the dabrafenib monotherapy arm to crossover to receive the 150/2 combination on investigator-assessed PD, which occurred in 83% patients. At the updated median follow-up of 24 months, there does not appear to be a detrimental effect of the 150/2 combination treatment on OS.

6.1.6 Other Endpoints

The review did not include an analysis of exploratory endpoints for Trial BRF113220 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 the combination of dabrafenib and trametinib treatment.

6.1.7 Subpopulations

FDA did not perform subgroup analyses based on race because the study population was almost entirely (99%) Caucasian. Subgroup analyses based on age, gender, and geographic region was performed based on the investigator-assessed ORR as shown in Tables Table 20, Table 21, and Table 22.

Table 20: Subgroup Analysis of ORR by Age

	D	D + T 1 mg	D + T 2 mg
Age <65	N=42	N=46	N=43
CR+PR (%) 95% CI Median DoR (95% CI)	22 (52%) (36.4%, 68.0%) 5.6 (4.5, 7.4)	26 (57%) (41.1%, 71.1%) 9.5 (7.4, NE)	32 (74%) (58.9%, 86.5%) 14.9 (7.6, 14.9)
Age ≥ 65	N=12	N=8	N=11
CR+PR (%) 95% CI Median DoR (95% CI)	7 (58%) (27.7%, 84.8%) 4.1 (2.8, 7.6)	1 (13%) (0.3%, 52.7%) NE	9 (82%) (48.2%, 97.7%) 7.4 (2.4, NE)

Source: FDA Statistical Review
Abbreviations: CI: confidence interval; CR, complete response; D, dabrafen b; DoR, duration of response; NE, not reached; PR, partial response; T, trametinib

Table 21: Subgroup Analysis of ORR by Gender

	D	D + T 1 mg	D + T 2 mg
Female	N=25	N=24	N=20
CR+PR (%) 95% CI Median DoR (95% CI)	15 (60%) (38.7%, 78.9%) 5.6 (4.1, 7.4)	11 (46%) (25.6%, 67.2%) NE (3.7, NE)	15 (75%) (50.9%, 91.3%) NE (7.0, NE)
Male	N=29	N=30	N=34
CR+PR (%) 95% CI Median DoR (95% CI)	14 (48%) (29.4%, 67.5%) 5.5 (3.7, 11.3)	16 (53%) (34.3%, 71.7%) 9.5 (5.5, NE)	26 (76%) (58.8%, 89.3%) 9.1 (5.7, 14.9)

Source: FDA Statistical Review
Abbreviations: CI: confidence interval; CR, complete response; D, dabrafen b; DoR, duration of response; NE, not reached; PR, partial response; T, trametinib

Table 22: Subgroup Analysis of ORR by Region

	D	D + T 1mg	D + T 2mg
USA	N=49	N=50	N=44
CR+PR (%) 95% CI Median DoR (95% CI)	27 (55%) (40.2%, 69.3%) 5.6 (4.1, 7.4)	24 (48%) (33.7%, 62.6%) 9.5 (7.4, NE)	33 (75%) (59.7%, 86.8%) 14.9 (7.4, 14.9)
Australia	N=5	N=4	N=10
CR+PR (%) 95% CI Median DoR (95% CI)	2 (40%) (5.3%, 85.3%) 4.7 (2.0, 7.4)	3 (75%) (19.4%, 99.4%) NE (3.7, NE)	8 (80%) (44.4%, 97.5%) 8.1 (3.7, NE)

Source: FDA Statistical Review
Abbreviations: CI: confidence interval; CR, complete response; D, dabrafenib; DoR, duration of response; NE, not reached; PR, partial response; T, trametinib

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Regarding dose response, ORR was 76% with dabrafenib 150 mg BID in combination with trametinib 2 mg QD as compared to 50% with 150 mg BID in combination with trametinib 1 mg QD.

There was limited exposure response data in the application. There appears to be a higher response rate with increased exposures of trametinib (at dose levels of 1 and 2 mg QD) administered in combination with dabrafenib.

See Clinical Pharmacology Review for further details.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Responses appear more durable with the 150/2 combination treatment than with dabrafenib monotherapy treatment. The investigator-assessed ORR was 76% with a median duration of 10.5 months in the 150/2 combination arm compared to an ORR of 54% with a median duration of 5.6 months with dabrafenib monotherapy.

Sequential therapy was evaluated in the crossover population of 81% (43/54) patients who received trametinib in addition to dabrafenib at the time of disease progression on the dabafenib monotherapy arm. The clinical efficacy observed with this sequential therapy was limited to 9% of patients who experienced a partial tumor response which were only observed in patients who had experienced an objective response on the prior dabrafenib therapy. This observation suggests that once secondary resistance to dabrafenib is established, the clinical activity of the combination regimen is limited to a small subpopulation of patients whose tumor appears to be still dependent on the MAPKpathway. The exact mechanism(s) of secondary resistance to dabrafenib that would sensitize a BRAF V600 mutation-positive melanoma to the combination regimen have not yet been elucidated.

6.1.10 Additional Efficacy Issues/Analyses

Gelatin and HPMC Capsules

Patients in Part C received both the gelatin and HPMC formulations. The Applicant was requested to perform sensitivity analyses on these patients. Results were generally similar between those who received HPMC (and gelatin) capsules and those who exclusively received gelatin capsules. However due to the limited time that patients received HPMC alone, it is difficult to draw any conclusions on the impact of the HPMC capsule shell on efficacy. Per the Applicant, the majority of patients who received the HPMC capsule shell type did so during the first two months of treatment and thus per protocol specified disease assessments (every 8 weeks), responses assessed would

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not have been confirmed while still on HPMC, but rather would have occurred once switched to gelatin capsules.

Table 23: ORR Results by Formulation

	150 mg BID	150 mg BID	150 mg BID
	--	1 mg QD	2 mg QD
HPMC (and gelatin) Dabrafenib	N=35	N=33	N=36
Investigator Assessed ORR (95% CI)	20 (57%) (39.4%,73.7%)	15 (45%) (28.1%,63.6%)	28 (78%) (60.8%,89.9%)
Investigator Asessed median PFS in months (95% CI)	6.5 (5.6,7.4)	8.3 (5.6,11.0)	9.3 (7.4,16.7)
Investigator Assessed DOR in months (95% CI)	5.6 (3.9,7.6)	9.2 (5.5,NR)	10.5 (7.4, 14.9)
BICR ORR (95% CI)	20 (57%) (39.4%,73.7%)	15 (45%) (28.1%,63.6%)	19 (53%) (35.5%,69.6%)
BICR median PFS in months (95% CI)	7.1 (5.6,9.4)	9.2 (5.6,13.1)	8.8 (7.4,NR)
BICR Assessed DOR months in months (95% CI)	7.6 (4.7, NR)	11.3 (5.8, NR)	7.6 (6.9, NR)
Gelatin only Dabrafenib	N=18	N=21	N=19
Investigator Assessed ORR	9 (47%) (24.4%,71.1%)	12 (57%) (34.0%,78.2%)	13 (72%) (46.5%,90.3%)
Investigator Assessed Median PFS in months (95% CI)	4.6 (4.1,7.6)	10.2 (5.6,11.3)	10.3 (8.7,NR)
Investigator Assessed DOR in months (95% CI)	5.6 (5.4,7.4)	9.5 (7.4,11.1)	NR (7.4, NR)
BICR ORR	5 (26%) (9.1%,51.2%)	6 (29%) (11.3%,52.2%)	14 (78%) (52.4%,93.6%)
BICR median PFS in months (95% CI)	7.5 (3.7,9.7)	8.0 (3.6,11.3)	11.0 (7.4,NR)
BICR Assessed DOR in months (95% CI)	NR (3.7, NR)	8.4 (6.2, NR)	NR (5.3, NR)

Source: Response to FDA Information Request, October 21, 2013

Companion Diagnostic Assay

Patients were eligible for enrollment on BRF113220 based on a locally performed BRAF mutation assay result. A total of 36 local laboratories provided BRAF mutation results. Subsequently, all BRAF results were confirmed using an analytically validated "investigational use only" (IUO) allele-specific PCR assay via a central reference laboratory (Response Genetics Inc; RGI). In some instances, RGI served as a local testing laboratory as well; thus, the RGI IUO was used either to screen or to confirm the BRAF mutation status of subjects who were eligible for the study BRF113220. Finally, a "bridging study" was performed whereby the bioMerieux THxID-BRAF kit was used to confirm the BRAF mutation status of all patient samples collected in Part C of BRF113220.

Per CDRH, GSK was unable to conduct an appropriate bridging study due to the missing local laboratory test negatives for the analytical concordance study but believes that safety and efficacy of the combination of dabrafenib and tramatenib claims supported by results in subjects selected with local lab test results will be similarly supported when subjects are selected by the bioMérieux THxID –BRAF assay. Refer to CDRH review.

Reviewer Comment:

> *The results of these analyses have been submitted in a clinical study report comparing the analytical concordance between local and RGI IUO and bMx THxID assay results and the clinical concordance between BRAF mutation-positive subjects based on results from the three assays (original BRAF mutation result from a local lab that was the basis for enrolment and randomization, RGI IUO, the bMx THxID-BRAF kit). In exploratory subgroup analyses of patients with retrospectively confirmed BRAF V600E or V600K mutation-positive melanoma with the THxID™-BRAF assay, the ORR results were similar to the primary analysis of ORR intent-to-treat analysis. Refer to CDRH Review for further details.*

7 Review of Safety

Safety Summary

The safety of the combination of dabrafenib and trametinib was primarily evaluated in Part C in 162 patients with BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma who received up to at least one prior therapy. The review of safety primarily focused on analyses of data submitted for Part C because it is the only randomized component submitted by the Applicant to support the safety of the combination of dabrafenib and trametinib. Part C enrolled 162 patients, 53 of whom received treatment with dabrafenib monotherapy and 55 of whom received treatment

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with the 150/2 combination treatment. The integrated safety database included 202 patients who were treated with the combination of dabrafenib 150 mg orally twice daily and trametinib 2 mg orally once daily in Trial BRF113220.

A summary of the important safety results from trial BRF113220 based on the results of 150/2 combination group compared to the dabrafenib monotherapy group are the following:

- The median daily dose in the 150/2 combination group of dabrafenib was 94% (281.8) and trametinib was 97% (1.9) of the intended dose.
- The median duration of treatment with the 150/2 combination treatment was 10 months (range 2 to 17)
- Deaths within 28 days of treatment occurred in 5 (9%) of patients in the 150/2 combination group compared to one death in the dabrafenib monotherapy group; 3 deaths in the combination group were due to treatment-emergent adverse events (TEAEs).
- Fatal serious adverse events (SAEs) occurred in 3 (5%) patients in the 150/2 combination group compared to none of patients in the dabrafenib monotherapy group. Two patients died of intracranial hemorrhage and one of pulmonary embolism.
- SAEs occurred in 34 patients (62%) in the 150/2 combination group compared to 13 (25%) patients in the dabrafenib monotherapy group. Pyrexia was the most common SAE.
- Permanent discontinuations due to TEAEs occurred in 5 (9%) in the 150/2 combination group compared to 1 (2%) patients in the dabrafenib monotherapy group. Pyrexia was the most common AE leading to permanent discontinuation.
- Dose interruptions due to AEs occurred in 34 (62%) of patients in the 150/2 combination group compared to 15 (28%) of patients in the dabrafenib monotherapy group. Pyrexia was the most common AE leading to dose interruption.
- Dose reductions due to AEs occurred in 30 (55%) of patients in the 150/2 combination group compared to 10 (19%) of patients in the dabrafenib monotherapy group. Pyrexia was the most common AE leading to dose reduction.
- Grade 3 or Grade 4 TEAEs occurred in 35 (64%) of patients in the 150/2 combination group compared to 23 (43%) of patients in the dabrafenib monotherapy group. Neutropenia and hyponatremia were the most common Grade 3 and 4 TEAEs.
- TEAEs that occurred in ≥ 20% (with a between-arm difference of ≥ 5) include pyrexia (71% with 150/2 combination treatment vs. 26% with dabrafenib monotherapy), chills (58% vs. 17%), fatigue (53% vs. 40%), nausea (44% vs. 21%), vomiting (40% vs. 15%), diarrhea (36% vs. 28%), cough (29% vs. 21%), peripheral edema (29% vs. 17%),night sweats (24% vs. 6%) and constipation (22% vs. 11%).

- The 90-day safety update did not identify the emergence of previously undetected toxicities with ongoing observation or exposure, although dose reductions, discontinuations and SAEs were slightly increased in the 150/2 combination group
- Review of submission specific primary safety concerns revealed the following:
    - Cutaneous squamous cell carcinoma including keratoacanthoma occurred in 10 (19%) patients treated with dabrafenib compared to 4 (7%) patients treated with the 150/2 combination
    - One case of superficial spreading melanoma occurred with dabrafenib monotherapy. No cases of new primary melanoma occurred with the combination treatment.
    - Treatment-emergent non-cutaneous malignancies occurred in one patient (150/2 combination group) in Part C. In the ISS database, there were five malignancies reported: glioblastoma, head and neck squamous cell carcinoma, pancreatic adenocarcinoma, renal cell carcinoma, and colorectal carcinoma.
    - Basal cell carcinoma occurred in 5 (9%) patients in the 150/2 combination group compared to one (2%) patient in the dabrafenib monotherapy group
    - Decreased ejection fraction and cardiac failure occurred in 5 (9%) patients in the 150/2 combination group compared to none in the dabrafenib monotherapy group
    - Hemorrhagic events including intracranial and gastric hemorrhage occurred in 11 (20%) patients in the 150/2 combination group compared to one (2%) in the dabrafenib monotherapy group.
    - Thromboembolic events of pulmonary embolism and deep venous thrombosis occurred in four (7%) patients in the 150/2 combination group compared to none in the dabrafenib monotherapy group.
    - Renal failure occurred in four (7%) patients in the 150/2 combination group compared to none in the dabrafenib monotherapy group
    - Pyrexia occurred in 39 (71%) patients in the 150/2 combination group compared to 14 (26%) patients in the dabrafenib monotherapy group
    - Dermatitis acneiform, erythema, generalized rash occurred at a higher incidence with the 150/2 combination treatment, whereas plantar-palmar erythrodysesthesia, maculopapular and exfoliative rash occurred at a higher incidence with dabrafenib monotherapy
    - Hepatic events including increases in AST, ALT, and bilirubin occurred at a higher incidence with the 150/2 combination treatment compared with dabrafenib monotherapy
    - Myelosuppression events of Grades 3 and 4 neutropenia, anemia and thrombocytopenia occurred at a higher incidence with the 150/2 combination treatment compared with dabrafenib monotherapy
    - Ocular events occurred in 14 (25%) patients in the 150/2 combination group compared to eight (15%) patients in the dabrafenib monotherapy group. Most common ocular events were blurred vision and dry eye.

The reviewer does not recommend a Risk Evaluation and Mitigation Strategies (REMS) based on the information provided in the submission.

7.1 Methods

The Applicant mapped and coded verbatim adverse events (AE) terms for the BRF113220 trial using MedDRA version 15.0. Adverse events datasets included MedDRA 15.0 preferred terms (PTs) and the corresponding investigator entered terms, which were reviewed to check for accuracy of MedDRA coding. The MedDRA-based Adverse Event Diagnostics (MAED) tool was utilized to support screening for safety signals and relative risk analysis across all levels of the MedDRA hierarchy and select standardized MedDRA queries (SMQ) definitions. Post-marketing data was reviewed in an exploratory manner.

The following safety concerns are reviewed in detail in Section 7.3.5 of the review:

- New primary malignancies:
- Cardiac events
- Hemorrhagic events
- Thromboembolic events
- Renal failure
- Pyrexia
- Rash and skin-related events
- Hepatic events and drug-induced liver injury
- Ocular events
- Diarrhea
- Hypertension
- Sepsis and infections
- Electrolytes abnormalities
- Hematopoietic cytopenias
- Depression
- Rhabdomyolysis

Reviewer Comment:

1. *The Applicant did not include a treatment-emergent AE flag per ADaM. Based on their clarification, for Parts A, B, and D, the APHASE variable and for Part C the APHASE and AINTVLC variables were used to analyze the treatment-emergent AEs.*
2. *The Applicant converted the original data sources to the CDISC format. The data sources used in the safety assessments were adequate. The Applicant's categorization of data and coding methods were deemed appropriate.*

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The sNDA submission contained a single phase 1/2 trial, BRF113220. The review of safety primarily focused on Part C, the randomized component of study BRF113220, in support of the safety of the combination of dabrafenib and trametinib (subsequently referred to as Part C in the Clinical Review of Safety).

The safety population in Part C consisted of patients who had received at least one dose of trial medication and had at least one safety follow-up (All Treated Population) and included 53 patients in the dabrafenib monotherapy group, 54 patients in the combination of dabrafenib and trametinib 1mg (150/1 combination group) and 55 patients in the combination of dabrafenib and trametinib 2 mg (150/2 combination group) [N=162]. One patient randomized to the dabrafenib monotherapy group received treatment on trial upfront with the 150/2 combination treatment.

(b) (4) a hydroxypropyl methylcellulose (HPMC) capsule shell of dabrafenib was selected and is the approved commercial formulation, instead of the gelatin capsule shell used in the early clinical development program (i.e., the phase 1 dabrafenib monotherapy study and Parts A, B, and C of trial BRF113220). The Applicant conducted Part D (N=110) to assess the potential impact of this change in capsule shell on the PK and safety profile. Although the planned formulation for trial BRF113220 Part B and Part C was gelatin capsules, 79/138 patients in Part B and 104/162 patients in Part C were also treated with the HPMC formulation. Sensitivity analyses were conducted in these populations in Part C. All safety analyses are based on the All Treated Population. Supportive data was provided in trial BRF113220 Part D in which the Applicant investigated the impact of the change in the dabrafenib capsule shell from gelatin to HPMC on the safety profile of the combination.

The integrated summary of safety (ISS) safety database consists of data from trial BRF113220 and includes patients with metastatic melanoma who received combination therapy irrespective of the dose of either dabrafenib (75 or 150 mg twice daily) or trametinib (1, 1.5, or 2 mg once daily) in Parts B, C and D (ISS database, N=365):

- BRF 113220, Part B (N=103)
- BRF 113220, Part C (N=109 in randomized phase and 43 patients who crossed over from dabrafenib monotherapy group to the 150/2 combination group)
- BRF 113220, Part D (N=110)

The pooled integrated summary of safety (ISS) safety data also includes data from patients treated with the 150/2 combination in trial BRF113220 Parts B, C, and D (Pooled 150/2 combination group, N=202) to further investigate the safety profile of the highest dose combination regimen.

The Applicant also included ISS data from the dabrafenib monotherapy (N=586) and trametinib monotherapy (N=329) in summary tables. Although cross-study comparisons, the information is useful for an assessment of the adverse event rates in the monotherapy populations.

As requested by the FDA, the Applicant submitted the 4-month safety update as a 90-day safety update. Safety data from Part C, Part D (N=39, follow-up ≥ 6 months) and safety information from the ongoing phase 3 confirmatory trial MEK115306 (N=40) were reviewed in order to determine whether the proposed safety database will be sufficient to evaluate the clinical impact on tolerability of the dabrafenib HPMC capsule in combination with trametinib.

Reviewer Comments:

1. *For Part C, the review of safety focused primarily on the patients in the randomized phase as crossover leads to difficulties in the attribution of adverse events that occur in later treatment periods to the appropriate treatment.*
2. *Although data from Part B, Part C, and Part D are pooled for the combination dose(s), and while patients in Part D were treated solely with the HPMC formulation, patients in Part B and Part C were treated with both the gelatin and HPMC formulation leading to confounding of the interpretation of the results. Interpretation is further confounded by the fact that 79/138 in Part B and 104/162 patients in Part C were treated with both the gelatin formulation and the HPMC formulation. The HPMC formulation is not bioequivalent to the gelatin capsule formulation; administration of HPMC capsules results in approximately 20% higher exposures than that observed following administration of the gelatin capsule.*
3. *The size of the integrated safety database and duration of the combination of dabrafenib and trametinib exposure were sufficient to characterize the safety of the combination for treatment of a serious and life-threatening condition with the expectation of updated safety data from the ongoing phase 3 trials.*

7.1.2 Categorization of Adverse Events

The Applicant graded the severity of AEs observed onTrial BRF113220 using NCI CTCAE version 4. The Applicant mapped and coded verbatim AE terms for Trial BRF13220 using the MedDRA version 15.0.

Reviewer Comments:

1. *The clinical review of safety assessed the adequacy of the Applicant's mapping of AE verbatim terms to MedDRA preferred terms (PT) for 100% of the BRF113220 raw AE dataset. Of the 7,961 AE line listings in the AE.xpt dataset,*

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the review used programmatic matching of identical verbatim and MedDRA PTs as well as manual evaluation of the remaining verbatim terms (N=3,497) to assess the acceptability of the Applicant's mapping from the verbatim term to MedDRA PT. Particular attention was paid to identifying any "splitting" (coded terms too narrow) or "lumping" (coded terms too broad) to check whether the adverse events were coded with accuracy. The MedDRA PTs listed in the datasets adequately represented the investigator recorded term (i.e., verbatim term) and did not raise any significant issues.

2. *The ISS database had records of Grade 2 pulmonary embolism. Uncomplicated pulmonary embolism is Grade 3 by CTCAE definition. The Applicant provided an updated analysis of pulmonary embolism (Refer to section 7.3.5).*
3. *The clinical review of safety included an audit of AE case report forms randomly in 10% of cases to assess the completeness and verify the accuracy of the raw AE datasets. The review did not raise any significant issues.*

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

The Applicant's ISS presented the most common treatment-emergent adverse events (TEAE) (≥10% of patients) reported in the patients treated with the 150/2 combination in Part C and the ISS pooled 150/2 combination group along with historical safety data from the ISS dabrafenib and ISS trametinib single-agent populations. This analysis is presented in the Table 24 below.

The most common AEs (≥ 10%) reported in the 150/2 combination group were pyrexia, chills, nausea, vomiting, insomnia, abdominal pain, dizziness, muscle spasms, actinic keratosis, erythema, neutropenia, oropharyngeal pain, urinary tract infection, dehydration, dry mouth and generalized rash .

Table 24: Adverse Events Experienced by ≥ 10% of Patients in Part C, Pooled ISS 150/2 Group, Single-agent Trametinib and Single-agent Dabrafenib

	Combination Therapy		Monotherapy		
	Dabrafenib + Trametinib		Trametinib	Dabrafenib	
	BRF113220 Part C	BRF113220 Pooled	ISS	ISS	BRF113220 Part C
Dabrafenib	150 mg BID	150 mg BID	--	150 mg BID	150 mg BID
Trametinib	2 mg QD	2 mg QD	2 mg QD	--	--
N	55	202	329	586	53
Any AE, n (%)	**55 (100)**	**201 (>99)**	**326 (>99)**	**566 (97)**	**53 (100)**
Pyrexia	39 (71)	116 (57)	40 (12)	176 (30)	14 (26)
Chills	32 (58)	87 (43)	18 (5)	77 (13)	9 (17)
Fatigue	29 (53)	77 (38)	109 (33)	151 (26)	21 (40)
Nausea	24 (44)	81 (40)	99 (30)	149 (25)	11 (21)
Vomiting	22 (40)	73 (36)	66 (20)	107 (18)	8 (15)
Diarrhea	20 (36)	54 (27)	162 (49)	91 (16)	15 (28)
Cough	16 (29)	47 (23)	37 (11)	78 (13)	11 (21)
Headache	16 (29)	55 (27)	38 (12)	177 (30)	15 (28)
Edema peripheral	16 (29)	40 (20)	109 (33)	54 (9)	9 (17)
Arthralgia	15 (27)	56 (28)	33 (10)	172 (29)	18 (34)
Rash	15 (27)	55 (27)	191 (58)	115 (20)	19 (36)
Night sweats	13 (24)	39 (19)	3 (<1)	22 (4)	3 (6)
Constipation	12 (22)	38 (19)	61 (19)	61 (10)	6 (11)
Decreased appetite	12 (22)	38 (19)	42 (13)	82 (14)	10 (19)
Myalgia	12 (22)	26 (13)	8 (2)	86 (15)	12 (23)
Back pain	10 (18)	22 (11)	23 (7)	65 (11)	6 (11)
Dry skin	10 (18)	23 (11)	57 (17)	52 (9)	3 (6)
Insomnia	10 (18)	15 (7)	28 (9)	37 (6)	4 (8)
Abdominal pain upper	9 (16)	13 (6)	20 (6)	33 (6)	4 (8)
Dermatitis acneiform	9 (16)	26 (13)	74 (22)	17 (3)	2 (4)
Dizziness	9 (16)	29 (14)	25 (8)	37 (6)	5 (9)
Muscle spasms	9 (16)	22 (11)	18 (5)	15 (3)	2 (4)
Pain in extremity	9 (16)	25 (12)	23 (7)	92 (16)	10 (19)
Abdominal pain	8 (15)	18 (9)	43 (13)	42 (7)	7 (13)
Actinic keratosis	8 (15)	19 (9)	3 (<1)	52 (9)	5 (9)
Erythema	8 (15)	15 (7)	18 (5)	38 (6)	1 (2)
Neutropenia	8 (15)	18 (9)	6 (2)	16 (3)	1 (2)
Anemia	7 (13)	34 (17)	31 (9)	52 (9)	3 (6)
Oropharyngeal pain	7 (13)	22 (11)	12 (4)	20 (3)	0
Urinary tract infection	7 (13)	26 (13)	15 (5)	16 (3)	5 (9)
Dehydration	6 (11)	21 (10)	14 (4)	17 (3)	1 (2)
Dry mouth	6 (11)	20 (10)	34 (10)	9 (2)	3 (6)
Pruritus	6 (11)	15 (7)	54 (16)	41 (7)	7 (13)
Rash generalized	6 (11)	12 (6)	1 (<1)	7 (1)	4 (8)

Source: Summary of Clinical Safety, Table 16. Data from Trial BRF113220 verified with ADAE.xpt. Historical data from single-agent trametinib and single-agent dabrafen b provided by the Applicant.
Abbreviations: AE, adverse event; BID, twice daily; QD, once daily

Reviewer Comments:

1. *Although a cross-study comparison, the reviewer agrees with the Applicant's side-by-side comparison of the incidence of AEs observed in Part C to the incidence of AEs observed with dabrafenib and trametinib in the monotherapy registration trials. Dabrafenib and trametinib monotherapy were approved recently (May 29, 2013) and the data are based on the cutoff date of June 2012 which included 586 patients in the dabrafenib ISS population and 329 patients in the trametinib ISS population.*
2. *Given the several different doses used for dabrafenib and trametinib in the combination groups across Trial BRF113220, comparisons limited to the pooled 150/2 combination groups, the recommended doses of dabrafenib and trametinib for use in combination, is appropriate to include in the ISS tables.*
3. *Overall, the incidences of common TEAEs occurring in the pooled ISS 150/2 combination group were similar to or higher than the incidences of TEAEs in the historical dabrafenib and trametinib monotherapy populations. The differences may be due to the population size or the use of two different formulations in Part C, or the inclusion in the pooled ISS population of 43 patients who initially received dabrafenib monotherapy and crossed over to receive 150/2 combination therapy, or the longer median time on treatment with the 150/2 combination compared to the monotherapy trials, or a combination of these factors.*

7.2 Adequacy of Safety Assessments

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

In Part C, 53 patients received treatment with dabrafenib monotherapy, 54 patients received treatment with the combination of dabrafenib and trametinib 1 mg (150/1 combination group), and 55 patients received treatment with the combination of dabrafenib and trametinib 2mg (150/2 combination group). The median daily dose of dabrafenib was higher in the dabrafenib monotherapy group (98.6%, 295.9/300 mg) compared to the two combination groups. The median daily dose of dabrafenib in the 150/1 combination group was 94.2% (282.6/300 mg) and in the 150/2 combination group was 93.9% (281.8/300 mg). Patients treated with dabrafenib in the two combination groups remained on treatment longer than patients treated with dabrafenib monotherapy (median of 10.9 months vs. 10.5 months vs. 6 months). The median daily dose of trametinib was 1.92/2 mg (96%) in the 150/2 combination group and 0.97/1 mg (94%) in the 150/1 combination group. Patients treated with the 150/2 combination remained on treatment longer than patients treated with the 150/1 combination (median of 10.9 months vs. 9.7 months). Table 25 summarizes the exposure to dabrafenib and trametinib for each treatment group in Part C.

Reference ID: 3422378

Table 25: Summary of Exposure to Dabrafenib and Trametinib (All Treated Population)

		D N=53	D + T 1 mg N=54	D + T 2 mg N=55
Dabrafenib				
Daily dose (mg)	Mean	288.4	252.9	253.3
	SD	20.8	59.8	56.1
	Median	295.9	282.6	281.8
	Min.	165.6	39.1	121.5
	Max.	300.0	300.0	300.0
Time on study treatment (months)	Mean	6.5	9.3	9.9
	SD	3.3	4.6	4.2
	Median	6.1	10.5	10.9
	Min.	1.8	0.9	1.9
	Max.	15.2	16.4	17.3
Trametinib				
Daily dose (mg)	Mean	N/A	0.93	1.76
	SD	N/A	0.10	0.35
	Median	N/A	0.97	1.92
	Min.	N/A	0.5	0.3
	Max.	N/A	1.0	2.0
Time on study treatment (months)	Mean	N/A	9.1	9.7
	SD	N/A	4.7	4.2
	Median	N/A	9.7	10.9
	Min.	N/A	0.9	1.8
	Max.	N/A	16.4	17.3

Source: ADEX.xpt
Abbreviations in Table: D, dabrafenib; Min, minimum; max, maximum; N/A, Not applicable; SD, standard deviation; T, trametin b

The median daily dabrafenib dose in the crossover patients (N=43) treated with the 150/2 combination was 290.63/300 mg (97%). The median duration of dabrafenib exposure was shorter in the crossover 150/2 combination group (3.6 months) compared to the dabrafenib monotherapy group (6.1 months) at the time of data cutoff. The median daily dose of trametinib was 1.97/2 mg (99%) in the crossover 150/2 combination group and 1.92/2 mg (96%) in the 150/2 combination group. The median duration of trametinib exposure was shorter (3.6 months) in the crossover 150/2 combination group compared to the trametinib exposure in the 150/2 combination group (10.9 months) at the time of data cutoff.

Within the ISS database, in the 202 patients in the pooled 150/2 combination group, the median duration of exposure of dabrafenib was 6.6 months and trametinib was 6.4 months.

Reviewer Comment:
The mean and median daily dose of dabrafenib in the 150/2 combination group was less than the other two groups per the targeted daily dose for the groups which was likely due to the higher dose interruptions and dose reductions in the 150/2 combination group (See Section 7.3.3).

7.2.2 Explorations for Dose Response

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

The routine clinical testing of clinical trial subjects, including efforts to elicit adverse event data by monitoring laboratory parameters, vital signs, and ECGs, appear to have been adequate.

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 adverse events known to be associated with BRAF inhibitors are pyrexia, skin-related toxicities, new malignancies, uveitis, and iritis. AEs known to be associated with MEK inhibitors are decreased LVEF, RPED, retinal vein occlusion, interstitial lung disease (ILD), pneumonitis, diarrhea, and skin-related toxicities. The Applicant identified AEs of special interest and the analyses included in the application. These included pyrexia, cardiac-related AEs, hepatic events, ocular events, new malignancies, skin-related toxicities, diarrhea, and renal failure.

7.3 Major Safety Results

7.3.1 Deaths

Table 26 summarizes the primary causes of death reported in Part C eCRFs. Four (18%) patients in the dabrafenib monotherapy group, 18 (33%) patients in the 150/1 combination group, and 14 (25%) patients in the 150/2 combination group died during the randomized phase of the study. Disease under study was the most commonly reported primary cause of death and accounted for all but one death in the 150/1 combination group and 3 in the 150/2 combination group. Two patients in the 150/2 combination group died of intracranial hemorrhage and one patient died of pulmonary embolism. Overall, treatment-emergent deaths (within 28 days of investigational product dosing) occurred in one patient (2%) in the dabrafenib monotherapy group, two (4%) patients in the 150/1 combination group, and five (9%) patients in the 150/2 combination group.

Table 26: Primary Causes of Death by Treatment Group (All Treated Population)

	Treatment Groups			
Dabrafenib	150 mg BID		150 mg BID	150 mg BID
Trametinib	--		1 mg QD	2 mg QD
Study Treatment	Randomized	Crossover[a]	Randomized	Randomized
N	53	43	54	55
Death Status, n (%)				
Dead	4 (8)	15 (35)	18 (33)	14 (25)
Alive at last contact, follow-up ended	0	0	4 (7)	0
Alive at last contact, follow-up ongoing	6 (11)	28 (65)	32 (59)	41 (75)
Alive at crossover	43 (81)	NA	0	0
Primary cause of death, n (%)				
Disease under study	4 (8)	15 (35)	17 (31)	11 (20)
SAE possibly related to study treatment	0	0	0	1 (2)[b]
Other	0	0	1 (2)[c]	2 (4)[d]
Time to Death From Last Dose, n (%)				
≤28 days	1 (2)	5 (12)	2 (4)	5 (9)
>28 days	3 (6)	10 (23)	16 (30)	9 (16)

Source: Applicant's analysis, brf113220-c-report, Table 35. Verified in XD.xpt.
Abbreviations: BID=Twice daily; NA=Not applicable; QD=Once daily.
a. All subjects crossed over to the 150/2 combination therapy dose group.
b. The "Summary of Deaths" table was based on data entered on the study conclusion form of the eCRF. On this form, the primary cause of death for this subject (Subject (b) (6) was noted by the investigator as "SAE possibly related to study treatment because the only other option listed was "Other". However, on the SAE form of the eCRF, the investigator clarified that the fatal pulmonary embolism SAE was related to the underlying disease and not related to study treatment.
c. Subject (b) (6)
d. Subjects (b) (6) and (b) (6)

Four patients, one in the 150/1 combination group and three in the 150/2 combination group, experienced fatal SAEs. None of the four fatal SAEs were considered drug-related by the investigator. Review of the patient narratives and CRFs are as follows:

Patient (b) (6) was a 71-year-old Caucasian female with malignant blue nevus metastatic to the subcutaneous tissue, skin, and head and neck with a relevant history of colon polyps, rheumatoid arthritis, hypertension, depression, hyperlipidemia, diverticulosis, tinnitus, lower extremity swelling, dyspnea, incontinence and type 2 diabetes on prednisone, meloxicam, venlafaxine, lisinopril, tramadol, ibuprofen, and hydroxyzine. On Day 33 after the start of the 150/1 combination treatment, the patient was hospitalized due to Grade 3 colitis and was reported as resolved on Day 35. On Day 37, the subject died at a hospice facility due to sepsis (Grade 5). Death was considered due to sepsis in the setting of disease progression.

Patient (b) (6) was a 55-year-old Caucasian female with malignant melanoma metastatic the skin and lymph nodes with a relevant history of breast cancer, lower extremity edema, hypercholesterolemia, scoliosis, basal cell carcinoma, and hypertension on isoprolol / hydrochlorothiazide, telmisartan, celecoxib, bupropion, clonazepam, escitalopram and hydroxyzine. On Day 260 after start of treatment with the 150/2 combination, the patient was hospitalized due to the Grade 3 chest pain (muscular) and Grade 3 respiratory failure and both study drugs were discontinued. On Day 261, the

patient developed nausea, vomiting, and pain and laboratory results included thrombocytopenia (15 Gi/L) and anemia. On Day 262, the patient died due to brain stem hemorrhage and intracerebral hemorrhage. There was no autopsy performed. The Applicant clarified that the patient had no prior history of brain metastases at study entry and the head CT scan report performed at the time of the assessment of hemorrhage makes no mention of brain metastases. They also state that per the investigator, a tiny brain metastasis is suggested given the patient's clinical status (disease under study) and cerebral hemorrhage (Response to FDA Information Request, October 18, 2013).

Patient (b) (6) was a 67 year-old Caucasian male with malignant melanoma metastatic to the anus, bone, liver, lungs, and lymph nodes with a relevant history of pulmonary embolism, deep venous thrombosis of lower extremity, dyspnea on exertion, chest pain (positional, right sided, non-cardiac), right bundle branch block, nephrolithiasis, renal cysts, and hypertension on dabigatran, metoprolol, acyclovir, gabapentin, and IV denosumab, and hydrocodone/paracetamol. The patient received treatment with the 150/2 combination. On Days 122, 123, and 124 the patient received palliative radiation treatment to vertebrae T10 to reduce pain secondary to vertebral metastases. On Day 124, the subject was hospitalized for Grade 3 acute renal failure Grade 3 hypoxemia, Grade 3 paroxysmal tachycardia, and Grade 3 elevated cardiac troponin Relevant laboratory results included thrombocytopenia and anemia. The acute renal failure was reported as resolved on Day 125. On Day 127, the patient died due to the pulmonary embolism. The investigator initially considered PE related to study drug but later clarified that it was related to underlying disease.

Patient (b) (6) was a 74 year-old Caucasian male with nodular melanoma metastatic to the thigh with a relevant history of decreased platelet count, hypothyroidism, bilateral ankle edema, hyperglycemia, and emphysema on tamsulosin, levothyroxine and naproxen. On Day 336 after the start of the 150/2 combination treatment, the patient was hospitalized for Grade 3 pulmonary emboli. Both study drugs were interrupted. Patient had an acute left deep vein thrombosis in the left popliteal vein and treated with subcutaneous enoxaparin and IV heparin. The pulmonary embolism was reported as resolved on Day 340, the patient discharged and both study drugs were re-initiated on Day 341. Exposure information was not available for trametinib from Day 341 to 376 or for dabrafenib from Day 373 to 376 because the patient did not return his diary to the investigator. On Day 375, the patient was again hospitalized due to altered mental status and vision changes and found to have left parieto-occipital hemorrhage with intraventricular extensions. Relevant laboratory results included thrombocytopenia. On Day 376, the patient died due to intracranial hemorrhage. The Applicant clarified that the patient had no prior history of brain metastases at study entry nor did the patient develop brain metastases while on study (Response to FDA Information Request, October 18, 2013).

Of the 43 subjects who crossed over to the 150/2 combination group, 15 (35%) patients had died as of the data cutoff date. Disease under study was the cause of death in all cases.

Of the 365 patients in the ISS database, there were 130 (35.6%) deaths listed, the most frequent cause of death was disease under study [119/130 (91.5%)]. Thirty seven of the 130 deaths (28.5%) occurred within 28 days of the last dose of the drug(s). Eight patients in the ISS database experienced a Grade 5 AE (Table 27).

Table 27: All Grade 5 Adverse Events (ISS Database)

Subject ID	Age/Sex	Grade 5 AE	Last Dose (day)	Onset AE (day)	Death (day)	Investigator Reported Primary Cause of Death
BRF113220-Part B-(b) (6)	39/F	Hyponatremia	68	61	70	Disease under study
BRF113220-Part B-(b) (6)	69/M	Ventricular arrhythmia	326	328	345	SAE possibly related to study medication
BRF113220-Part C-(b) (6)	55/F	Brain stem/ cerebral hemorrhage	250	261	262	Intracerebral hemorrhage, deemed unlikely related to study drugs
BRF113220-Part C-(b) (6)	74/M	Hemorrhage intracranial	371	375	376	Other: thromboembolic event
BRF113220-Part C-(b) (6)	71/F	Sepsis	33	33	37	Disease under study
BRF113220-Part C-(b) (6)	67/M	Pulmonary embolism	106	124	127	SAE possibly related to study medication
BRF113220-Part D-(b) (6)	81/M	Completed suicide	77	78	78	Other: Suicide
BRF113220-Part D-(b) (6)	90/F	Pulmonary embolism	290	315	315	Other: SAE, not related to study medication

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

Reviewer Comment:

1. *A 100% audit of the raw dataset (XD.xpt) and corresponding eCRFs of deaths for Part C was conducted and did not reveal major discrepancies.*
2. *Sudden death due to ventricular arrhythmia was the only Grade 5 AE considered by the investigator related to the combination of dabrafenib and trametinib.*

Pulmonary embolism (PE) occurred in three cases. In one case, the PE was initially considered related to the study drug, but the investigator later clarified that the fatal PE was related to the underlying disease. PE due to hypercoagulability secondary to metastatic melanoma cannot be ruled out in these cases. Intracranial hemorrhage occurred in two cases. Intracranial hemorrhage, myocardial infarction, and acute coronary syndrome fatalities has been previously reported with dabrafenib, and myocardial infarction with trametinib. Hyponatremia leading to death was considered due to the disease under study by the investigator, but one case of hyponatremia was reported as a non-fatal SAE. Review of the data provided for the Grade 5 AEs as individual cases suggest that most deaths were possibly related to underlying metastatic melanoma, including sequelae thereof or underlying comorbidities which possibly contributed to the deaths. Refer to Section 7.3.5 for further details on unexpected adverse events.

7.3.2 Nonfatal Serious Adverse Events

In Part C, non-fatal SAEs occurred in 25% (13/53) of patients in the dabrafenib monotherapy group, 37% (20/54) of the 150/1 combination group and 62% (34/55) of the 150/2 combination group. The most frequently reported non-fatal SAEs in the 150/2 and 150/1 combination groups were pyrexia (25%, 19%) and chills (18%, 15%) which were higher compared to the dabrafenib monotherapy group (2%, 2%). Renal failure was higher in the 150/2 combination arm compared to the dabrafenib monotherapy arm (6% vs. 0). All cases were considered as related to the study drug by the investigator. Decreased ejection fraction and dehydration were higher in the 150/2 combination group compared to the dabrafenib monotherapy group (4% vs. 0). Table 28 summarizes the non-fatal SAEs which occurred in the three groups in at least two patients.

Table 28: Non-fatal SAE (≥ 2 Subjects in any Group) by Treatment Group (All Treated Population)

AE	**D N=53** n (%)	**D + T 1 mg N=54** n (%)	**D + T 2 mg N=55** n (%)
Any SAE	13 (25)	20 (37)	34 (62)
Pyrexia	1 (2)	10 (19)	14 (25)
Chills	1 (2)	8 (15)	10 (18)
Renal failure acute[1]	0	1 (2)	3 (6)
Pneumonia	1 (2)	1 (2)	2 (4)
Ejection fraction decreased	0	1 (2)	2 (4)
Dehydration	0	1 (2)	2 (4)
Squamous cell carcinoma	3 (6)	1 (2)	2 (4)
Anemia	1 (2)	2 (4)	0
Nausea	0	2 (4)	0
Vomiting	0	2 (4)	0
Keratoacanthoma	2 (4)	0	0
Squamous cell carcinoma of skin	4 (8)	0	0

Source: ADAE.xpt
Abbreviations: AE, Adverse Event; D, dabrafen b; SAE, Serious Adverse Event; T, trametinib
[1] composite endpoint including renal failure and renal failure acute

Narratives on the patients who experienced renal failure and decreased ejection fraction in the 150/2 combination group are given below.

Patient (b) (6) was a 58 year old Caucasian male with epithelioid cell melanoma with metastases to the liver, lungs, and rib soft tissue with a relevant history of hypertension, hypercholesterolemia, and back pain on paracetamol, atorvastatin, esomeprazole, perindopril, pregabalin, prochlorperazine, and dexamethasone. On Day 100 after the start of the 150/2 combination treatment, he was hospitalized due to Grade 3 neutropenia, Grade 3 fever, Grade 2 chills, and Grade 2 thrombocytopenia and dabrafenib was interrupted. No infection was identified. Dabrafenib was re-initiated on day 108 and increased to 200 mg. On Day 110, the patient was again hospitalized due to Grade 3 acute renal failure. Both dabrafenib and trametinib were interrupted. The acute renal failure resolved on Day 126. Dabrafenib was re-initiated at 75 mg and trametinib at 1 mg.

Patient (b) (6) was a 54 year old Caucasian male with atypical intra-epidermal melanocytic proliferation with metastases to the lungs with a relevant history of hypertension, COPD, sleep apnea and obesity on nicotine patch, aspirin and tramadol. On Day 56 after the start of the 150/2 combination treatment, he developed blurry vision and optic nerve edema and trametinib was interrupted. On Day 85, he was hospitalized due to Grade 3 renal insufficiency. He also had fever (102.8^{o}F) and chills. On Day 85, dabrafenib was interrupted. The renal insufficiency was resolved on Day 88. The patient was discontinued from the study.

Patient (b) (6) was a 63 year old Caucasian male with metastatic melanoma to the chest wall, liver, lung, lymph nodes and thigh with a relevant history of hypercholesterolemia and hypothyroidism on levothyroxine and simvastatin. On Day 132 after the start of the 150/2 combination treatment, the patient developed chills and both study drugs were discontinued. No documentation of fever was noted. On Day 136, he was hospitalized due to Grade 3 acute renal failure and was afebrile. Trametinib was re-initiated on day 164, dabrafenib was not re-initiated. The acute renal failure resolved on Day 183.

Patient (b) (6) was a 74 year old Caucasian male with nodular melanoma metastatic to the liver and lung with a relevant history of arthritis, ischemic heart disease, hypercholesterolemia, GERD and Paget's disease and a history of coronary angioplasty and revascularization with multiple stent placements. Concomitant medication included clopidogrel, acetylsalicylic acid, ranitidine, diclofenac, oxazepam, rosuvastatin, and simvastatin/ezetimibe. On Day 86 after the start of the 150/2 combination treatment, the patient developed Grade 2 decreased ejection fraction and an ECHO showed an LVEF of 48%. Both study drugs were interrupted on Day 106. After LVEF increased to 64%, both drugs were re-initiated on Day 122.

Patient (b) (6) was a 27 year old Caucasian male with melanoma metastatic to the adrenal gland, retrosplenic tissue, lung and lymph nodes on allopurinol and betamethasone/calcipotriol. On Day 171 after the start of the 150/2 combination treatment, the patient developed Grade 2 decreased ejection fraction. Both study drugs were interrupted on Day 177. They were re-initiated at a reduced dose after it resolved on Day 205.

In the ISS database, the most frequently reported, non-fatal SAEs were pyrexia (60%), fatigue (49%), chills (45%), nausea (44%), vomiting (38%), arthralgia (34%), headache (32%), diarrhea (32%), rash (30%), cough (24%), peripheral edema (22%) and decreased appetite (22%). Other non-fatal SAEs reported (>10%) were myalgia, night sweats, anemia, dizziness, pain in extremity, abdominal pain, dermatitis, alopecia, dry skin, UTI, increased ALT, AST, GGT, and back pain.

Reviewer Comment:
Non-fatal SAEs were higher in the combination groups compared to the dabrafenib monotherapy group. Most non-fatal SAEs in the combination groups were consistent with safety profile of each drug. However, of concern were renal insufficiency, and decreased ejection fraction which occurred more frequently in the 150/2 combination group compared to none in the dabrafenib monotherapy group with a reasonable possibility of the study drugs as the cause. Of note, SCC skin and keratoacanthoma occurred more frequently in the dabrafenib monotherapy group.

7.3.3 Dropouts and/or Discontinuations

In Part C, 2% (1/53) of patients in the dabrafenib monotherapy group, 6% (3/54) of the 150/1 combination group and 9% (5/55) of the 150/2 combination group had treatment permanently discontinued due to AEs at the time of data cutoff, as summarized in Table 29.

Table 29: Treatment Discontinuation due to Adverse Events (All Treated Population)

AE*	**D** **N=53**	**D + T 1 mg** **N=54**	**D + T 2 mg** **N=55**
	n (%)	n (%)	n (%)
Any AE leading to discontinuation	1 (2)	3 (6)	5 (9)
Pyrexia	0	1 (2)	2 (4)
Chills	0	1 (2)	0
Fatigue	0	0	1 (2)
Cerebral hemorrhage	0	0	1 (2)
Renal failure	0	0	1 (2)
Nausea	0	0	1 (2)
Colitis	0	1 (2)	0
Dyspnea	0	0	1 (2)

AE*	D N=53	D + T 1 mg N=54	D + T 2 mg N=55
	n (%)	n (%)	n (%)
Pain in extremity	0	1 (2)	0
Blood creatinine increased	1 (2)	0	0

Source: ADAE.xpt
Abbreviations: AE, Adverse Event; D, dabrafen b; SAE, Serious Adverse Event; T, trametinib

Table 30 lists the AEs leading to treatment discontinuation in Trial BRF113220. One patient had a fatal cerebral hemorrhage [details in Section 7.3.1(Deaths)]. Pyrexia, Grades 1 and 2, led to treatment discontinuation in three patients. The following AEs led to treatment discontinuation in one patient each: Grade 1 nausea, Grade 3 fatigue, Grade 1 dyspnea, Grade 1 chills, Grade 2 increased blood creatinine, Grade 3 colitis and Grade 3 pain in extremity. All the AEs were assessed as related to the treatment with the exception of dyspnea and colitis. All occurred in the combination treatment 150/2 group with the exception of increased blood creatinine which occurred in the dabrafenib monotherapy group.

Table 30: Treatment Discontinuations due to Adverse Events (All Treated Population)

Subject ID	Age / Sex	Treatment Group	AE	Onset (days)	Duration (days)	Related	Outcome
BRF113220-Part C-(b) (6)	77/F	150/2	Nausea	2	227	N	R
			Fatigue	43	N/A	N	O
			Dyspnea	155	N/A	Y	O
BRF113220-Part C-(b) (6)	48/F	150/2	Pyrexia	24	41	N	R
BRF113220-Part C-(b) (6)	28/F	150/1	Chills	14	N/A	N	O
BRF113220-Part C-(b) (6)	75/F	150/2	Cerebral hemorrhage	261	2	N	Fatal
BRF113220-Part C-(b) (6)	47/M	150	Blood creatinine increased	309	N/A	N	O
BRF113220-Part C-(b) (6)	54/M	150/2	Renal failure	85	4	N	R
BRF113220-Part C-(b) (6)	71/F	150/1	Colitis	33	3	Y	R
BRF113220-Part C-(b) (6)	65/M	150/1	Pain in extremity	37	21	N	R
			Pyrexia	37	8	N	R
BRF113220-Part C-(b) (6)	64/M	150/2	Pyrexia	87	13	N	R

Source: ADAE.xpt
Abbreviations: F, female; M, male; N/A, not applicable; N, No; O, ongoing; R, resolved/recovered; Y, Yes

Table 31 lists the AEs leading to treatment discontinuation in the ISS database. Deaths are detailed in Section 7.3.1. Most of the AEs were assessed as related to the

treatment, with the exception of dyspnea, pulmonary embolism and mental disorder. All AEs occurred in the two combination groups and none in the dabrafenib monotherapy group. AEs reported in more than one patient were pyrexia (n=3), decreased ejection fraction (n=2), pulmonary embolism (n=2), nausea (n=2) and fatigue (n=2).

Table 31: Treatment Discontinuations due to Adverse Events (ISS Database)

Subject ID	Age /Sex	Treatment Group	AE	Onset (days)	Duration (days)	Toxicity Grade	Related	Outcome
BRF113220-Part B-(b) (6)	64/M	150/2	Optic neuritis	15	69	3	Y	R
BRF113220-Part B-(b) (6)	31/F	150/2	Ejection fraction decreased	29	225	1	Y	R
BRF113220-Part C-(b) (6)	77/F	150/2	Nausea	2	227	1	Y	R
			Fatigue	43	N/A	3	Y	NR
			Dyspnea	155	N/A	1	N	NR
BRF113220-Part C-(b) (6)	48/F	150/2	Pyrexia	24	41	2	Y	R
BRF113220-Part C-(b) (6)	78/M	150/2	Ejection fraction decreased	168	N/A	3	Y	NR
BRF113220-Part C-(b) (6)	28/F	150/1	Chills	14	N/A	1	Y	NR
BRF113220-Part C-(b) (6)	54/M	150/2	Renal failure	85	4	3	Y	R
BRF113220-Part C-(b) (6)	71/F	150/1	Colitis	33	3	3	N	R
BRF113220-Part C-(b) (6)	65/M	150/1	Pain in extremity	37	21	3	Y	R
			Pyrexia	37	8	1	Y	R
BRF113220-Part C-(b) (6)	64/M	150/2	Pyrexia	87	13	2	Y	R
BRF113220-Part D-(b) (6)	71/M	75/2	Pulmonary embolism	233	N/A	3	N	NR
BRF113220-Part D-(b) (6)	59/F	150/2	Uveitis	35	88	4	Y	R
BRF113220-Part D-(b) (6)	74/F	75/2	Pulmonary embolism	134	10	3	N	RS
BRF113220-Part D-	91/M	75/2	Fatigue	218	N/A	2	Y	NR

Subject ID	Age /Sex	Treatment Group	AE	Onset (days)	Duration (days)	Toxicity Grade	Related	Outcome
(b) (6)								
BRF113220-Part D-(b) (6)	52/F	150/2	Liver function test abnormal	45	N/A	3	Y	RG
			Headache	46	4	2	Y	R
BRF113220-Part D-(b) (6)	55/F	150/2	Glioblastoma	214	N/A	3	Y	NR
BRF113220-Part D-(b) (6)	49/F	150 -> 150/2	Optic ischemic neuropathy	50	N/A	3	Y	NR
BRF113220-Part D-(b) (6)	25/M	75/2	Mental disorder	28	N/A	3	N	NR
BRF113220-Part D-(b) (6)	65/M	150/2	Influenza like illness	4	N/A	2	Y	NR
			Nausea	4	82	2	Y	R
			Vomiting	4	56	1	Y	R
BRF113220-Part D-(b) (6)	57/M	150 -> 150/2	Colorectal cancer	95	N/A	3	Y	NR

Source: ADAE.xpt
Abbreviations in Table: F, female; M, male; N/A, not applicable; N, No; NR, Not recovered/not resolved; R, Recovered/resolved; RG, Recovering/resolving; RS, Recovered/resolved with sequelae; Y, Yes.

Reviewer Comment:

1. *In Part C, most of the patients who discontinued treatment were in the 150/2 combination group compared to the 150/1 combination group and the dabrafenib monotherapy group. AEs leading to discontinuation are consistent with the safety profiles of dabrafenib and trametinib when used as monotherapy for treatment of unresectable and metastatic melanoma.*
2. *The Applicant stated that two additional patients (Subjects (b) (6), pulmonary embolism; and (b) (6), hemorrhage intracranial) experienced AEs leading to permanent discontinuation of study drugs but the information for inclusion of these events was updated by the sites after the database was locked, and therefore,* Table 31 *does not include these two patients. Review of these two cases, both which lead to death, are detailed in Section 7.3.1.*

7.3.4 Significant Adverse Events

Treatment Modifications

Table 32 summarizes the incidence of treatment modifications (discontinuations, dose reductions and dose interruptions) due to AEs in the Part C. The overall incidence of treatment modifications was higher in the 150/2 combination group and increased with increasing dose of trametinib in the combination.

Table 32: Incidence of Treatment Modifications for Adverse Events (All Treated Population)

	D **N=53** **n (%)**	**D + T 1 mg** **N=54** **n (%)**	**D + T 2 mg** **N=55** **n (%)**
Investigational product(s) withdrawn	1 (2)	3 (6)	5 (21)
Dose reduction	11 (21)	25 (46)	27 (49)
Dose interruption	18 (34)	32 (59)	37 (67)

Source: ADAE.xpt
Abbreviations: D, dabrafenib; T, trametinib

Dose Reductions

Table 33 summarizes the AEs leading to dose reduction in Part C. The most frequent AE leading to dose reduction of the 150/2 combination group was pyrexia (35% vs. 28 % in the 150/1 combination group and 4% in the dabrafenib monotherapy group). Other AEs (>2%) in the 150/2 combination group were chills, nausea, vomiting, diarrhea, decreased ejection fraction, and myalgia.

Table 33: Dose Reductions due to AEs in at least 2 Patients (All Treated Population)

AE	**D** **N=53** n (%)	**D + T 1 mg** **N=54** n (%)	**D + T 2 mg** **N=55** n (%)
Any AE	11 (21)	25 (46)	27 (49)
Pyrexia	2 (4)	15 (28)	19 (35)
Chills	1 (2)	6 (11)	5 (9)
Fatigue	0	2 (4)	1 (2)
Influenza like illness	1 (2)	4 (7)	1 (2)
Nausea	0	0	5 (9)
Vomiting	0	0	4 (7)
Diarrhea	1 (2)	0	2 (4)
Ejection fraction decreased	0	0	4 (7)
ALT increased	0	2 (4)	0
Myalgia	0	1 (2)	2 (4)
Arthralgia	0	2 (4)	1 (2)
Photopsia	0	2 (4)	0
Vitreous floaters	0	2 (4)	0

Source: ADAE.xpt
Abbreviations: D, dabrafenib; T, trametinib

In the ISS database, the most frequent AEs (>2%) that led to dose reduction were pyrexia (26%), chills (10%), vomiting (4%), nausea (4%), and influenza like illness (3%). Most AEs were in the combination treatment 150/2 group.

Dose Interruptions

Table 34 summarizes the AEs leading to dose interruptions in Part C. The most frequent AE leading to dose interruption of the 150/2 combination group was pyrexia (42% vs. 37 % in the 150/1 combination group and 6% in the dabrafenib monotherapy group). Other AEs (>2%) in the combination treatment 150/2 group were chills, fatigue, decreased ejection fraction, increased GGT, increased liver enzymes, neutropenia, nausea, vomiting, myalgia, arthralgia, and influenza.

Table 34: Dose Interruptions due to AEs in at least 2 Patients (All Treated Population)

AE	**D** **N=53** n (%)	**D + T 1 mg** **N=54** n (%)	**D + T 2 mg** **N=55** n (%)
Any AE	18 (34)	32 (59)	37 (67)
Pyrexia	3 (6)	20 (37)	23 (42)
Chills	3 (6)	10 (19)	12 (22)
Fatigue	2 (4)	3 (6)	4 (7)
Influenza like illness	1 (2)	4 (7)	1 (2)
Edema peripheral	0	2 (4)	0
Ejection fraction decreased	0	2 (4)	5 (9)
Gamma-glutamyltransferase increased	0	3 (6)	2 (4)
ALT increased	0	5 (9)	1 (2)
Blood alkaline phosphatase increased	0	2 (4)	1 (2)
AST increased	0	3 (6)	0
Blood creatinine increased	1 (2)	2 (4)	0
Blood phosphorus decreased	0	2 (4)	0
Neutropenia	1 (2)	1 (2)	4 (7)
Anemia	1 (2)	3 (6)	1 (2)
Diarrhea	0	0	4 (7)
Nausea	1 (2)	1 (2)	4 (7)
Vomiting	1 (2)	3 (6)	4 (7)
Arthralgia	0	3 (6)	4 (7)
Myalgia	0	1 (2)	3 (5)
Muscular weakness	0	2 (4)	0
Dehydration	0	1 (2)	2 (4)
Hyponatremia	0	1 (2)	2 (4)
Headache	0	1 (2)	2 (4)
Renal failure acute	0	1 (2)	2 (4)
Atrial fibrillation	2 (4)	0	1 (2)
Photopsia	0	2 (4)	0

AE	D N=53	D + T 1 mg N=54	D + T 2 mg N=55
Vitreous floaters	0	2 (4)	0
Hyperhidrosis	0	3 (6)	1 (2)
Palmar-plantar erythrodysesthesia syndrome	1 (2)	2 (4)	0
Fall	0	2 (4)	0
Mental status changes	0	2 (4)	0

Source: ADAE.xpt
Abbreviations: D, dabrafenib; T, trametinib

In the ISS database, the most frequent AEs (>2%) which led to dose interruptions in the ISS 150/2 combination group were pyrexia (35%), chills (20%), vomiting (8%), nausea (6%), fatigue (5%), ejection fraction decreased (4%), influenza like illness (4%), alanine aminotransferase increased (4%), diarrhea (4%), arthralgia (4%), dehydration (4%), hypotension (4%), aspartate aminotransferase increased (3%), hyperhidrosis (3%), neutropenia (3%), gamma-glutamyltransferase increased (3%), and generalized rash (3%).

The incidence of both dose reductions and dose interruptions are higher in the 150/2 combination group as compared to dabrafenib monotherapy. The most common AEs leading to dose reductions and interruptions (>35%) were pyrexia and chills.

Reviewer Comment:
The incidence of both dose reductions and dose interruptions are higher in the 150/2 combination group compared to both the 150/1 combination group and the dabrafenib monotherapy group and are also higher than the incidence seen in the trials evaluating single-agent trametinib.

Grade 3 and 4 Adverse Events

Grades 3 and 4 AEs were higher in the 150/2 combination group compared to both the 150/1 combination group and the dabrafenib monotherapy group. The most frequent (> 2%) Grade 3 or 4 AEs in the combination 150/2 combination group compared to the dabrafenib monotherapy group were pyrexia (5% vs. 0%), neutropenia (5% vs. 2%), back pain (5% vs. 2%), fatigue (4% vs. 6%) and anemia (4% vs. 0%). Most AEs in the 150/2 combination group were Grade 3, the most common reported were pyrexia, neutropenia and back pain; neutropenia was the most common Grade 4 event. Of note, Grade 3 and 4 squamous cell carcinoma and squamous cell carcinoma of skin occurred in 6% of the 150/2 combination group compared to 17% of the dabrafenib monotherapy group. Table 35 summarizes the incidence of Grade 3 and 4 AEs in ≥2 patients in Part C.

Table 35: Incidence of Grade 3 & 4 Adverse Events in at least 2 Patients (All Treated Population)

AE	D Grade 3 N=53 n (%)	D Grade 4 N=53 n (%)	D + T 1 mg Grade 3 N=54 n (%)	D + T 1 mg Grade 4 N=54 n (%)	D + T 2 mg Grade 3 N=55 n (%)	D + T 2 mg Grade 4 N=55 n (%)
Neutropenia	1 (2)	0	1 (2)	0	4 (7)	3 (5)
Hyponatremia	0	0	4 (7)	0	4 (7)	0
Back pain	1 (2)	0	0	0	3 (5)	0
Lymphopenia	0	0	0	0	3 (5)	0
Pyrexia	0	0	5 (9)	0	3 (5)	0
Renal failure acute	0	0	0	0	3 (5)	0
ALT increased	0	0	2 (4)	0	2 (4)	0
Anemia	0	0	3 (6)	0	2 (4)	0
Fatigue	3 (6)	0	1 (2)	0	2 (4)	0
GGT increased	0	0	6 (11)	0	2 (4)	0
Pneumonia	1 (2)	0	1 (2)	0	2 (4)	0
Pulmonary embolism	0	0	1 (2)	0	2 (4)	0
SCC	4 (8)	0	1 (2)	0	2 (4)	0
Syncope	0	0	1 (2)	0	2 (4)	0
cuSCC	5 (9)	0	0	0	1 (2)	0
Vomiting	0	0	2 (4)	0	1 (2)	0
Hypokalemia	2 (4)	0	1 (2)	0	0	1 (2)
Atrial fibrillation	2 (4)	0	0	0	0	0
Alkaline phosphatase increased (blood)	0	0	3 (6)	0	0	0
Hypophosphatemia	0	0	2 (4)	0	0	0
Hyperbilirubinemia	0	0	2 (4)	0	0	0
Hypophosphatemia	0	0	2 (4)	0	0	0
Keratoacanthoma	2 (4)	0	0	0	0	0
Lymphopenia	0	0	3 (6)	0	0	0

Source: ADAE.xpt
Abbreviations in Table: cuSCC, squamous cell carcinoma of skin; D, dabrafenib; SCC, squamous cell carcinoma; T, trametinib.

7.3.5 Submission Specific Primary Safety Concerns

The review further analyzed the following primary safety concerns:

- New Malignancies including cutaneous and non-cutaneous
- Decreased ejection fraction and cardiac failure
- Hemorrhage events
- Thromboembolic events
- Renal failure
- Pyrexia
- Skin-related toxicities
- Hepatic events
- Ocular events
- Diarrhea

- Electrolyte abnormalities
- Hypertension
- Sepsis and infections
- Hematopoietic cytopenias
- Depression
- Rhabdomyolysis

New Primary Malignancies

Cutaneous squamous cell carcinoma (CuSCC) and keratoacanthoma occurred in 7% of patients treated with dabrafenib (Tafinlar USPI). The incidence of new primary malignant melanomas was 2% for patients receiving dabrafenib (Tafinlar USPI).

Patients were closely monitored in Study BRF113220 for occurrence of SCC or keratoacanthoma , and the Applicant required investigators to report all instances as SAEs.

The incidence of cuSCC, including SCC of skin, squamous cell carcinoma, and keratoacanthoma was higher in the dabrafenib monotherapy group reported compared to the two combination groups (Table 36). The majority of cuSCC events were Grade 3 in severity and reported as SAEs, as required per protocol. With the exception of SCC experienced by two patients (Patient (b) (6), dabrafenib monotherapy group; and Patient (b) (6), 150/1 combination group), all cuSCCs were considered drug-related by the investigator. The onset of cuSCC events was earlier in the dabrafenib monotherapy group with the majority of patients experiencing cuSCC events within the first 56 days, whereas all cuSCC events in the combination groups occurred after 112 days of treatment. None of the cuSCC events required a change in dose, and all events resolved following surgical excision.

One case (Patient (b) (6)) of new primary malignant melanoma was reported in the dabrafenib monotherapy group. This case was a Grade 1 superficial spreading melanoma of unspecified stage which was diagnosed 66 days after the first dose of study drug. No dose change was necessitated for this event and the AE was resolved with surgical excision. The subject discontinued treatment on Day 330 due to disease progression.

One patient (Patient (b) (6)) had Grade 3 renal cell carcinoma. The patient had metastatic lesions in the left kidney on screening. One year after starting the 150/2 combination treatment, a biopsy of the kidney lesion, which was performed because the other metastatic lesions shrunk but the kidney lesion continued to grow, revealed it to be a primary renal cell carcinoma (clear cell type; Fuhrman Grade 2). The reviewer agrees with the Applicant’s analysis that the lesion was not likely to be related as it was present

but undiagnosed at baseline. Mutation analysis was not performed (Response to FDA Information Request October 15, 2013).

Table 36: Summary of New Malignancies (All Treated Population)

AE	D N=53 n (%)	D + T 1 mg N=54 n (%)	D + T 2 mg N=55 n (%)
Any malignancy	10 (20)	3 (6)	8 (16)
Basal cell carcinoma	1 (2)	3 (6)	5 (9)
Squamous cell carcinoma*	4 (8)	1 (2)	2 (4)
Keratoacanthoma	6 (11)	0	1 (2)
Squamous cell carcinoma of skin	6 (11)	0	1 (2)
Renal cell carcinoma	0	0	1 (2)
Superficial spreading melanoma stage unspecified	1 (2)	0	0

Source: ADAE.xpt
Abbreviations: D, dabrafenib; T, trametinib
*Sites included arm, leg, thigh, helix, and pre-auricular area.

The original primary endpoint of Part C was the incidence rate of cutaneous squamous cell carcinoma (cuSCC). The results of the cuSCC (which composite includes squamous cell carcinoma of skin, squamous cell carcinoma, and keratoacanthoma) analyses, based on the ITT population (i.e. planned treatment) and the safety population (i.e. actual treatment) are summarized in Table 37. The difference between the 150/2 combination group and the dabrafenib monotherapy group were not statistically significant.

Table 37: Cutaneous Squamous Cell Carcinoma Analyses

	D	D + T 1 mg	D + T 2 mg
Actual Treatment	**N=53**	**N=54**	**N=55**
SCC Rate (%)	10 (19%)	1 (2%)	4 (7%)
95% CI	(9.4%, 32.0%)	(0.1%, 9.9%)	(2.0%, 17.6%)
Difference (95% CI)		-17% (-34.9%, 2.1%)	-12% (-30.3%, 6.9%)
p-value, left-sided		0.004	0.065
p-value, two-sided		0.004	0.09
Planned Treatment	**N=54**	**N=54**	**N=54**
SCC Rate (%)	10 (19%)	1 (2%)	4 (7%)
95% CI	(9.3%, 31.4%)	(0.1%, 9.9%)	(2.1%, 17.9%)
Difference (95% CI)		-17% (-35.5%, 3.1%)	-11% (-30.2%, 8.6%)
p-value, left-sided		0.004	0.075
p-value, two-sided		0.008	0.15

Source: FDA Statistical Review
Abbreviations: CI, confidence interval; D, dabrafenib; SCC, squamous cell carcinoma; T, trametinib

The incidence of basal cell carcinomas was higher in the two combination groups (9% in the 150/2 combination group, 6% in the 150/1 combination group) compared to the dabrafenib monotherapy group (2%) (**Error! Reference source not found.**Table 38).

The majority of these 9 patients had Grade 1 or 2 AEs, were drug related and non-serious AEs. All the cases recovered/resolved.

Table 38: Patients with Basal Cell Carcinoma

Subject ID	Age	Sex	Treatment Arm	Toxicity Grade	Related	Serious	Outcome
BRF113220-Part C-(b) (6)	61	M	150/2	1	Y	N	R
BRF113220-Part C-(b) (6)	60	M	150/2	1	Y	N	R
BRF113220-Part C-(b) (6)	68	M	150/2	3	Y	N	R
BRF113220-Part C-(b) (6)	60	M	150/1	3	Y	N	R
BRF113220-Part C-(b) (6)	78	F	150/1	1	N	N	R
BRF113220-Part C-(b) (6)	78	M	150/1	1	N	N	R
BRF113220-Part C-(b) (6)	45	F	150	1	Y	Y	R
BRF113220-Part C-(b) (6)	74	M	150/2	2	Y	N	R
BRF113220-Part C-(b) (6)	79	M	150/2	1	N	N	R

Source: ADAE.xpt
Abbreviations: D, dabrafenib;F, female; R, recovered/resolved; M, male; N, no; T, trametinib; Y, yes

There were five non-cutaneous malignancies identified and provided in the 90-day safety update as shown in Table 39**.**

Table 39: Non-cutaneous Malignancies (ISS Database)

Subject ID	Age	Sex	AE*	Treatment	Start Day	Related	Action Taken	Outcome
BRF113220-Part C-(b) (6)	48	M	Renal cell carcinoma	150/2		N	dose not changed	NR
BRF113220-Part D-(b) (6)	61	M	Head and neck squamous cell carcinoma	150/2	422	Y	dose not changed	R
BRF113220-Part D-(b) (6)	55	F	Glioblastoma	150/2	164	Y	drug withdrawn	R
BRF113220-Part D-(b) (6)	62	M	Adenocarcinoma pancreas	150/2	223	Y	drug withdrawn	NR
BRF113220-Part D-(b) (6)	57	M	Colorectal cancer	150> 150/2	95	Y	drug withdrawn	NR

Source: 90-day safety update, ADAE.xpt
Abbreviations: BID, twice daily; F, female; M, male; N, no; NR, not recovered/not resolved; QD, once daily; Y, yes
*Pancreatic adenocarcinoma positive for KRAS mutation, colorectal carcinoma positive for NRAS mutation.

Reviewer Comment:

1. *Although the incidence of cuSCC was lower in the 150/2 combination group, it was not statistically significant. The incidence of basal cell carcinoma was higher in the 150/2 combination group compared to the dabrafenib monotherapy group.*
2. *The incidence of cuSCC was higher in the dabrafenib monotherapy group and higher than the incidence reported with single-agent dabrafenib. In Part C, dermatologic assessments were conducted in 4 weeks, then every 8 weeks, and more frequently for any new or change in lesions. Skin photographs were taken at baseline and for new or changing lesions. cuSCC or keratoacanthoma were identified as adverse events of special interest and were reported as SAEs. In the single-agent dabrafenib trial, dermatologic skin assessments were conducted at week 3, 6, 15, 24, 30, 42, 51 and at discontinuation. The investigator performed the dermatologic assessments and referral to a dermatologist was at the discretion of the investigator. There were no skin photographs taken. The difference in monitoring and reporting may account for the difference in cuSCC seen in the single-agent dabrafenib monotherapy trials (7%) vs. the dabrafenib monotherapy group in Part C (19%).*
3. [redacted] (b) (4)
4. *All the non-cutaneous malignancies occurred in patients treated with 150/2 combination.*

Cardiac Events

Cardiomyopathy (defined as cardiac failure, left ventricular dysfunction, or decreased left ventricular ejection fraction (LVEF) occurred in 7% of patients treated with trametinib (Mekinist USPI).

The Applicant reported the AE terms of decreased ejection fraction and cardiac failure. The reviewer has included other cardiac-related AE terms of interest. The incidence of decreases in ejection fraction was higher in the combination groups (4% in the 150/1 combination group, 9% in the 150/2 combination group) compared with none in the dabrafenib monotherapy group (Table 40).

Table 40: Summary of Cardiac Events (All Treated Population)

AE	D N=53 n (%)	D + T 1 mg N=54 n (%)	D + T 2 mg N=55 n (%)
Ejection fraction decreased	0	2 (4)	5 (9)
Tachycardia[1]	3 (6)	4 (8)	5 (9)
Atrial fibrillation	2 (4)	0	1 (2)
Bundle branch block[2]	1 (2)	0	1 (2)

Mitral valve incompetence	0	0	1 (2)
Cardiac failure	0	1 (2)	0

Source: ADAE.xpt
[1]Tachycardia is a composite term which includes palpitations and tachycardia paroxysmal
[2]Bundle branch block includes left and right bundle branch block

The Applicant reported that seven patients met LVEF stopping criteria (LVEF decrease >10% and below LLN) by ECHO while the FDA analysis identified 10 patients.

Of these 10 patients, six were in the 150/1 combination group and four were in the 150/2 combination group. (Table 41). One of the six LVEF decreases meeting stopping criteria in the 150/1 combination group, and four of the LVEF decreases in the 150/2 combination group were reported as AEs. Patient (b) (6) in the 150/1 group had decreased ejection fraction associated with Grade 3 cardiac failure, and patient (b) (6) in the 150/2 group had Grade 3 syncope. Two of the AEs (LVEF decrease AE experienced by Patient (b) (6) and syncope AE in Patient (b) (6)) were not considered drug-related by the investigator, the other four LVEF decreases reported as AEs were considered drug-related by the investigator. Study drugs were reduced in three patients, and doses were interrupted in five patients. The LVEF decreases recovered /resolved in all the patients.

Table 41: Patients Meeting LVEF Stopping Criteria (All Treated Population)

Subject ID	Age	Sex	Treatment Group	Assessment	LVEF ECHO			Associated cardiac AEs / Grade	AE Outcome
					Baseline %	Worst %	Study Day		
BRF113220-Part C-(b) (6)	74	M	150/2	CRD	62	48	86	Ejection fraction decreased /2	Dose reduced. R
BRF113220-Part C-(b) (6)	27	M	150/2	CRD	64	46	171	Ejection fraction decreased /2	Dose reduced. R
BRF113220-Part C-(b) (6)	49	F	150/2	CRD	65	45	253	Ejection fraction decreased /1 Syncope/3	Dose reduced. R Dose unchanged, R
BRF113220-Part C-(b) (6)	65	M	150;/1	CRD	66	53	167	Ejection fraction decreased/ 1	Dose interrupted , R

Subject ID	Age	Sex	Treatment Group	Assessment	LVEF ECHO			Associated cardiac AEs / Grade	AE Outcome
					Baseline %	Worst %	Study Day		
BRF113220-Part C-(b) (6)	78	F	150/1	CRD	50	21	41	Cardiac failure /3 Ejection fraction decreased /3	Drug interrupted, R Drug interrupted, R
BRF113220-Part C-(b) (6)	48	M	150/2	IND	56	32	336	Ejection fraction decreased /2	Dose reduced, R
BRF113220-Part C-(b) (6)	49	M	150/1	IND	57	47	28	none	N/A
BRF113220-Part C-(b) (6)	63	F	150/1	IND	61	48	169	none	N/A
BRF113220-Part C-(b) (6)	34	M	150/1	CRD	64	52	222	none	N/A
BRF113220-Part C-(b) (6)	49	F	150/1	CRD	63	52	334	none	N/A

Source: ADXI.xpt
Abbreviations: CRD, investigator review; F, female; IND, independent review; LVEF, left ventricular ejection fraction; M, male: N/A, not applicable; R, recovered/resolved.

In the ISS database, the incidence of decreased ejection fraction in the pooled 150/2 combination groups was 7% and in the ISS trametinib single-agent group 11%. The incidence of tachyarrhythmia, which included atrial fibrillation, atrial tachycardia, tachycardia and paroxysmal tachycardia, was 5% in the pooled 150/2 combination groups. The incidence of atrial fibrillation was < 1% in the dabrafenib monotherapy group with no tachycardia events.

Reviewer Comment:
The incidence of decreased ejection fraction in the 150/2 combination group (9%) is higher than in the dabrafenib monotherapy group (0%) and is consistent with single-agent trametinib. Tachyarrhythmias were seen more frequently in the 150/2 combination group compared to single-agent therapy. Decreased ejection fraction was seen frequently in post-marketing reports of both single-agent dabrafenib and single-agent trametinib use. Recommend inclusion in the label.

Hemorrhage Events

Hemorrhage occurred in 13% of patients treated with trametinib monotherapy (Mekinist USPI). The term included the following terms: epistaxis, gingival bleeding, hematochezia, rectal hemorrhage, melena, vaginal hemorrhage, hemorrhoidal hemorrhage, hematuria, and conjunctival hemorrhage. Less than 1% was Grade 3 or 4.

The incidence of hemorrhagic events, including mucocutaneous and major hemorrhage, was 20% in the 150/2 combination group and 2% in the dabrafenib monotherapy group (Table 42). The reviewer identified major hemorrhagic events based on bleeding which occurred in critical areas (e.g., intracranial) or organs. The incidence of major hemorrhagic events was higher in both the combination groups compared to none in the dabrafenib monotherapy group. Bleeding events in the combination groups included brain stem hemorrhage, cerebellar hemorrhage, gastric hemorrhage, eye and vitreous hemorrhage. The incidence of major hemorrhagic events (brain stem hemorrhage, cerebral hemorrhage, gastric hemorrhage) in the 150/2 combination group is 6% compared to none in the dabrafenib monotherapy group. Other hemorrhagic events included epistaxis, gingival bleeding, hematuria and vaginal bleeding.

Table 42: Summary of Hemorrhage Events (All Treated Population)

AE	**D** **N=53** n (%)	**D + T 1 mg** **N=54** n (%)	**D + T 2 mg** **N=55** n (%)
Any Hemorrhage Event	1 (2)	6 (11)	11 (20)
Hemorrhage intracranial[1]	0	0	3 (6)
Epistaxis	0	1 (2)	6 (11)
Gastric Hemorrhage	0	0	1 (2)
Hematuria	1 (2)	1 (2)	1 (2)
Tumor hemorrhage	0	0	1 (2)
Eye hemorrhage	0	1 (2)	0
Vaginal hemorrhage	0	1 (2)	0
Vitreous hemorrhage	0	1 (2)	0
Gingival hemorrhage	0	1 (2)	0

Source: AE.xpt
[1] Intracranial hemorrhage is a composite term that includes intracranial hemorrhage, brain stem hemorrhage and cerebral hemorrhage
Abbreviations: D, dabrafenib; T, trametinib

Six patients had a major hemorrhage event. All the major hemorrhagic events occurred in patients who received the combination of dabrafenib and trametinib, three in the 150/1 combination and three in the 150/2 combination (Table 43). Three hemorrhage events were SAEs, two patients had fatal intracranial hemorrhage, and one patient had Grade 4 gastric hemorrhage. The remaining hemorrhage AEs were Grade 1. With the exception of the intracranial and vitreous hemorrhage, all other AEs recovered/resolved. All events were considered not related to study drugs by the investigator.

Reference ID: 3422378

Table 43: Patients with Major Hemorrhage (All Treated Population)

Subject ID	Age	Sex	Treatment Group	AE	Grade	Serious	Related	Outcome
BRF113220-Part C-(b) (6)	38	F	150/1	Eye hemorrhage (D 56-59)	1	N	N	R
BRF113220-Part C-(b) (6)	65	M	150/1	Vitreous hemorrhage (D 109- -)	1	N	N	NR
BRF113220-Part C-(b) (6)	55	F	150/2	Brain stem hemorrhage/ Cerebral hemorrhage (D261-262)	5	Y	N	FATAL
BRF113220-Part C-(b) (6)	61	F	150/1	Vaginal hemorrhage (D7-15)	1	N	N	R
BRF113220-Part C-(b) (6)	74	M	150/2	Hemorrhage intracranial (D 375-376)	5	Y	N	FATAL
BRF113220-Part C-(b) (6)	79	M	150/2	Gastric hemorrhage (D 150-154)	4	Y	N	R

Source: ADAE.xpt
Abbreviations: D, day; N, no; NR, not recovered/ not resolved; R, recovered/resolved; Y, yes

In the ISS safety database, 5% (18/365) patients had major hemorrhagic events, all occurred in patients receiving the 150/2 combination of dabrafenib and trametinib. In the pooled 150/2 safety database, 9% (18/202) had major hemorrhage events. Three (6%) patients (Patient (b) (6) and (b) (6)) had intracranial hemorrhage. There were no major hemorrhage events seen in the dabrafenib monotherapy group. Table 44 shows the details of the 18 patients in the ISS safety database.

Table 44: Patients with Major Hemorrhage (ISS Database)

Subject ID	Age	Sex	Treatment*	AE	Serious	Related	Toxicity Grade	Action taken	Start Day	End Day	Outcome
BRF113220-Part B-(b) (6)	55	F	B-150/2	Vaginal hemorrhage	N	N	2	DOSE NOT CHANGED	63	67	R
BRF113220-Part B-(b) (6)	35	M	B-150/1	Rectal hemorrhage	N	N	1	DOSE NOT CHANGED	350	363	R
BRF113220-Part B-(b) (6)	45	M	B-150/1	Conjunctival hemorrha	N	N	1	dose not changed	337	345	R

Subject ID	Age	Sex	Treatment*	AE	Serious	Related	Toxicity Grade	Action taken	Start Day	End Day	Outcome
				ge							
BRF113220-Part B-(b) (6)	58	F	B-150/2	Cerebral hemorrhage	N	N	1	dose not changed	111	146	R
BRF113220-Part B-(b) (6)	41	F	B-75/1	Skin hemorrhage	N	N	1	dose not changed	356	356	R
BRF113220-Part B-(b) (6)	57	F	B-150/1.5	Hemorrhoidal hemorrhage	N	N	1	dose not changed	111	169	R
BRF113220-Part B-(b) (6)	32	F	B-150/2	Rectal hemorrhage	N	N	1	dose not changed	217	220	R
BRF113220-Part C-(b) (6)	38	F	C-150/1	Eye hemorrhage	N	N	1	dose not changed	56	59	R
BRF113220-Part C-(b) (6)	65	M	C-150/1	Vitreous hemorrhage	N	N	1	dose not changed	109		NR
BRF113220-Part C-(b) (6)	78	M	C-150	Tumor hemorrhage	Y	N	4	drug interrupted	144	155	R
BRF113220-Part C-(b) (6)	55	F	C-150/2	Brain stem hemorrhage / Cerebral hemorrhage	Y	N	5	dose not changed	261	262	FATAL
BRF113220-Part C-(b) (6)	61	F	C-150/1	Vaginal hemorrhage	N	N	1	dose not changed	7	15	R
BRF113220-Part C-(b) (6)	74	M	C-150/2	Hemorrhage intracranial	Y	N	5	not applicable	375	376	FATAL
BRF113220-Part C-(b) (6)	79	M	C-150/2	Gastric hemorrhage	Y	N	4	drug interrupted	150	154	R
BRF113220-Part D-(b) (6)	72	F	D-75 -> 75/2	Eye hemorrhage	N	N	1	dose not changed	327	368	R
BRF113220-Part D-(b) (6)	56	M	D-75/2	Wound hemorrhage	N	N	1	dose not changed	6	7	R
BRF113220-Part	50	M	D-75/2	Tumor hemorrha	Y	N	3	drug interrupt	165	170	R

Subject ID	Age	Sex	Treatment*	AE	Serious	Related	Toxicity Grade	Action taken	Start Day	End Day	Outcome
D-(b) (6)				ge				ed			
BRF113220-Part D-(b) (6)	49	M	D-150/2	Rectal hemorrhage	N	N	1	dose not changed	103	108	R

Source: ADAE.xpt
Abbreviations: F, female; M, male; N, no; R, recovered/resolved; Y, yes
*Doses of dabrafen b and trametinib in Parts B, C, and D of trial BRF113220

The Applicant provided updated analyses of hemorrhagic events as shown in Table 45. The incidence of hemorrhagic events were higher in the 150/2 combination group (29%) compared to the dabrafenib monotherapy group (6%). Most were major hemorrhagic events which occurred in critical areas or organs. Both Grade 5 events were intracranial hemorrhagic events.

Table 45: Summary of Hemorrhagic Events (All Treated Population, Updated Pooled ISS Database)

Dabrafenib	**Part C 150 mg BID**	**Part C 150 mg BID**	**Part C 150 mg BID**	**ISS Pooled 150 mg BID**
Trametinib	**--**	**1 mg QD**	**2 mg QD**	**2 mg QD**
	N=53	N=54	N=55	N=204*
Number of events	4	19	30	66
Number of subjects with event (%)	3 (6%)	12 (22%)	16 (29%)	46 (23%)
Maximum Toxicity Grade	N=3	N=12	N=16	N=46
Grade 1	2 (67%)	10 (83%)	10 (63%)	33 (72%)
	0	2 (17%)	2 (13%)	7 (15%)
Grade 2	1 (33%)	0	1 (6%)	2 (4%)
	0	0	1 (6%)	2 (4%)
Grade 3 Grade 4 Grade 5	0	0	2 (13%)	2 (4%)

Dabrafenib	**Part C 150 mg BID**	**Part C 150 mg BID**	**Part C 150 mg BID**	**ISS Pooled 150 mg BID**
Trametinib	**--**	**1 mg QD**	**2 mg QD**	**2 mg QD**
Action Taken	N=3	N=12	N=16	N=46
IP withdrawn	0	0	2 (13%)	2 (4%)
Dose Reduced	0	0	0	1 (2%)
Dose not changed	3 (100%)	12 (100%)	13 (81%)	40 (87%)
Dose Interrupted/Delayed	0	0	3 (19%)	5 (11%)
N/A	0	0	0	1 (2%)

Source: Response to FDA Information Request, October 18, .2013
*N=204 is based on the updated pooled ISS database in the 90-day safety review provided by the Applicant

Reviewer Comment:
The definition of major hemorrhagic events included symptomatic bleeding in a critical area or organ or bleeding resulting in an SAE. The incidence of hemorrhage including major hemorrhage and mucosal hemorrhage was higher in the 150/2 combination group compared to the dabrafenib monotherapy group. The major hemorrhagic events reported with the 150/2 combination group is a different profile from the primary mucosal hemorrhage reported with single-agent trametinib. Most of the major hemorrhagic events occurred in a critical area or organ, including intracranial, gastric and intraocular. The intracranial and gastric bleeding resulted in serious adverse drug experience. This reviewer recommends including risk of hemorrhage in the Warnings and Precautions section in the label.

Thromboembolic Events

Thromboembolic events were not reported in the USPI of dabrafenib or trametinib monotherapy (Tafinlar USPI; Mekinist USPI). The Applicant states that the incidence with trametinib monotherapy was 6% and with dabrafenib monotherapy was 4% (Response to FDA Information Request, October 18, 2013).

The incidence of thromboembolic events was higher in the 150/2 combination group (8%) compared to none in the dabrafenib monotherapy group (0%).

Table 46: Summary of Thromboembolic Events (All Treated Population)

AE	D N=53 n (%)	D + T 1 mg N=54 n (%)	D + T 2 mg N=55 n (%)
Any event	0	2 (4)	4 (8)
Pulmonary embolism	0	1 (2)	3 (6)
Deep vein thrombosis	0	0	2 (4)
Pelvic venous thrombosis	0	1 (2)	0

Source: ADAE.xpt
Abbreviations: D, dabrafenib; T, trametinib

Table 47 summarizes the seven thromboembolic events which occurred in six patients. One patient had pulmonary embolism which was fatal. All events were Grade 2 or Grade 3 in severity. With the exception of the patient who died, all others were considered to be not serious. None were considered related to the study drugs by the investigator.

Table 47: Patients with Thromboembolic Events (All Treated Population)

Subject ID	Age	Sex	Treatment Group	AE	Toxicity Grade	Serious	Related	Outcome
BRF113220-Part C-(b) (6)	37	F	150/2	Deep vein thrombosis	2	N	N	R
BRF113220-Part C-(b) (6)	72	M	150/2	Deep vein thrombosis	2	N	N	NR
				Pulmonary embolism	3	N	N	NR
BRF113220-Part C-(b) (6)	67	M	150/2	Pulmonary embolism	5	Y	N	FATAL
BRF113220-Part C-(b) (6)	63	F	150/1	Pelvic venous thrombosis	2	N	N	R
BRF113220-Part C-(b) (6)	34	M	150/1	Pulmonary embolism	3	N	N	RG
BRF113220-Part C-(b) (6)	74	M	150/2	Pulmonary embolism	3	Y	N	R

Source: ADAE.xpt
Abbreviations: D, dabrafenib; F, female; M, male; N, no; NR, not recovered/not resolved; R, recovered/resolved; RG, recovering/resolving; T, trametinib; Y, yes

In the ISS database, 13 (3.6%) patients had an episode of DVT or PE, 10 of which occurred in patients who received the 150/2 combination dose. In the pooled 150/2 combination group, there were 10 (5%) patients with a thromboembolic episode. Table 48 summarizes the cases of thromboembolic events. All thromboembolic events were Grade 2 or Grade 3 in severity with the exception of one fatal PE.

Reference ID: 3422378

Table 48: All Patients with Thromboembolic Events (ISS Database)

Subject ID	Age	Sex	Treatment	AE	Serious	Related	Grade	Start Day	End Day	Hospitalization	Outcome
BRF113220-Part B-(b) (6)	58	F	B-150/2	PE	N	N	2	55	111		R
				PE	Y	N	3	166	175	Y	R
				DVT	N	N	3	167	224		R
BRF113220-Part B-(b) (6)	28	M	B-150/1.5	PE	N	N	2	268	296		R
BRF113220-Part B-(b) (6)	56	M	B-150/2	PE	Y	N	3	110		Y	NR
BRF113220-Part C-(b) (6)	37	F	C-150/2	DVT	N	N	2	58	147		R
BRF113220-Part C(b) (6)	72	M	C-150/2	DVT	N	N	2	225			NR
				PE	N	N	3	225			NR
BRF113220-Part C-(b) (6)	48	F	C-150	PE	Y	N	3	162	163	Y	R
BRF113220-Part C-(b) (6)	67	M	C-150/2	PE	Y	N	5	124	127	Y	FATAL
BRF113220-Part C-(b) (6)	34	M	C-150/1	PE	N	N	3	222			RG
BRF113220-Part C-(b) (6)	74	M	C-150/2	PE	Y	N	3	337	340	Y	R
BRF113220-Part D-(b) (6)	71	M	D-75/2	PE	Y	N	3	233		Y	NR
BRF113220-Part D-(b) (6)	74	F	D-75/2	PE	Y	N	3	107	109	Y	R
				DVT	N	N	2	108	111		R
				PE	Y	N	3	134	143	Y	RS
BRF113220-Part D-(b) (6)	52	F	D-150/2	DVT	N	N	2	133			NR
BRF113220-Part D-(b) (6)	90	F	D-150 -> 150/2	PE	Y	N	5	315	315		FATAL

Source: ADAE.xpt

Abbreviations: D, dabrafenib; DVT, deep venous thrombosis; F, female; M, male; N, no; NR, not recovered/not resolved; PE: pulmonary embolism; R, recovered/resolved; RG, recovering/resolving; RS, recovered/resolved with sequelae; T, trametinib; Y, yes

Reviewer Comment:
FDA requested that the Applicant upgrade the toxicity Grade and provide an analysis of thromboembolic events in the updated ISS database and include incidences from the dabrafenib and trametinib monotherapy ISS database. Uncomplicated PE is Grade 3 by CTCAE definition. In the response to the FDA information request (October 18, 2013), the Applicant stated that the investigator has clarified that the Grade 2 AEs of pulmonary embolism for patients # (b) (6) and # (b) (6) are data entry errors; the database has been corrected to Grade 3 for these events.

The Applicant provided updated analyses for thromboembolic events including the 90-day safety update database (Table 49). There was a higher incidence of thromboembolic events in the 150/2 combination group (15%) compared to the dabrafenib monotherapy (0%). Five of the eight were Grade 1 and 2 and did not result in discontinuation of drug. Thromboembolic events reported in the ISS pooled 150/2 group was 9% with 47% of events Grade 1 or Grade 2. All Grade 3/4/5 thromboembolic events in the pooled 150/2 ISS population primarily consisted of pulmonary emboli (9 patients); deep vein thrombosis and cerebrovascular accident each occurred in one patient.

Table 49: Summary of Characteristics of Thromboembolic Events

	Part C 150 mg	**Part C 150 mg**	**Part C 150 mg**	**ISS Pooled 150**
	--	**1 mg QD**	**2 mg QD**	**2 mg QD**
	N=53	N=54	N=55	N=204*
	0	2 (4%)	8 (15%)	19 (9%)
	0	2	9	23
	N=0	**N=2**	**N=8**	**N=19**
	0	0	2 (25%)	5 (26%)
Grade 1	0	1 (50%)	3 (38%)	4 (21%)
	0	1 (50%)	2 (25%)	7 (37%)
Grade 2	0	0	0	1 (5%)
	0	0	1 (13%)	2 (11%)
	N=0	**N=2**	**N=8**	**N=19**
	0	0	1 (13%)	2 (11%)
	0	0	1 (13%)	2 (11%)
	0	2(100%)	4 (50%)	13 (68%)
	0	0	2 (25%)	4 (21%)
	0	0	1 (13%)	2 (11%)

Source: Response to FDA Information Request, October 18, 2013
*N=204 is based on the updated pooled ISS database in the 90-day safety review provided by the Applicant

Reviewer Comment:
The incidence of thromboembolic events was higher in the 150/2 combination group compared to none in the dabrafenib monotherapy group. The incidence is higher than events reported with either single-agent dabrafenib or single-agent trametinib. This

reviewer recommends the addition of thromboembolic events to the Warnings and Precautions section in the label.

Renal Failure

Renal failure complicating febrile drug reactions was observed with dabrafenib monotherapy (Tafinlar USPI). Renal failure was defined as an AE of special interest following the identification of renal insufficiency and renal failure with a possible causal relationship to dabrafenib in ongoing clinical studies.

The Applicant defined renal failure as a composite of renal failure and acute renal failure. The reviewer also included the AE term blood creatinine increased in the analysis of renal failure events. The incidence of renal failure was higher in the 150/2 combination group (13%) compared to the 150/1 combination group (11%) and the dabrafenib monotherapy group (4%) (Table 50). Six patients, all in the combination groups, experienced renal failure.

Table 50: Summary of Renal Failure (All Treated Population)

AE	D N=53 n (%)	D + T 1 mg N=54 n (%)	D + T 2 mg N=55 n (%)
Renal Failure	2 (4)	5 (9)	5 (9)
Renal failure [1]	0	1 (2)	5 (9)
Blood creatinine increased	2 (4)	5 (9)	2 (4)

Source: ADAE.xpt
[1] Renal failure is a composite endpoint of renal failure and renal failure acute
Abbreviations: D, dabrafenib; T, trametinib

Twelve patients had renal failure. All Grade 3 renal failure events occurred in patients in the 150/2 combination group (Patient [redacted] (b) (6), and [redacted] (b) (6)). In three patients, the study drug dose was interrupted, withdrawn or reduced. All the events in these four patients recovered/resolved. Two of these events were considered serious AEs. Most AEs were considered drug-related. Drug was withdrawn in two patients. The outcome was not recovered/resolved in five patients. See Table 51for details.

Table 51: Patients with Renal Failure

Subject ID	Age	Sex	Treatment Group	AE*	Toxicity Grade	Related	Serious	Action	Onset (day)	End (day)	Outcome
BRF113220-Part C-(b) (6)	28	M	150/1	Blood creatinine increased	2	N	N	dose not changed	227	233	R
BRF113220-Part C-(b) (6)	58	M	150/2	Renal failure acute	3	Y	Y	drug interrupted	110	126	R
				Pyrexia	3	Y	Y	dose reduced	98	140	R
BRF113220-Part C-(b) (6)	47	M	150	Blood creatinine increased	2	Y	N	drug withdrawn	309		NR
BRF113220-Part C-(b) (6)	64	M	150/2	Blood creatinine increased	1	Y	N	dose not changed	84	335	R
				Blood creatinine increased	1	N	N	dose not changed	365		NR
BRF113220-Part C-(b) (6)	64	M	150	Blood creatinine increased	2	N	N	dose not changed	13	27	R
				Blood creatinine increased	2	Y	N	dose not changed	54		NR
BRF113220-Part C-(b) (6)	54	M	150/2	Renal failure	3	Y	Y	drug withdrawn	85	88	R
				Pyrexia	2	Y	N	dose reduced	43	88	R

BRF113220-Part C-(b) (6)	71	F	150/1	Blood creatinine increased	1	Y	N	dose not changed	17	18	R
BRF113220-Part C-(b) (6)	65	M	150/1	Blood creatinine increased	2	Y	N	drug interrupted	25	32	R
				Pyrexia	2	Y	Y	drug interrupted	23	27	R
BRF113220-Part C-(b) (6)	54	M	150/1	Blood creatinine increased	2	Y	N	drug interrupted	311	367	R
			150/1	Renal failure acute	2	Y	Y	drug interrupted	312		NR
BRF113220-Part C-(b) (6)	67	M	150/2	Renal failure acute	3	N	N	dose not changed	124	125	R
BRF113220-Part C-(b) (6)	47	M	150/1	Blood creatinine increased	1	Y	N	dose not changed	85	280	R
BRF113220-Part C-(b) (6)	63	M	150/2	Renal failure acute	1	Y	N	dose not changed	46	50	R
				Blood creatinine increased	4	Y	N	dose not changed	85		NR
				Renal failure acute	3	Y	Y	dose reduced	136	183	R

Source: ADAE.xpt
Abbreviations: AE, adverse event; D, dabrafenib; F, female; M, male; N, no; NR, not recovered/not resolved; R, recovered/resolved; T, trametinib; Y, yes
*Events of pyrexia were included if it preceded renal failure

Confounding factors were present in four of the five patients with renal failure: Patient (b) (6) (anemia, fever, and chills associated with Grade 4 neutropenia, renal cyst); Patient (b) (6) (anemia, hypercalcemia); Patient (b) (6) (possible urinary tract infection); and Patient (b) (6) (prior episodes of acute kidney injury due to cytokine release syndrome and rigors, rhabdomyolysis, hypovolemia, severe chills, metabolic acidosis, and dehydration). Renal failure AEs led to permanent discontinuation of study drugs in one patient (Patient (b) (6)), and to dose interruptions/reductions in three patients (Patient (b) (6), (b) (6), and (b) (6)). One patient (Patient (b) (6)) was not taking study drugs at the time of the event and subsequently experienced a fatal SAE of pulmonary embolism on the same day on which he experienced Grade 3 acute renal failure. Of the three patients who had dose interruptions, the AEs resolved in two patients (Patient (b) (6) and (b) (6)) and was ongoing in one patient (Patient (b) (6)) when treatment was resumed Patient (b) (6) and (b) (6) resumed both study drugs with dabrafenib administered at a reduced dose and trametinib at the full dose, whereas Patient (b) (6) resumed only trametinib (dose reduced).Three patients (Patient (b) (6) and (b) (6)) also had pyrexia during the duration of the renal insufficiency, the first two patients from the 150/2 combination group. In patient (b) (6), pyrexia occurred on Days 18-136 which was before acute renal failure. The reviewer does not consider the acute renal failure to be related to the pyrexia. Thus two out of five patients in the 150/2 combination group had renal failure together with pyrexia.

The incidence of renal failure was 4% in the pooled 150/2 combination group and 2% in the ISS trametinib monotherapy database. Grade 3 /4 renal failure occurred in 2% patients in the pooled 150/2 group compared to none in the trametinib monotherapy group.

Reviewer Comment:
The incidence of renal failure was higher in the 150/2 combination group compared to the dabrafenib monotherapy group, including an increase in serious cases of renal failure. Recommend inclusion in the label and post-marketing surveillance.

Pyrexia

Pyrexia (serious and non-serious) is a common AE with single-agent dabrafenib; pyrexia occurs in 28% of patients based on the Tafinlar USPI.

In Part C, there was a higher incidence of pyrexia events (composite term which included pyrexia, chills, influenza-like illness, cytokine release syndrome and febrile neutropenia) in the two combination groups (72% in the 150/1 combination group and 76% in the 150/2 combination group) compared with the dabrafenib monotherapy group (32%) (Table 52).

The majority of pyrexia AEs in the two combination groups (85% in the 150/1 and 90% in the 150/2 combination groups) and all the pyrexia AEs in the monotherapy group

were Grades 1 or 2 in severity. A higher proportion in the monotherapy group (41%) compared with the combination groups (15% in 150/1 combination group, and 22% in 150/2 combination group) experienced pyrexia in the first 2 weeks of treatment. Beyond two weeks, the incidence of pyrexia was higher in the two combination groups. A higher proportion of patients in the combination groups experienced multiple episodes of pyrexia (72% in 150/1 combination group, and 52% in 150/2 combination group) compared to dabrafenib monotherapy (18%). The median time to onset of first occurrence of pyrexia was 31 days in the 150/1 combination group, 30 days in the 150/2 combination group and 23 days in the dabrafenib monotherapy group. The duration of the first occurrence of pyrexia was higher in the combination groups (median of 6.0 days in 150/1 and 7.5 days in 150/2 combination groups) compared to the dabrafenib monotherapy group (median of 4.5 days). The majority of pyrexia events in all treatment groups were considered drug-related by the investigator.

Serious events reported as required per protocol were patients with pyrexia of any grade accompanied by hypotension and/or rigor and chills or renal failure, regardless of whether the patients required hospitalization. Serious adverse events of pyrexia developed in 16 (38%) patients in the 150/2 combination group, 11 (28%) in the 150/1 combination group and one (6%) patient in the dabrafenib monotherapy group.

The incidence of dose reductions due to pyrexia was higher in the combination groups (44% in 150/1, 48% in 150/2 combination group) compared with the dabrafenib monotherapy group (18%). The incidence of dose interruptions or delays due to pyrexia was also higher in the combination groups (56% in 150/1, 57% in 150/2 combination group) compared to the dabrafenib monotherapy group (24%). The number of patients with dabrafenib dose reductions associated with pyrexia events were higher in the combination groups (28 /52% in 150/1, 30 55% in 150/2 combination group) compared with the dabrafenib monotherapy group (6/11%). None of the patients in the 150/1 combination group, and 10 patients in the 150/2 combination group had trametinib dose reductions associated with pyrexia. A dose reduction was considered associated with a pyrexia event if the dose was either reduced during the pyrexia event, or if the dose was reduced after the resolution of the pyrexia event, but was immediately preceded by a dose interruption that occurred during the pyrexia event. In a majority of cases in all 3 treatment groups (> 80%), the dabrafenib dose was re-escalated back to the scheduled dose following the initial reduction. The majority (≥90%) of patients in all the three treatment groups recovered from pyrexia events. Three patients, one (3%) in the 150/1 combination group, two (5%) patients in the 150/2 combination group and none in the dabrafenib monotherapy group permanently discontinued either investigational product due to pyrexia events.

Most of the patients experiencing pyrexia events in all three treatment groups were treated with anti-pyretics or NSAIDs, and the usage of these agents were higher in the combination groups compared with the dabrafenib monotherapy group. Twenty nine (54%) patients in the 150/1 combination group, 28 (51%) patients in the 150/2

combination group and eight (15%) patients in the dabrafenib monotherapy group received medications for pyrexia which included anti-pyretics, NSAIDS and corticosteroids. In the 150/2 combination group, these medications included anti-pyretics [n=22 (40%)], NSAIDS [n=22 (40%)], and corticosteroids [n=14 (26%)]. A higher proportion of patients in the 150/2 combination group [n=14 (26%)] required corticosteroids to manage pyrexia events compared with the 150/1 combination group [n=6 (11%)] and dabrafenib monotherapy group [n=1 (2%)].

The median duration of corticosteroid usage (including prednisone) was highest in the 150/2 combination group, with 10 patients out of 14 (71%)] using these agents for ≥ 21 days, compared to none in the 150/1 combination group and one patient in the dabrafenib monotherapy group.

Table 52: Summary of Pyrexia Events (All Treated Population)

AE	**D** **N=53** n (%)	**D + T 1 mg** **N=54** n (%)	**D + T 2 mg** **N=55** n (%)
Any Pyrexia	17 (32)	39 (72)	42 (76)
Pyrexia	14 (26)	37 (69)	39 (71)
Chills	9 (17)	27 (50)	32 (58)
Influenza like illness	4 (8)	11 (20)	5 (9)
Cytokine release syndrome	0	1 (2)	1 (2)
Febrile neutropenia	0	1 (2)	1 (2)

Source: ADAE.xpt
Abbreviations: D, dabrafenib; T, trametinib

In the ISS database, the incidence of pyrexia was observed in 62% of patients. In the pooled ISS 150/2 combination group, the incidence was 63%. All incidences are higher than the incidences observed with single-agent dabrafenib (33%), including serious febrile reactions.

Pyrexia events, including serious events, were higher in the 150/2 combination group compared to the dabrafenib monotherapy group and compared to dabrafenib single-agent. Although > 90% pyrexia AEs recovered/resolved, the frequency of dose reductions and interruptions/delays was high (48-57%). Five percent of the pyrexia events required disontinuation of either investigational product. Usage of anti-pyretics, NSAIDS and corticosteroids was also higher in the 150/2 combination group.

Reviewer Comment:
The incidence or pyrexia was higher in the groups treated with the combination of dabrafenib and trametinib than in the single-agent dabrafenib treatment group. The Clinical Pharmacology review identified evidence for an exposure-response relationship between pyrexia and hydroxy-dabrafenib, a metabolite of dabrafenib. Pyrexia is likely

due to a synergistic effect. Recommend inclusion in the trametinib label in the Warnings and Precautions Section.

Rash and Skin-related Adverse Events

The overall incidence of skin toxicity including rash, dermatitis, acneiform rash, palmar-plantar erythrodysesthesia syndrome (PPES) and erythema was 87% in patients treated with trametinib (Mekinist USPI). Severe skin toxicity occurred in 12% of patients. Skin toxicity requiring hospitalization occurred in 6% of patients, most commonly for secondary infections of the skin requiring intravenous antibiotics or severe skin toxicity without secondary infection. Dry skin and pruritus was also reported with trametinib monotherapy (Mekinist USPI).

Hyperkeratosis, alopecia, PPES and rash, maculopapular rash has been reported with dabrafenib monotherapy (Tafinlar USPI).

The reviewer included all skin-related AEs in the analysis of rash. Rash was the most common skin-related toxicity across all treatment groups, and was higher in the dabrafenib monotherapy group compared with the combination groups (Table 53). Dermatitis acneiform, dry skin and erythema were reported more frequently in the 150/2 combination group, whereas PPES and alopecia were more frequently reported in the dabrafenib monotherapy group. All skin-related toxicities in the dabrafenib monotherapy group and in the 150/2 combination group, and all but two skin-related toxicity events in the 150/1 combination group were Grades 1 or 2 in severity.

Two patients in the 150/1 combination group experienced Grade 3 skin-related toxicities. Patient (b) (6) experienced Grade 3 PPES 85 days after the first dose of study drug. Only dabrafenib was interrupted, and resumed at a lower dose. The AE was considered drug-related by the investigator, and had not resolved as of the data cutoff date; treatment was ongoing in this patient at the data cutoff date (Day 330). Patient (b) (6) experienced an SAE of Grade 3 generalized rash 391 days after the first dose of study drug. Both study drugs were briefly interrupted, and then subsequently resumed; treatment was ongoing at the data cutoff date (Day 400). The AE was considered by the investigator as not related to study drug, and had not resolved at the time of the data cutoff date.

Table 53: Summary of Rash and Skin-related Events (All Treated Population)

AE	**D** **N=53** n (%)	**D + T 1 mg** **N=54** n (%)	**D + T 2 mg** **N=55** n (%)
Rash	19 (36)	11 (20)	15 (27)
Dry skin	3 (6)	5 (9)	10 (18)
Dermatitis acneiform	2 (4)	6 (11)	9 (16)

AE	D N=53 n (%)	D + T 1 mg N=54 n (%)	D + T 2 mg N=55 n (%)
Erythema	1 (2)	3 (6)	8 (15)
Pruritus	7 (13)	6 (11)	6 (11)
Rash generalized	4 (8)	2 (4)	6 (11)
Hyperkeratosis	16 (30)	3 (6)	5 (9)
Eczema	0	2 (4)	4 (7)
Palmar-plantar erythrodysesthesia syndrome	9 (17)	4 (7)	4 (7)
Alopecia	18 (34)	5 (9)	3 (5)
Rash macular	2 (4)	2 (4)	3 (5)
Rash maculo-papular	3 (6)	4 (7)	3 (5)
Urticaria	0	0	3 (5)
Acne	0	1 (2)	2 (4)
Rash pruritic	1 (2)	2 (4)	2 (4)
Rash erythematous	0	4 (7)	1 (2)
Skin chapped	0	0	1 (2)
Skin exfoliation	1 (2)	1 (2)	1 (2)
Dermatitis	0	1 (2)	0
Exfoliative rash	1 (2)	0	0
Papule	1 (2)	0	0
Pruritus generalized	8 (15)	3 (6)	0
Rash papular	0	4 (7)	0
Rash vesicular	0	1 (2)	0

Source: ADAE.xpt
Abbreviations: D, dabrafenib; T, trametinib

The incidence of skin-related toxicities in the pooled ISS 150/2 combination group was 53% with less than 1% Grade 3 /4 AE. The incidence of PPES was slightly lower in the 150/2 combination group.

Reviewer Comment:
With the exception of PPES which was reduced in incidence in the 150/2 combination group compared to the dabrafenib monotherapy group, other skin-related toxicities did not show a particular trend. Dermatitis acneiform occurred more frequently in the 150/2 combination group compared to dabrafenib monotherapy.

Hepatic Adverse Events and Drug Induced Liver Injury (DILI)

ALT and AST elevations can occur with single-agent trametinib ((60% and 39%, respectively) Mekinist USPI) and increased alkaline phosphatase with single-agent dabrafenib (19%, Tafinlar USPI).

The reviewer included jaundice and gamma-glutamyl transferase (GGT) as AE terms which were not included in the Applicant's analysis of hepatic AEs (Table 54). The proportion of hepatic events reported as AEs was higher in the combination groups

(28% in the 150/1 combination group and 15% in the 150/2 combination group) compared with the dabrafenib monotherapy group (4%) . Increased ALT and AST were the most common hepatic events in the combination groups (39% in the 150/1 combination group and 18% in the 150/2 combination group), and were the main hepatic events reported in the dabrafenib monotherapy group (4%). The hepatic events in the dabrafenib monotherapy group and the majority of hepatic events in the two combination groups were Grades 1 or 2 in severity. Three patients (6%) in the 150/1 combination group and two (4%) patients in the 150/2 combination group experienced Grade 3 hepatic events: Patient (b) (6) (AST increased and SAE of hyperbilirubinemia), Patient (b) (6) (ALT increase), and Patient (b) (6) (ALT increase, transaminase increase, and hyperbilirubinemia), all in the 150/1 combination group; Patient (b) (6) (ALT increase) and Patient (b) (6) (ALT and AST increase), both in the 150/2 combination group. Out of these five patients (Patient (b) (6) and (b) (6) in the 150/1 combination group, and Patient (b) (6) and (b) (6) in the 150/2 combination group) met liver chemistry stopping criteria of ALT >5x ULN. In all except one patient (Patient (b) (6)), the events were considered drug related by the investigator. Both study drugs were interrupted in all five patients (in Patient (b) (6), the study drugs were interrupted a day earlier due to Grade 1 pyrexia). In four patients, both study drugs were resumed after the AEs had resolved, and these patients did not experience any recurrence of hepatic events; as of the data cutoff date, two patients (Patient (b) (6) and (b) (6)) were receiving ongoing treatment and two patients (Patient (b) (6) and (b) (6)) had permanently discontinued study treatment due to disease progression. In one patient (Patient (b) (6)), the hepatic events had not fully resolved when the study drugs were resumed and were ongoing (Grade 1) when the patient permanently discontinued study treatment due to disease progression.

Table 54: Summary of Hepatic Adverse Events (All Treated Population)

AE	**D** **N=53** n (%)	**D + T 1 mg** **N=54** n (%)	**D + T 2 mg** **N=55** n (%)
Any Hepatic Events	2 (4)	15 (28)	8 (15)
Alanine aminotransferase increased	1 (2)	11 (20)	5 (9)
Gamma-glutamyltransferase increased	1 (2)	11 (20)	5 (9)
Aspartate aminotransferase increased	1 (2)	10 (19)	5 (9)
Blood bilirubin increased	0	0	1 (2)
Drug-induced liver injury	0	0	1 (2)
Liver function test abnormal	1 (2)	0	1 (2)
Hyperbilirubinemia	0	3 (6)	0
Transaminases increased	0	4 (7)	0
Jaundice	0	1 (2)	0

Source: ADAE.xpt
Abbreviations: D, dabrafenib; T, trametinib

Table 55 describes all cases of hepatic adverse events including the hepatobiliary laboratory abnormalities.

Table 55: Patients with Hepatic Adverse Events (All Treated Population)

Patient ID	Age / Sex	Hepatobiliary History (Grade)	AE / Lab	Grade	Rel	Onset (Day)	Duration (days)	Action	Outcome
BRF113220-Part C-(b) (6)	37/F	150/2	Increased ALT	3	Y	64	22	drug interrupted	R
BRF113220-Part C-(b) (6)	51/M	150/2	drug induced liver injury	1	Y	31	8	drug interrupted	R
BRF113220-Part C-(b) (6)	64/M	150/2	increased AST	1	Y	25	15	dose not changed	R
			increased ALT	1	Y	28	12	dose not changed	R
BRF113220-Part C-(b) (6)	45/F	150/2	liver function test abnormal	1	Y	332	1	dose not changed	R
BRF113220-Part C-(b) (6)	41/F	150/2	increased ALT	1	N	29	44	dose not changed	R
			increased ALT	1	N	29	59	dose not changed	R
BRF113220-Part C-(b) (6)	45/F	150/2	increased ALT	1	N	30		dose not changed	NR
			increased AST	1	N	30		dose not changed	NR
BRF113220-Part C-(b) (6)	63/M	150/2	Increased AST	1	Y	29	29	dose not changed	R
BRF113220-Part C-(b) (6)	57/F	150/2	increased ALT	3	Y	66		dose not changed	NR
			increased AST	3	Y	66		dose not changed	NR
			increased blood bilirubin	1	N	66	5	dose not changed	R
BRF113220-Part C-(b) (6)	28/M	150/1	Increased ALT	2	Y	251	23	dose not changed	R
			Increased ALT	3	Y	308	8	dose reduced	R

Patient ID	Age / Sex	Hepatobiliary History (Grade)	AE / Lab	Grade	Rel	Onset (Day)	Duration (days)	Action	Outcome
BRF113220-Part C-(b) (6)	65/M	150/1	increased AST	1	N	113	29	dose not changed	R
BRF113220-Part C-(b) (6)	40/F	150/1	increased ALT	2	Y	20	17	drug interrupted	R
			increased AST	2	Y	20	17	drug interrupted	R
BRF113220-Part C-(b) (6)	37/M	150/1	increased ALT	1	Y	56	169	dose not changed	RS
			increased AST	1	Y	56	57	dose not changed	R
			increased AST	1	Y	141	57	dose not changed	R
BRF113220-Part C-(b) (6)	85/M	150/1	Increased ALT	1	N	1	43	dose reduced	R
			Increased AST	3	N	1	43	dose reduced	R
			hyperbilirubinemia	1	Y	29	15	drug interrupted	R
			hyperbilirubinemia	3	Y	29	8	drug interrupted	R
BRF113220-Part C-(b) (6)	65/M	150/1	Increased ALT	1	N	25	3	drug interrupted	R
			Increased AST	2	N	25	8	drug interrupted	R
BRF113220-Part C-(b) (6)	45/F	150/1	hyperbilirubinemia	3	N	135	13	dose not changed	R
			Increased ALT	3	N	135	13	drug interrupted	R
			Increased transaminases	3	N	135	13	dose not changed	R
BRF113220-Part C-(b) (6)	54/M	150/1	Increased ALT	2	Y	143	113	dose not changed	R
			Increased AST	1	Y	143	113	dose not changed	R
BRF113220-Part C-	78/M	150/1	Increased transaminases	1	Y	58		dose not changed	NR

Patient ID	Age / Sex	Hepatobiliary History (Grade)	AE / Lab	Grade	Rel	Onset (Day)	Duration (days)	Action	Outcome
(b) (6)									
BRF113220-Part C-(b) (6)	49/M	150/1	Increased ALT	2	N	28	21	dose not changed	R
			Increased AST	1	N	28	21	dose not changed	R
			hyperbilirubinemia	2	N	28	8	dose not changed	R
BRF113220-Part C-(b) (6)	47/M	150/1	Increased transaminases	1	Y	15	43	dose not changed	R
BRF113220-Part C-(b) (6)	60/F	150/1	Increased transaminases	1	Y	141	28	dose not changed	R
BRF113220-Part C-(b) (6)	46/M	150/1	increased AST	1	Y	86	6	drug interrupted	R
			increased AST	1	Y	86	2	drug interrupted	R
BRF113220-Part C-(b) (6)	39/M	150/1	increased ALT	2	Y	44	8	dose not changed	R
			increased AST	2	Y	44	8	dose not changed	R
BRF113220-Part C-(b) (6)	53/M	150/1	increased AST	1	Y	37	21	dose not changed	R
			increased ALT	2	Y	43	5	dose not changed	R
BRF113220-Part C-(b) (6)	51/F	150	liver function test abnormal	1	N	101	13	dose not changed	R
BRF113220-Part C-(b) (6)	69/F	150	increased ALT	1	N	175		dose not changed	NR
			increased AST	1	N	175	2	dose not changed	R

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; D, dabrafenib; Lab, Laboratory abnormality; F, female; M, male; R, recovered/resolved; Rel, related; T, trametinib.

The review of safety included an analysis of the laboratory datasets to identify any patients meeting the criteria for Hy's law. One patient (Patient (b) (6)) in the 150/1 combination group experienced concurrent increases in ALT (>3x ULN), total bilirubin (BIL> 2x ULN), and ALKP (2x ULN) on Day 135. The patient had ongoing

gallbladder/liver disease and liver metastases at the time of study entry. Concurrent with the liver enzyme increases, the patient also had Grade 4 lipase increase, Grade 3 cholangitis, and Grade 3 pancreatitis. The liver enzyme increases were considered related to the patient's underlying medical condition, and not drug-related. The reviewer agrees with the Applicant that this patient did not meet the criteria for Hy's law. Both drugs were interrupted briefly, and resumed after the AEs resolved; no further liver enzyme abnormalities were recorded after resumption of the study drugs. The patient permanently discontinued study drugs on Day 286 due to disease progression.

The incidence of Grade 3 /4 hepatic events was 14% in the pooled 150/2 combination group and 13% in the ISS trametinib monotherapy database. There were no Hy's Law cases. An excess of AST or ALT elevations to >3xULN in the pooled 150/2 combination group was 13%, elevations of AST or ALT to > 5xULN in the pooled 150/2 combination group was 3% and there were five cases (2%) of bilirubin ≥ 2xULN.

Reviewer Comment:

1. *Hepatic AEs are higher in the 150/2 combination group compared to the dabrafenib monotherapy group and consistent with single-agent trametinib.*
2. *There were no Hy's Law cases identified. However, the 150/2 combination has a potential for severe DILI as signaled by the following set of findings:*
   - *An excess of AST or ALT elevations to >3xULN in the 150/2 combination group (11%) compared to the dabrafenib monotherapy group (2%)*
   - *Elevations of AST or ALT to > 5xULN in the 2 combination groups (4%) and compared to none in the dabrafenib monotherapy group.*
   - *One (2%) case of newly elevated total serum bilirubin to >2xULN in a setting of pure hepatocellular injury, accompanied by an overall increased incidence of AST or ALT elevations >3xULN in the 150/2 combination group compared to none in the dabrafenib monotherapy group.*
3. *Although the hepatic AEs were consistent with single-agent trametinib and no Hy's Law cases identified, the 150/2 combination has a potential for severe DILI. Recommend inclusion of the hepatic test results in the label and post-marketing surveillance.*

Ocular Events

Clinically important ocular events can occur with single-agent trametinib, including retinal vein occlusion and retinal pigmented epithelial detachments.

One patient (0.5%) receiving trametinib developed retinal pigment epithelial detachment (RPED) (Mekinist USPI). Across all clinical trials of trametinib, the incidence of RPED was 0.8% (14/1749) and the incidence of retinal vein occlusion (RVO) was 0.2% (4/1749) (Mekinist USPI).

Reference ID: 3422378

Uveitis (including iritis) occurred in 1% (6/586) across single-agent trials of dabrafenib (Tafinlar USPI).

Because of the known risk of ocular events, the protocol specified that patients with a history or RVO or central serous retinopathy (CSR) or predisposing factors to RVO or CSR were excluded from Trial BRF113220.

The reviewer included the AE terms of transient blindness, eye pain, keratitis, ocular hyperemia, cataracts, eye hemorrhage, retinal degeneration, vitreous detachment and vitreous hemorrhage in addition to the Applicant chosen AE terms. A higher proportion of patients in the combination groups (25%) experienced ocular events compared with the dabrafenib monotherapy group (15%) (Table 56). The incidence in the combination groups was similar. Blurred vision was the most common ocular event across all three treatment groups. No cases of RPED or RVO were reported in any treatment group. All ocular events in the dabrafenib monotherapy group were Grade 1, whereas almost all of the ocular events in the 2 combination groups were Grades 1 or 2 in severity. Two patients experienced Grade 3 ocular events, both of which were considered drug related (Patient (b) (6), 150/1 combination group, uveitis; Patient (b) (6), 150/2 combination group, SAE of chorioretinopathy). Patient (b) (6) interrupted only dabrafenib and after resolution of the AE, resumed treatment at a lower dose until disease progression without recurrence. Patient (b) (6) interrupted both study drugs and after resolution of the SAE, resumed treatment of dabrafenib and a reduced dose of trametinib. A subsequent event of Grade 1 chorioretinopathy (also reported as an SAE) led to only trametinib interruption. After resolution of the AE, the patient resumed trametinib treatment and was ongoing treatment (Day 347) at the data cutoff date.

Table 56: Summary of Ocular Events in ≥ 2 Patients (All Treated Population)

AE	**D** **N=53** n (%)	**D + T 1 mg** **N=54** n (%)	**D + T 2 mg** **N=55** n (%)
Any Ocular Event	8 (15)	13 (24)	14 (25)
Vision blurred	4 (8)	5 (9)	5 (9)
Dry eye	2 (4)	3 (6)	3 (5)
Visual impairment	0	2 (4)	2 (4)
Eye pain	0	2 (4)	1 (2)
Ocular hyperemia	0	2 (4)	1 (2)
Photopsia	0	2 (4)	1 (2)
Vitreous floaters	2 (4)	3 (6)	0

Source: ADAE.xpt
Abbreviations: D, dabrafenib; T, trametinib

In both the ISS database and in the pooled ISS 150/2 combination group, the incidence of ocular events was 20%. In the ISS database, three cases of CSR, one case of RVO,

one case of papilledema, one case of optic neuropathy accompanied by papilledema, four cases of uveitis, one case of iridocyclitis and two cases of iritis were observed.

Reviewer Comment:
The incidence of ocular events was higher in the 150/2 combination group compared to the dabrafenib monotherapy group and slightly higher than single-agent trametinib. Although a high incidence of RPED and RVO events were not seen, there was one case of transient blindness and two cases of chorioretinopathy in the 150/2 combination compared to none in the dabrafenib monotherapy group. Ophthalmology monitoring is recommended in the label.

Diarrhea

Diarrhea is a common AE with trametinib monotherapy, with an incidence of 43% (Mekinist USPI).

The incidence of diarrhea was higher in the 150/2 combination group (36%) compared with the dabrafenib monotherapy (28%) and 150/1 combination treatment (26%) groups (Table 57).

All diarrhea events in the dabrafenib monotherapy and the 150/1 combination groups, and all but one diarrhea event in the 150/2 combination group were Grades 1 or 2 in severity. Patient (b) (6) treated with the 150/2 combination experienced Grade 3 diarrhea on Day 114, which was considered drug-related by the investigator. Study treatment (patient was on dabrafenib only at the time of the AE) was interrupted, and resumed following resolution of the AE. The patient reported no further recurrences of diarrhea, and permanently discontinued study treatment on Day 252 due to disease progression. Including Patient (b) (6), four patients (7%) in the 150/2 combination group required dose interruptions to manage diarrhea, and three patients, including one patient (2%) in the dabrafenib monotherapy group and two patients (4%) in the 150/2 combination group required dose reductions to manage diarrhea. No patients permanently discontinued study treatment due to diarrhea. Usage of concomitant medication to manage diarrhea (e.g., loperamide hydrochloride) was <10% in all three treatment groups.

Table 57: Summary of Diarrhea (All Treated Population)

AE	D N=53 (%)	D + T 1 mg N=54 (%)	D + T 2 mg N=55 (%)
Diarrhea	15 (28)	14 (26)	20 (36)

Source: ADAE.xpt
Abbreviations: D, dabrafenib; T, trametinib

The incidence of diarrhea in the pooled 150/2 combination group was 27%, none an SAE. The incidence of diarrhea in the ISS trametinib single-agent database was 49% with an SAE rate of < 1%.

Reviewer Comment:
The incidence of diarrhea is higher in the 150/2 combination treatment group than in the dabrafenib monotherapy group and is consistent with the incidence reported for single-agent trametinib

Hypertension

Hypertension occurred in 15% of patients treated with trametinib (Mekinist USPI). Hypertension AEs as well as increases in blood pressure measurements have been observed with trametinib monotherapy per the Applicant in the results of the MEK113583 and MEK114267 studies.

In Trial BRF113220, uncontrolled hypertension was an exclusion criterion based on as the list of predisposing factors to RVO and CSR.

The Applicant reported hypertension AEs in nine patients. The reviewer also included the AE term 'blood pressure increased' which included an additional patient for a total of 10 patients with a hypertension AE. A higher proportion of patients in the 150/2 combination group (n=5, 9%) experienced hypertension AEs compared with the dabrafenib monotherapy group (n=3, 6%) and the 150/1 combination group (n=2, 4%) (Table 58). Nine of the 10 patients experienced Grade 1 or 2 hypertension AEs; one patient (Patient (b) (6)) in the 150/2 combination group experienced a Grade 3 hypertension AE) which recovered/resolved. Four of the Grade 2 hypertension did not recover. Five of the events were considered as not related to the study drugs by the investigator, and five were considered as related. None of the hypertension AEs led to permanent discontinuation of either investigational product in any treatment group, or necessitated dose interruptions or reductions in any treatment group.

Table 58: Summary of Hypertension (All Treated Population)

AE	D N=53 (%)	D + T 1 mg N=54 (%)	D + T 2 mg N=55 (%)
Hypertension[1]	3 (6)	2 (4)	5 (9)

Source: ADAE.xpt
[1]Hypertension also includes the term blood pressure increased
Abbreviations: D, dabrafenib; T, trametinib

In the reviewer analysis of hypertension, twenty one patients had increases in systolic blood pressure (BP) to Grade 3 and Grade 4. Twelve (22%) patients were in the 150/2 combination group, four (7%) patients in the 150/1 combination group and five (9%) patients were in the dabrafenib monotherapy group. Grades 3 and 4 elevation in

systolic BP occurred in association with AEs, including SAEs, in 8 of the 12 patients in the 150/2 combination treatment group: dizziness, lethargy, headache, brain stem/cerebral hemorrhage, hemiparesis, motor dysfunction and ataxia. One patient (Patient (b) (6)) died on Day 62 from brain stem/cerebral hemorrhage (Table 59). Two patients ((b) (6)) in the 150/1 combination group were associated with headache, photopsia and vitreous hemorrhage. In the dabrafenib monotherapy group, three patients ((b) (6)) had AEs of headache and blurred vision. The majority of AEs were Grade 1; only two AEs, hemiparesis and hypertension, were more severe (both were Grade 2). Most of the AEs recovered/resolved except in three patients in whom the AEs were not recovered/not resolved: one patient with photopsia, hypertension and vitreous hemorrhage; one patient with brain stem/cerebral hemorrhage and one patient with hemiparesis, motor dysfunction and ataxia. The majority of AEs were considered related to study drugs by the investigator. See Table 59 for details.

Table 59: Patients with ≥ Grade 3 Systolic Blood Pressures

Subject ID	AGE	SEX	Treatment Arm	AE*	Hypertension onset (day)	AE Onset (day)	AE end (day)	Grade	Related	Outcome
BRF113220-Part C-(b) (6)	77	F	150/2	Hot flush	114	6	216	1	Y	R
				Dizziness	114	79	228	1	Y	R
BRF113220-Part C-(b) (6)	66	F	150/2	Lethargy	9	9	80	1	Y	R
				Dizziness	9	9	12	1	N	R
				Headache	9	110	126	1	Y	R
BRF113220-Part C-(b) (6)	70	F	150/2	Lethargy	254	28		1	Y	NR
				Headache	254	78	268	1	Y	R
				Dizziness	254	262		1	Y	NR
				Dizziness	254	262	356	1	Y	R
				Headache	254	331	331	1	N	R
				Amnesia	254	331	332	1	N	R
BRF113220-Part C-(b) (6)	74	M	150/2	Hot flush	29	2	32	1	Y	R
				Dizziness	29	38	39	1	Y	R
BRF113220-Part C-(b) (6)	73	F	150	Vision blurred	8	12	169	1	Y	R
BRF113220-Part C-(b) (6)	65	M	150/1	Photopsia	59	11		1	N	NR
				Vitreous floaters	59	11	85	1	N	R
				Hypertension	59	59		2	N	NR
				Vitreous hemorrhag	59	109		1	N	NR

Subject ID	AGE	SEX	Treatment Arm	AE*	Hypertension onset (day)	AE Onset (day)	AE end (day)	Grade	Related	Outcome
				e						
BRF113220-Part C-(b) (6)	78	M	150	Hypertension	56	107	172	2	N	R
BRF113220-Part C-(b) (6)	63	M	150/2	Headache	85	57	85	1	N	R
				Hypertension	85	116		1	N	NR
BRF113220-Part C-(b) (6)	55	F	150/2	Vision blurred	15	125		1	N	NR
				Brain stem hemorrhage	15	261	262	5	N	FATAL
				Cerebral hemorrhage	15	261	262	5	N	FATAL
BRF113220-Part C-(b) (6)	61	F	150/1	Headache	57	6	6	1	N	R
BRF113220-Part C-(b) (6)	64	M	150	Headache	118	1	42	1	Y	R
BRF113220-Part C-(b) (6)	72	M	150/2	Vision blurred	29	113	141	1	Y	R
BRF113220-Part C-(b) (6)	62	M	150/2	Eye pain	275	165		1	Y	R
				Hypertension	275	270	295	3	Y	R
				Hypertension	275	327	347	3	Y	R
				Hemiparesis	275			2	N	NR
				Motor dysfunction	275	367		1	N	NR
				Ataxia	275	367		1	N	NR

Source: ADAE.xpt, ADXI.xpt
Abbreviations: F, female; M, male; N, no; NR, not recovered/not resolved; R, recovered/resolved; Y, yes
*Treatment-emergent AEs selected based on possible symptoms of an increase in blood pressure

The incidence of hypertension in the pooled 150/2 combination groups was 8% (3% Grades 3 and 4) and in the ISS trametinib single-agent database 15% (9% Grades 3 and /4).

Reviewer Comment:
The incidence of hypertension is higher in the 150/2 combination group compared to dabrafenib monotherapy group and is consistent with the incidence described for single-agent trametinib. The 150/2 combination treatment group had a slightly higher incidence of treatment-emergent Grades 3 and 4 systolic hypertension. Blood pressure monitoring during treatment with the 150/2 combination is recommended in the labeling.

Sepsis and Infections

Sepsis and infections were not reported with dabrafenib (Tafinlar USPI). Paronychia was reported at an incidence of 10% with trametinib (Mekinist USPI).

The incidence of overall infections was increased in the two combination groups (50% with 150/1, 60% with 150/2 combination group) compared to the dabrafenib monotherapy group (38%) (Table 60). Infections which occurred at an incidence of ≥ 10% in the 150/2 combination group were urinary tract infections (13% in 150/2 combination group vs. 9% in dabrafenib monotherapy group). The incidence of paronychia was 2% in the 150/2 combination group and none in the dabrafenib monotherapy group.

Table 60: Summary of Sepsis and Infections in ≥ 2 Patients (All Treated Population)

AE	D N=53 n (%)	D + T 1 mg N=54 n (%)	D + T 2 mg N=55 n (%)
Any Infection	17 (38)	25 (50)	29 (60)
Bacterial Infection			
Urinary tract infection[1]	5 (9)	3 (6)	6 (15)
Folliculitis	1 (2)	1 (2)	4 (7)
Ear infection	0	1 (2)	3 (5)
Nasopharyngitis	0	5 (9)	2 (4)
Pneumonia	1 (2)	1 (2)	2 (4)
Upper respiratory tract infection	5 (9)	4 (7)	2 (4)
Cellulitis[2]	0	0	2 (4)
Viral Infection			
Gastroenteritis viral	0	2 (4)	0
Oral herpes	2 (4)	1 (2)	0
Fungal Infection			
Candidiasis	0	0	2 (4)

Source: ADAE.xpt
[1] Urinary tract infection includes escherechia urinary tract infection

Reference ID: 3422378

[2] Cellulitis included catheter site cellulitis
Abbreviations: D, dabrafenib; T, trametinib

Reviewer Comment:
The incidence of paronychia was decreased in the 150/2 combination group compared to single-agent trametinib. The incidence of infections is slightly increased in the 150/2 combination group compared to dabrafenib monotherapy.

Electrolytes

With dabrafenib, the incidence of hypophosphatemia was 37% and hyponatremia 8% (Tafinlar USPI). There were no electrolyte abnormalities reported with trametinib (Mekinist USPI).

Overall, electrolyte abnormalities occurred with a similar incidence in the 150/2 combination group and the dabrafenib monotherapy group (Table 61). The incidence of hyponatremia was higher in the 150/2 combination arm compared to dabrafenib monotherapy. Refer to Section 7.4.2.

Table 61: Summary of Electrolyte Abnormalities (All Treated Population)

AE	D N=53 n (%)	D + T 1 mg N=54 n (%)	D + T 2 mg N=55 n (%)
Any electrolyte	15 (30)	19 (40)	14 (30)
Hyponatremia	1 (2)	6 (11)	5 (9)
Hypokalemia	3 (6)	1 (2)	5 (9)
Hypomagnesemia	1 (2)	0	2 (4)
Hyperkalemia	4 (8)	1 (2)	1 (2)
Hypocalcemia	0	1 (2)	1 (2)
Hypercalcemia[1]	1 (2)	2 (4)	0
Hypophosphatemia[2]	4 (8)	6 (13)	0

Source: ADAE.xpt
[1]Hypercalcemia is a composite term which includes blood calcium increased
[2]Hypophosphatemia is a composite term which includes blood phosphorus decreased
Abbreviations: D, dabrafenib; T, trametinib

Hematopoietic Cytopenias

The incidence of anemia reported with trametinib was 38% (Mekinist USPI). Hematopoietic cytopenias were not reported with dabrafenib (Tafinlar USPI).

Neutropenia, anemia and thrombocytopenia were increased in the 150/2 combination group compared to the dabrafenib monotherapy group (Table 62). Refer to Section 7.4.2.

Table 62: Summary of Hematopoietic Cytopenias (All Treated Population)

AE	D N=53 n (%)	D + T 1 mg N=54 n (%)	D + T 2 mg N=55 n (%)
Any cytopenia	8 (16)	19 (40)	18 (36)
Neutropenia[1]	2 (4)	7 (13)	9 (17)
Anaemia[2]	4 (8)	12 (22)	8 (15)
Leukopenia[3]	2 (4)	2 (4)	3 (6)
Lymphopenia	1 (2)	0	3 (5)
Thrombocytopenia[4]	0	3 (6)	3 (5)

Source: ADAE.xpt
[1] Neutropenia is a composite term which includes neutrophil count decreased
[2] Anemia is a composite term which includes hemoglobin decreased
[3] Leukopenia is a composite term which includes white blood cell count decreased
[4] Thrombocytopenia is a composite term which includes platelet count decreased
Abbreviations: D, dabrafenib; T, trametinib

Depression

A higher incidence of depression was observed in patients taking the 150/2 combination (8%) compared to the patients taking dabrafenib monotherapy (2%) (Table 63). Depression can be related to the underlying disease.

Table 63: Summary of Depression (All Treated Population)

AE	D N=53 (%)	D + T 1 mg N=54 (%)	D + T 2 mg N=55 (%)
Depression	1 (2)	5 (10)	4 (8)

Source: ADAE.xpt
Abbreviations: D, dabrafenib; T, trametinib

Rhabdomyolysis

Rhabdomyolysis has been reported with trametinib at an incidence of < 10% (Mekinist USPI).

There was one case of rhabdomyolysis reported in the 150/2 combination group (2%) and none in the dabrafenib monotherapy group.

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 all treatment groups in Part C are the following:

- General disorders and administration site conditions (87% in the dabrafenib monotherapy group vs. 91% in the 150/1 combination group vs. 89% in the 150/2 combination group)
- Gastrointestinal disorders (85% vs. 76% vs. 85%)
- Skin and subcutaneous disorders (92% vs. 74% vs. 82%)
- Musculoskeletal and connective tissue disorders (89% vs. 67% vs. 71%)
- Nervous system disorders (62% vs. 61% vs. 62%)
- Investigations (42% vs. 44% vs. 40%)
- Psychiatry (23% vs. 26% vs. 35%)
- Neoplasms benign, malignant and unspecified (including cysts and polyps) (49% vs. 30% vs. 33%)
- Eye Disorders (25%vs. 31% vs. 31%)
- Blood and lymphatic (26% vs. 30% vs. 29%)
- Vascular (23% vs. 26% vs. 24%)
- Renal and Urinary (13% vs. 11% vs. 22%)
- Injury, poisoning and procedural complication (25% vs. 17% vs. 20%)
- Cardiac (17% vs. 9% vs. 13%)

Treatment emergent adverse events occurred in all patients in both the 150/2 combination group and in the dabrafenib monotherapy group. Table 64 lists TEAEs occurring at ≥ 10% incidence in the 150/2 combination group.

Table 64: Incidence of Treatment-Emergent Adverse events (≥ 10% of 150/2 Combination Group) (All Treated Population)

Body System	AE	D N=53 n (%)	D + T 1 mg N=54 n (%)	D + T 2 mg N=55 n (%)
General disorders and administration site conditions	Pyrexia	14 (26)	37 (69)	39 (71)
	Chills	9 (17)	27 (50)	32 (58)
	Fatigue	21 (40)	31 (57)	29 (53)
	Edema peripheral	9 (17)	13 (24)	16 (29)
Gastrointestinal disorders	Nausea	11 (21)	25 (46)	24 (44)
	Vomiting	8 (15)	23 (43)	22 (40)
	Diarrhea	15 (28)	14 (26)	20 (36)
	Constipation	6 (11)	9 (17)	12 (22)
	Abdominal pain upper	4 (8)	4 (7)	9 (16)
	Abdominal pain	7 (13)	8 (15)	8 (15)
	Dry mouth	3 (6)	6 (11)	6 (11)
Respiratory, thoracic and mediastinal disorders	Cough	11 (21)	6 (11)	16 (29)
	Oropharyngeal pain	0	4 (7)	7 (13)
Nervous system disorders	Headache	15 (28)	20 (37)	16 (29)
Skin and	Rash	19 (36)	11 (20)	15 (27)

Body System	AE	D N=53 n (%)	D + T 1 mg N=54 n (%)	D + T 2 mg N=55 n (%)
subcutaneous tissue disorders	Night sweats	3 (6)	8 (15)	13 (24)
	Dry skin	3 (6)	5 (9)	10 (18)
	Dermatitis acneiform	2 (4)	6 (11)	9 (16)
	Actinic keratosis	5 (9)	4 (7)	8 (15)
	Erythema	1 (2)	3 (6)	8 (15)
	Pruritus	7 (13)	6 (11)	6 (11)
	Rash generalized	4 (8)	2 (4)	6 (11)
Musculoskeletal and connective tissue disorders	Arthralgia	18 (34)	24 (44)	15 (27)
	Myalgia	12 (23)	13 (24)	12 (22)
	Back pain	6 (11)	6 (11)	10 (18)
	Muscle spasms	2 (4)	1 (2)	9 (16)
	Pain in extremity	10 (19)	6 (11)	9 (16)
Metabolism and nutrition disorders	Decreased appetite	10 (19)	16 (30)	12 (22)
	Dehydration	1 (2)	3 (6)	6 (11)
Psychiatric disorders	Insomnia	4 (8)	6 (11)	10 (18)
Nervous system disorders	Dizziness	5 (9)	7 (13)	9 (16)
Blood and lymphatic system disorders	Neutropenia	1 (2)	5 (9)	8 (15)
	Anemia	3 (6)	11 (20)	7 (13)
Infections and infestations	Urinary tract infection	5 (9)	3 (6)	7 (13)

Source: ADAE.xpt
Abbreviations: D. dabrafenib; T, trametinib

The composite term stomatitis, which included stomatitis, mouth ulceration, and mucosal inflammation, occurred in 9% of patients in the 150/2 combination group and none in the dabrafenib monotherapy group. The composite endpoint of peripheral edema, which included peripheral edema, edema and lymphedema, occurred in 44% (24/55) of patients in the 150/2 combination and in 17% (9/53) in the dabrafenib monotherapy group.

Reviewer Comment:
The assessment of differences in the incidences of common AEs between treatment groups may be confounded by the fact that in Part C, some patients received both the gelatin and the HPMC formulations of dabrafenib, some patients received only gelatin formulation and some patients received only HPMC formulation. The HPMC formulation causes > 20% increase in the exposure. The expectation is that the increased incidence of AEs in the 150/2 combination group will be higher in the Phase 3 study and in the post-marketing population in which only the HPMC formulation is used and is the current commercial formulation.

The clinical review also included safety analyses of Part C using a narrow-based Standardized MedDRA Queries (SMQ). Table 65 summarizes the incidence of narrow based SMQ terms in the three groups.

Table 65: Analyses of Narrow Standardized MedDRA Queries (All Treated Population)

	D N=53	**D + T 1 mg N=54**	**D + T 2 mg N=55**
	n (%)	n (%)	n (%)
Hematopoietic cytopenias	5 (9)	13 (24)	13 (24)
Hemorrhage terms (excl laboratory terms)	1 (2)	11 (20)	13 (24)
Hemorrhages	1 (2)	11 (20)	13 (24)
Oropharyngeal disorders	6 (11)	13 (24)	13 (24)
Oropharyngeal lesions, non-neoplastic, non-infectious and non-allergic	3 (6)	11 (20)	13 (24)
Drug related hepatic disorders - comprehensive search	4 (8)	19 (35)	11 (20)
Hematopoietic leukopenia	5 (9)	11 (20)	11 (20)
Hepatic disorders	4 (8)	19 (35)	11 (20)
Liver related investigations, signs and symptoms	3 (6)	19 (35)	10 (18)
Accidents and injuries	2 (4)	5 (9)	7 (13)
Hyponatremia/SIADH	1 (2)	6 (11)	5 (9)
Depression (excl suicide and self injury)	1 (2)	5 (9)	4 (7)
Depression and suicide/self-injury	1 (2)	5 (9)	4 (7)

Abbreviations: D, dabrafenib; T, trametinib

The clinical review included additional analyses of the following narrow-based SMQs:

- Hemorrhage
- Oropharyngeal disorders
- Hepatic disorders
- Hyponatremia/SIADH

Hemorrhage

The incidence of the SMQ hemorrhage was 2% in the dabrafenib monotherapy group, 20% in the 150/1 combination group and 24% in the 150/2 combination group. Grade 3 to Grade 5 hemorrhage occurred in one patient treated with dabrafenib monotherapy and three patients treated with the 150/2 combination. The patient treated with dabrafenib monotherapy had decreased hemoglobin which was not an SAE. All three patients treated with the 150/2 combination experienced SAEs of intracranial or gastric hemorrhage. The two patients who had intracranial hemorrhage died of the events. The patient with gastric hemorrhage required hospitalization. The reviewer considers these events to be major hemorrhagic events. Other hemorrhage AEs were mucocutaneous bleeding. Table 66 summarizes the most common AEs (preferred term) within the SMQ of hemorrhage.

Table 66: Incidence of Hemorrhage (Narrow Based SMQ) (All Treated Population)

	D N=53	**D + T 1 mg N=54**	**D + T 2 mg N=55**
	n (%)	n (%)	n (%)
Epistaxis	0	1 (2)	5 (9)
Contusion	0	1 (2)	3 (5)
Hemoptysis	0	0	2 (4)
Petechiae	0	1 (2)	2 (4)
Brain stem hemorrhage	0	0	1 (2)
Cerebral hemorrhage	0	0	1 (2)
Ecchymosis	0	2 (4)	1 (2)
Gastric hemorrhage	0	0	1 (2)
Hematuria	1 (2)	1 (2)	1 (2)
Hemoglobin decreased	1 (2)	1 (2)	1 (2)
Hemorrhage intracranial	0	0	1 (2)
Eye hemorrhage	0	1 (2)	0
Gingival bleeding	0	1 (2)	0
Hematoma	0	2 (4)	0
International normalized ratio increased	1 (2)	0	0
Lip hematoma	0	1 (2)	0
Prothrombin time prolonged	1 (2)	0	0
Vaginal hemorrhage	0	1 (2)	0
Vitreous hemorrhage	0	1 (2)	0

Source: ADAE.xpt
Abbreviations: D, dabrafenib; T, trametinib

Reviewer Comment:
Mucocutaneous bleeding was seen with single-agent trametinib treatment but no major hemorrhagic events were noted. The overall incidence of SMQ hemorrhage was higher in the 150/2 combination group when compared to single-agent trametinib and resulted in major hemorrhagic events. Of note in patients treated with the 150/2 combination are three patients who experienced SAEs, two with intracranial hemorrhage which were fatal. See Section 7.3.5 for further details.

Oropharyngeal Disorders

The incidence of oropharyngeal disorders was 11% in the dabrafenib monotherapy group and 24% in both the 150/1 and 150/2 combination groups. All were Grade 1 and Grade 2 toxicities. There were no SAEs. As summarized in Table 67, the most common AEs (preferred term) within the SMQ of oropharyngeal disorders for the 150/2 combination group were oropharyngeal pain (13%), dry mouth (11%) and stomatitis (4%).

Table 67: Incidence of Oropharyngeal Disorders (Narrow Based SMQ) by Treatment Group (All Treated Population)

	D N=53 n (%)	**D + T 1 mg N=54** n (%)	**D + T 2 mg N=55** n (%)
Oropharyngeal pain	0	4 (7)	7 (13)
Dry mouth	3 (6)	6 (11)	6 (11)
Stomatitis	0	1 (2)	2 (4)
Mouth ulceration	0	0	1 (2)
Oral candidiasis	0	1 (2)	1 (2)
Tongue coated	0	0	1 (2)
Gingival bleeding	0	1 (2)	0
Gingival recession	1 (2)	0	
Oral herpes	2 (4)	1 (2)	0
Pharyngitis streptococcal	0	1 (2)	0

Source: ADAE.xpt
Abbreviations: D, dabrafenib; T, trametinib

Reviewer Comment:
The overall incidence of SMQ oropharyngeal disorders in the 150/2 combination group was consistent with the incidence seen with single-agent trametinib.

Hepatic Disorders

The incidence of hepatic disorders was 8% in the dabrafenib monotherapy group, 35% in the 150/1 combination group and 20% in the 150/2 combination group. Grade 3 toxicities occurred in 14 patients, all in the two combination groups; 4 of these occurred in the 150/2 combination group and included increased alanine aminotransferase, aspartate aminotransferase and gamma-glutamyl transferase (GGT). Three were SAEs, all in the 150/1 combination group and included hyperbilirubinemia and ascites. As summarized in Table 68, the most common AEs (preferred term) within the SMQ of hepatic disorders for the 150/2 combination group were increased alanine and aspartate aminotransferase, increased alkaline phosphatase and increased GGT (each 9%).

Table 68: Incidence of Hepatic Disorders (Narrow Based SMQ) by Treatment Group (All Treated Population)

AE	**D N=53**	**D + T 1 mg N=54**	**D + T 2 mg N=55**
	n (%)	n (%)	n (%)
Alanine aminotransferase increased	1 (2)	11 (20)	5 (9)
Aspartate aminotransferase increased	1 (2)	10 (19)	5 (9)
Blood alkaline phosphatase increased	1 (2)	12 (22)	5 (9)

AE	**D N=53**	**D + T 1 mg N=54**	**D + T 2 mg N=55**
	n (%)	n (%)	n (%)
Gamma-glutamyltransferase increased	1 (2)	11 (20)	5 (9)
Hypoalbuminemia	1 (2)	4 (7)	2 (4)
Blood bilirubin increased	0	0	1 (2)
Drug-induced liver injury	0	0	1 (2)
Liver function test abnormal	1 (2)	0	1 (2)
Ascites	0	1 (2)	0
Hyperbilirubinemia	0	3 (6)	0
International normalized ratio increased	1 (2)	0	0
Jaundice	0	1 (2)	0
Prothrombin time prolonged	1 (2)	0	0
Transaminases increased	0	4 (7)	0

Source: ADAE.xpt
Abbreviations: D, dabrafenib; T, trametinib

Reviewer Comment:
The overall incidence of SMQ hepatic events was higher in the 150/2 combination group when compared to single-agent trametinib. See Section 7.3.5 for further details.

Hyponatremia / SIADH

The incidence of hyponatremia / SIADH was 2% in the dabrafenib monotherapy group 11% in the 150/1 combination group and 9% in the 150/2 combination group. Grade 3 toxicities occurred in 4 (8%) patients in the two combination groups and none in the dabrafenib monotherapy group. Two patients were hospitalized (Patient (b) (6)), one in each combination group. Two events were considered related by the investigator, one in each combination group.

Table 69: Patients with Hyponatremia (All Treated Population)

ID	**Treatment Arm**	**Toxicity Grade**	**Serious**	**Onset date**	**End date**	**Action**	**Related**	**Outcome**
BRF113220-Part C-(b) (6)	150/2	3	N	9	167	dose not changed	N	R
BRF113220-Part C-(b) (6)	150/2	3	N	111	146	dose not changed	N	R
BRF113220-Part C-(b) (6)	150/1	1	N	141		not applicable	N	NR
BRF113220-Part C-(b) (6)	150/1	3	N	17		dose not changed	N	NR
BRF113220-Part C-(b) (6)	150/2	3	Y	113	155	drug interrupted	Y	R
BRF113220-Part C-(b) (6)	150/1	3	Y	42	57	not applicable	N	R

ID	Treatment Arm	Toxicity Grade	Serious	Onset date	End date	Action	Related	Outcome
BRF113220-Part C-(b) (6)	150/2	3	N	393	417	drug interrupted	N	R
BRF113220-Part C-(b) (6)	150/1	3	N	28	35	drug interrupted	N	R
BRF113220-Part C-(b) (6)	150/1	3	N	37	40	dose not changed	Y	R
BRF113220-Part C-(b) (6)	150/1	1	N	44	51	dose not changed	N	R
BRF113220-Part C-(b) (6)	150	1	N	175	177	dose not changed	N	R
BRF113220-Part C-(b) (6)	150/2	1	N	66	68	dose not changed	N	R

Source: ADAE.xpt
Abbreviations: N, no; R, recovered/resolved; Y, yes

Reviewer Comment:
Serum osmolality, urine osmolality and urine sodium concentration were not collected, therefore diagnosis of SIADH cannot be made in these patients with hyponatremia. Recommend including hyponatremia in the label and post-marketing surveillance for SIADH.

The review of safety evaluated the incidence of AEs based on a higher incidence in the dabrafenib monotherapy arm. Alopecia, hyperkeratosis, PPES and cuSCC were decreased in the 150/2 combination group compared to the dabrafenib monotherapy group, as shown in Table 70.

Table 70: Incidence of Treatment-Emergent Adverse Events in the Dabrafenib Monotherapy Group (All Treated Population)

Body System	AE	D N=53 n (%)	D + T 1 mg N=54 n (%)	D + T 2 mg N=55 n (%)
Skin and subcutaneous tissue disorders	Alopecia	18 (34)	5 (9)	3 (5)
	Hyperkeratosis	16 (30)	3 (6)	5 (9)
	Pruritus generalized	8 (15)	3 (6)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Skin papilloma	8 (15)	4 (7)	2 (4)
	Keratoacanthoma	6 (11)	0	1 (2)
	Squamous cell carcinoma of skin	6 (11)	0	1 (2)
	Squamous cell carcinoma	4 (8)	1 (2)	2 (4)
Nervous system disorders	Paresthesia	6 (11)	0	2 (4)
Infections and infestations	Upper respiratory tract infection	5 (9)	4 (7)	2 (4)

Body System	AE	D N=53 n (%)	D + T 1 mg N=54 n (%)	D + T 2 mg N=55 n (%)
General disorders and administration site conditions	Axillary pain	4 (8)	2 (4)	1 (2)
	Pain	4 (8)	6 (11)	2 (4)
Metabolism and nutrition disorders	Hyperkalemia	4 (8)	1 (2)	1 (2)
	Hypophosphatemia	4 (8)	5 (9)	0

Source: ADAE.xpt
Abbreviations: D, dabrafenib; T, trametinib

Reviewer Comment:
There was a decrease in the incidence of SCC, keratoacanthoma, hyperkeratosis and PPES in the 150/2 combination group. The decrease in cuSCC is not statistically significant (Refer to Section 7.3.5).

The review of safety evaluated additional potential toxicities of the 150/2 combination treatment 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.

Table 71 summarizes the incidence of high level terms occurring in ≥ 10% of the 150/2 combination group compared to the dabrafenib monotherapy treatment group. The common high level terms were febrile disorders (71%), feelings and sensations (61%), nausea and vomiting symptoms (56%) and asthenic conditions (53%).

Table 71: Incidence of Treatment Emergent Adverse Events (> 10% of 150/2 Combination Treatment Group) by High Level Terms (All Treated Population)

High Level Term	D N=53 n (%)	D + T 1 mg N=54 n (%)	D + T 2 mg N=55 n (%)
Febrile disorders	14 (26)	37 (69)	39 (71)
Feelings and sensations NEC	9 (17)	27 (50)	33 (60)
Nausea and vomiting symptoms	14 (26)	29 (54)	31 (56)
Asthenic conditions	23 (43)	32 (59)	29 (53)
Diarrhea (excl infective)	15 (28)	14 (26)	20 (36)
Coughing and associated symptoms	13 (25)	10 (19)	17 (31)
Apocrine and eccrine gland disorders	6 (11)	13 (24)	16 (29)
Gastrointestinal and abdominal pains (excl oral and throat)	10 (19)	13 (24)	16 (29)
Edema NEC	9 (17)	15 (28)	16 (29)
Gastrointestinal atonic and hypomotility disorders NEC	7 (13)	10 (19)	14 (25)
Dermatitis and eczema	2 (4)	3 (6)	10 (18)

High Level Term	**D N=53** n (%)	**D + T 1 mg N=54** n (%)	**D + T 2 mg N=55** n (%)
Disturbances in initiating and maintaining sleep	4 (8)	6 (11)	10 (18)
Liver function analyses	3 (6)	18 (33)	10 (18)
Neurological signs and symptoms NEC	5 (9)	7 (13)	10 (18)
Upper respiratory tract signs and symptoms	2 (4)	7 (13)	10 (18)
Acnes	2 (4)	7 (13)	9 (16)
Muscle related signs and symptoms NEC	2 (4)	1 (2)	9 (16)
Sensory abnormalities NEC	2 (4)	7 (13)	9 (16)
Visual disorders NEC	4 (8)	9 (17)	9 (16)
Erythema	1 (2)	7 (13)	8 (15)
Neutropenia	1 (2)	5 (9)	8 (15)
Skin preneoplastic conditions NEC	5 (9)	4 (7)	8 (15)
Anemia NEC	3 (6)	11 (20)	7 (13)
Bacterial infections NEC	1 (2)	1 (2)	7 (13)
Urinary tract infections	5 (9)	5 (9)	7 (13)
Bladder and urethral symptoms	2 (4)	3 (6)	6 (11)
Disturbances in consciousness NEC	1 (2)	2 (4)	6 (11)
Oral dryness and saliva altered	3 (6)	6 (11)	6 (11)
Tissue enzyme analyses NEC	1 (2)	12 (22)	6 (11)
Total fluid volume decreased	1 (2)	4 (7)	6 (11)

Source: ADAE.xpt
Abbreviations: D, dabrafenib; T, trametinib

Table 72 summarizes the incidence of high level group terms occurring in the 150/2 combination group compared to the dabrafenib monotherapy treatment group. The common high level group terms occurring in the 150/2 combination group are general system disorders (84%), body temperature conditions (71%) and gastrointestinal signs and symptoms (69%).

Table 72: Incidence of Treatment Emergent Adverse Events (≥ 10% of 150/2 Combination Treatment Group) by High Level Group Term (All Treated Population)

High Level Group Term	**D N=53** n (%)	**D + T 1 mg N=54** n (%)	**D + T 2 mg N=55** n (%)
General system disorders NEC	33 (62)	47 (87)	46 (84)
Body temperature conditions	14 (26)	37 (69)	39 (71)
Gastrointestinal signs and symptoms	23 (43)	33 (61)	38 (69)
Gastrointestinal motility and defecation conditions	20 (38)	19 (35)	27 (49)
Respiratory disorders NEC	19 (36)	20 (37)	27 (49)
Muscle disorders	14 (26)	18 (33)	23 (42)
Infections - pathogen unspecified	15 (28)	17 (31)	21 (38)
Neurological disorders NEC	15 (28)	14 (26)	21 (38)
Electrolyte and fluid balance conditions	9 (17)	7 (13)	14 (25)

High Level Group Term	**D N=53** n (%)	**D + T 1 mg N=54** n (%)	**D + T 2 mg N=55** n (%)
Upper respiratory tract disorders (excl infections)	5 (9)	11 (20)	11 (20)
Bacterial infectious disorders	1 (2)	3 (6)	10 (18)
Hepatobiliary investigations	3 (6)	18 (33)	10 (18)
Sleep disorders and disturbances	4 (8)	6 (11)	10 (18)
White blood cell disorders	4 (8)	5 (9)	10 (18)
Urinary tract signs and symptoms	5 (9)	5 (9)	9 (16)
Vision disorders	4 (8)	11 (20)	9 (16)
Anemia nonhaemolytic and marrow depression	3 (6)	11 (20)	7 (13)
Enzyme investigations NEC	1 (2)	12 (22)	7 (13)
Injuries NEC	3 (6)	5 (9)	7 (13)
Cardiac arrhythmias	3 (6)	1 (2)	6 (11)
Salivary gland conditions	3 (6)	6 (11)	6 (11)

Source: ADAE.xpt
Abbreviations: D, dabrafenib; T, trametinib

Reviewer comments:
The AEs observed in the trial with the combination of dabrafenib and trametinib 2mg had higher incidences compared to dabrafenib monotherapy and in cross-study comparisons to AEs with trametinib as single-agent. The higher incidences of AEs may reflect the additive or synergistic effects of the combination of dabrafenib and trametinib.

7.4.2 Laboratory Findings

Laboratory testing of clinical chemistry parameters (sodium, potassium, BUN, creatinine, glucose, calcium, ALT, AST, alkaline phosphatase, total bilirubin, albumin, total protein, and LDH) and hematology parameters (WBC with differential, hemoglobin, platelet count) was performed at baseline and on Day 1 of each treatment cycle. As summarized in Table 73, the most common (≥50%) laboratory abnormalities (all Grades) in the 150/2 combination group were hyperglycemia (58% in the 150/2 combination group vs. 49% in the dabrafenib monotherapy group), increased AST (60% vs. 15%), decreased albumin (53% vs. 23%), anemia (55% vs. 28%), increased alkaline phosphatase (60% vs. 26%), hyponatremia (55% vs. 36%), lymphopenia (55% vs. 40%), neutropenia (55% vs. 9%), and leukopenia (62% vs. 21%).

Table 73: Treatment-Emergent Laboratory Abnormalities [>10% All Grades or > 2% Grades 3 or 4) (All Treated Population)

Test	D N=53		D + T 1 mg N=54		D + T 2 mg N=55	
	All Grades n (%)	Grades 3 and 4 n (%)	All Grades n (%)	Grades 3 and 4 n (%)	All Grades n (%)	Grades 3 and 4 n (%)
Liver Function Tests						
Increased AST	8 (15)	0	29 (54)	0	33 (60)	3 (5)
Increased alkaline phosphatase	14 (26)	1 (2)	36 (67)	3 (6)	33 (60)	1 (2)
Increased ALT	6 (11)	0	19 (35)	2 (4)	23 (42)	2 (4)
Increased total bilirubin	0	0	4 (7)	2 (4)	8 (15)	0
Chemistry						
Hyperglycemia	26 (49)	1 (2)	36 (67)	3 (6)	32 (58)	3 (5)
Increased GGT	20 (38)	1 (2)	29 (54)	9 (17)	31 (56)	6 (11)
Hyponatremia	19 (36)	1 (2)	26 (48)	8 (15)	30 (55)	6 (11)
Hypoalbuminemia	12 (23)	0	23 (43)	1(2)	29 (53)	0
Hypophosphatemia	21 (40)	0	22 (41)	6 (11)	26 (47)	3 (5)
Hypokalemia	12 (23)	3 (6)	8 (15)	1 (2)	16 (29)	1 (2)
Increased creatinine	5 (9)	0	11 (20)	1 (2)	13 (24)	3 (5)
Hypomagnesemia	3 (6)	0	1 (2)	0	10 (18)	1(2)
Hyperkalemia	8 (15)	2 (4)	12 (22)	0	10 (18)	0
Hypercalcemia	2 (4)	0	10 (19)	1(2)	8 (15)	0
Hypocalcemia	5 (9)	0	11 (20)	0	7 (13)	0
Hypernatremia	2 (4)	0	4 (7)	0	6 (11)	0
Hematology						
Anemia	15 (28)	0	25 (46)	4 (7)	30 (55)	2 (4)
Lymphopenia	21 (40)	3 (6)	32 (59)	9 (17)	30 (55)	12 (22)
Leukopenia	11 (21)	0	25 (46)	2 (4)	34 (62)	3 (5)
Neutropenia	5 (9)	1 (2)	20 (37)	1 (2)	30 (55)	7 (13)
Thrombocytopenia	4 (8)	0	17 (31)	1 (2)	17 (31)	2 (4)

Source: ADLB.xpt
Abbreviations: ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; D, dabrafenib; GGT, Gamma glutamyltransferase; T, trametinib

Reviewer Comment:
Most of the laboratory abnormalities occurred at a higher incidence in the 150/2 combination group as compared to the dabrafenib monotherapy group and at a higher incidence than trametinib single-agent. Recommend to include in the label.

7.4.3 Vital Signs

Vital signs were collected at baseline and every three weeks thereafter. The majority of patients in all treatment groups had normal temperatures recorded during clinic visits. The incidence of worst-case temperature increases (≥ 38°C) was higher in the 150/2 combination group compared with the dabrafenib monotherapy group.

The incidence of heart rate decreases to <60 bpm were generally similar across the three treatment groups, whereas the incidence of heart rate increases to >100 bpm was higher in the 150/2 combination group compared with the dabrafenib monotherapy group.

For blood pressure, refer to section 7.3.5.

Reviewer Comment:
Increase in temperature and heart rates occurred more frequently in the 150/2 combination group compared to the dabrafenib monotherapy group and is likely related to the higher incidence of pyrexia.

7.4.4 Electrocardiograms (ECGs)

There were seven (13%) patients with an increase of the QTcF to ≥ 501 msec or > 60 msec from baseline in the 150/2 combination group compared to two (4%) patients in the dabrafenib monotherapy group.

In the updated analyses provided by the Applicant, eight (15%) patients in the 150/2 combination group and two (4%) patients in the dabrafenib monotherapy group had a QT prolongation (Response to FDA Information Request, November 21, 2013). In these patients, the time to onset of QTc prolongation from the start of study treatment ranges from two weeks to approximately two years. Two patients had relevant associated adverse events of atrial fibrillation for which the doses were interrupted. There did not appear to be a trend in relevant associated adverse events coinciding with QTc prolongation events. Around the time of the QTc prolongation events, there were no reported dose interruptions, reductions or discontinuation due to the events themselves but rather due to either associated adverse events or concomitant medical conditions. None of the QTc prolongation events were deemed clinical significant by the Investigator and the events resolved to values within normal limit on subsequent ECGs.

Reviewer Comment:
In the single-agent trials of dabrafenib and trametinib, the effect of these drugs on the QT interval was inconclusive. The Applicant is performing dedicated QT studies to evaluate the effect of single-agent dabrafenib and single-agent trametinib on cardiac repolarization as a post-marketing requirement. In this trial, there was a higher incidence of QT prolongation with the 150/2 combination group compared to the dabrafenib group with no adverse outcomes. As discussed with the Clinical Pharmacology Reviewer, a separate inclusion in the label is not required at this time. Further requirements for a QT trial for the 150/2 combination will be assessed after review on the ongoing trials.

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7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies or clinical trials in this application.

7.4.6 Immunogenicity

There are no immunogenicity data in this application.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The randomized component of Part C compared two doses of trametinib (1mg and 2 mg) in combination with dabrafenib against dabrafenib monotherapy. Review of the adverse events in the safety assessments were performed for both the dose combinations and revealed that the safety profile for the combination of dabrafenib and trametinib 2 mg dose showed increased incidences compared to the combination of dabrafenib and trametinib 1 mg dose.

The Clinical Pharmacology Review identified an exposure-response relationship between pyrexia and the major metabolite for dabrafenib, hydroxy-dabrafenib trough concentration. Refer to Clinical Pharmacology review for details.

7.5.2 Time Dependency for Adverse Events

Please see Section 7.3.5 for analyses of time dependency for AEs. AEs occurred throughout the duration of the clinical trial.

7.5.3 Drug-Demographic Interactions

Subgroup analyses based on race was not performed as the study population was almost entirely (99%) Caucasian. Subgroup analyses based on age and gender is shown below.

In the pooled 150/2 population the proportion of patients experiencing any AE was similar in the patients aged <65 years and those aged ≥ 65 years (

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Table 74). A lower proportion of patients aged <65 years as compared to subjects ≥ 65 years reported SAEs, drug-related SAEs, and AEs leading to permanent discontinuation of study drug, dose reduction and dose interruption.

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Table 74: Adverse Events by Age (All Treated Population or ISS Database)

	Treatment Groups, n (%)									
	Combination Therapy				Monotherapy					
	BRF113220 Part C		BRF113220 Pooled		Trametinib ISS Update		Dabrafenib ISS Update		BRF113220 Part C	
Dabrafenib	150 mg BID		150 mg BID		--		150 mg BID		150 mg BID	
Trametinib	2 mg QD		2 mg QD		2 mg QD		--		--	
Age Group	<65 years	≥65 years	<65 years	≥65 years	<65 years	≥65 years	<65 years	≥65 years	<65 years	≥65 years
N	44	11	160	42	249	80	460	126	41	12
Any AE, n (%)	**44 (100)**	**11 (100)**	**159 (>99)**	**42 (100)**	**248 (>99)**	**78 (98)**	**441 (96)**	**125 (>99)**	**41 (100)**	**12 (100)**
Drug-related AE	44 (100)	11 (100)	144 (90)	40 (95)	240 (96)	74 (93)	395 (86)	122 (97)	39 (95)	12 (100)
AEs leading to permanent discontinuation of study drug	4 (9)	1 (9)	11 (7)	6 (14)	20 (8)	12 (15)	10 (2)	7 (6)	1 (2)	0
AEs leading to dose reduction	20 (45)	7 (64)	70 (44)	27 (64)	56 (22)	29 (36)	69 (15)	31 (25)	9 (22)	2 (17)
AEs leading to dose interruption	28 (64)	9 (82)	96 (60)	30 (71)	85 (34)	32 (40)	135 (29)	57 (45)	13 (32)	5 (42)
Any SAE, n (%)	**27 (61)**	**7 (64)**	**84 (53)**	**25 (60)**	**56 (22)**	**18 (23)**	**118 (26)**	**56 (44)**	**8 (20)**	**5 (42)**
Drug-related SAE	19 (43)	4 (36)	58 (36)	20 (48)	24 (10)	9 (11)	73 (16)	41 (33)	5 (12)	5 (42)
Fatal SAE	1 (2)	2 (18)	2 (1)	5 (12)	3 (1)	2 (3)	5 (1)	3 (2)	0	0
Drug-related fatal SAE	0	0	0	1 (2)	1 (<1)	0	0	1 (<1)	0	0

Source: Table 59, Summary Clinical Safety (Updated in Response to FDA Information Request, October 11, 2013)
Abbreviations: BID=Twice daily; QD=Once daily.

Analysis of AEs by gender was performed for the pooled 150/2 population only and not for the 150/2 combination or dabrafenib monotherapy groups due to the small numbers of patients in these subpopulations. In the pooled 150/2 population the proportion of patients experiencing AEs, drug-related AEs and AEs leading to permanent discontinuation of study drug were similar in the male and female subgroups (Table 75).

AEs leading to dose reduction and dose interruption were higher in females than in males, while SAEs and drug-related SAEs were higher in males than in females. The same trends were observed in the trametinib ISS population; SAE and drug-related SAEs were similar between genders in this population. In general, the most common AEs (>25%) for the 150/2 combination therapy arms by gender were consistent with the most common AEs observed in the overall study population.

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Table 75: Adverse Events by Gender (All Treated Population or ISS Database)

	Combination Therapy				Monotherapy					
	BRF113220 Part C		BRF113220 Pooled		Trametinib ISS Update		Dabrafenib ISS Update		BRF113220 Part C	
Dabrafenib	150 mg BID		150 mg BID		--		150 mg BID		150 mg BID	
Trametinib	2 mg QD		2 mg QD		2 mg QD		--		--	
Gender	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
N	21	34	86	116	131	198	ND	ND	24	29
Any AE, n (%)	**21 (100)**	**34 (100)**	**85 (99)**	**116 (100)**	**130 (>99)**	**196 (99)**	**ND**	**ND**	**24 (100)**	**29 (100)**
Drug-related AE	21 (100)	34 (100)	79 (92)	105 (91)	125 (95)	189 (95)	ND	ND	24 (100)	27 (93)
AEs leading to permanent discontinuation of study drug	3 (14)	2 (6)	9 (10)	8 (7)	11 (8)	21 (11)	ND	ND	0	1 (3)
AEs leading to dose reduction	12 (57)	15 (44)	45 (52)	52 (45)	38 (29)	47 (24)	ND	ND	5 (21)	6 (21)
AEs leading to dose interruption	17 (81)	20 (59)	62 (72)	64 (55)	50 (38)	67 (34)	ND	ND	10 (42)	8 (28)
Any SAE, n (%)	**12 (57)**	**22 (65)**	**44 (51)**	**65 (56)**	**31 (24)**	**43 (22)**	**ND**	**ND**	**8 (33)**	**5 (17)**
Drug-related SAE	7 (33)	16 (47)	29 (34)	49 (42)	18 (14)	15 (8)	ND	ND	7 (29)	3 (10)
Fatal SAE	1 (5)	2 (6)	3 (3)	4 (3)	1 (<1)	4 (2)	ND	ND	0	0
Drug-related fatal SAE	0	0	0	1 (<1)	1 (<1)	0	ND	ND	0	0

Source: Table 61, Summary Clinical Safety (Updated: Response to FDA Information Request, October 11, 2013)
Abbreviations: BID=Twice daily ; QD=Once daily.

7.5.4 Drug-Disease Interactions

Refer to Clinical Pharmacology Review.

7.5.5 Drug-Drug Interactions

Refer to Clinical Pharmacology Review.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The Applicant did not conduct carcinogenicity studies with the combination of dabrafenib and trametinib.

7.6.2 Human Reproduction and Pregnancy Data

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

7.6.3 Pediatrics and Assessment of Effects on Growth

The combination of dabrafenib and trametinib has not been studied in a pediatric population. The Applicant is requesting waiver of pediatric studies for this sNDA based on an exemption from PREA requirements as the combination received orphan drug designation.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Applicant reported one patient (Patient (b) (6)) treated with the combination of dabrafenib and trametinib who accidentally received dabrafenib at a dose of 225 mg BID for a period of 22 days and this event was considered as overdose by the investigator. The patient experienced multiple AEs including Grade 1 blurred vision, Grade 1 GGT increase, Grade 2 alkaline phosphatase increase, and Grade 1 diarrhea which were considered related to study drug by the investigator.

There is no evidence from the available data that treatment with the combination can result in dependence.

7.7 Additional Submissions / Safety Issues

Analysis of safety data by capsule shell type was also performed (Table 76). Overall, the most common AEs and AEs leading to dose modifications or discontinuation were similar in subjects receiving HPMC (and gelatin) versus gelatin only capsules. SAE rates appeared to be of higher incidence in patients who were on the combination arms and received only gelatin capsules, driven mostly by pyrexia and chills. The frequency of Grade 3 and Grade 4 events was similar in patients receiving HPMC (and gelatin) capsules as compared with gelatin only in part C.

Table 76: Overview Adverse Events Gelatin and HPMC

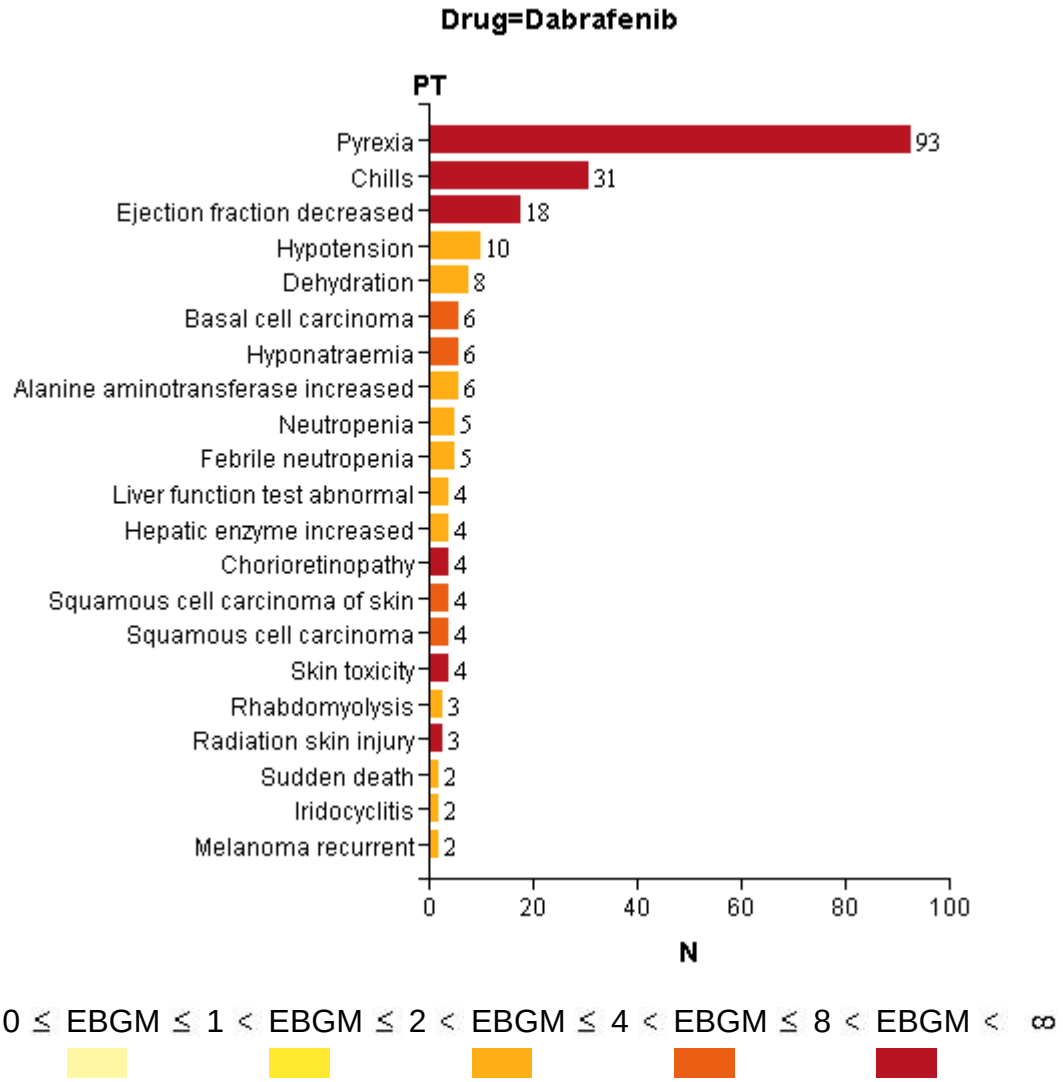
Preferred Term	Dabrafenib 150 mg BID / Trametinib 2 mg QD		
	Dabrafenib -Gelatin		Dabrafenib -HPMC
	Part C (N=55)	Part B (N=24)	Part D (N=39)
Any AE	**55(100)**	**24 (100)**	**38 (97)**
AEs related to study treatment	55 (100)	23 (96)	37 (95)
AEs leading to discontinuation	5 (9)	2 (8)	4 (10)
AEs leading to dose reduction	27 (49)	17 (71)	24 (62)
AEs leading to dose interruption	37 (67)	18 (75)	28 (72)
Any SAE	**34 (62)**	**15 (63)**	**25 (64)**
SAEs related to study treatment	23 (42)	13 (54)	24 (62)
Fatal SAEs	3 (5)	1 (4)	0
Fatal SAEs related to study treatment	0	1 (4)	0

Source: Table 65, Summary Clinical Safety
Abbreviations: BID=Twice daily; HPMC=Hydroxypropyl-methylcellulose; QD=Once daily.

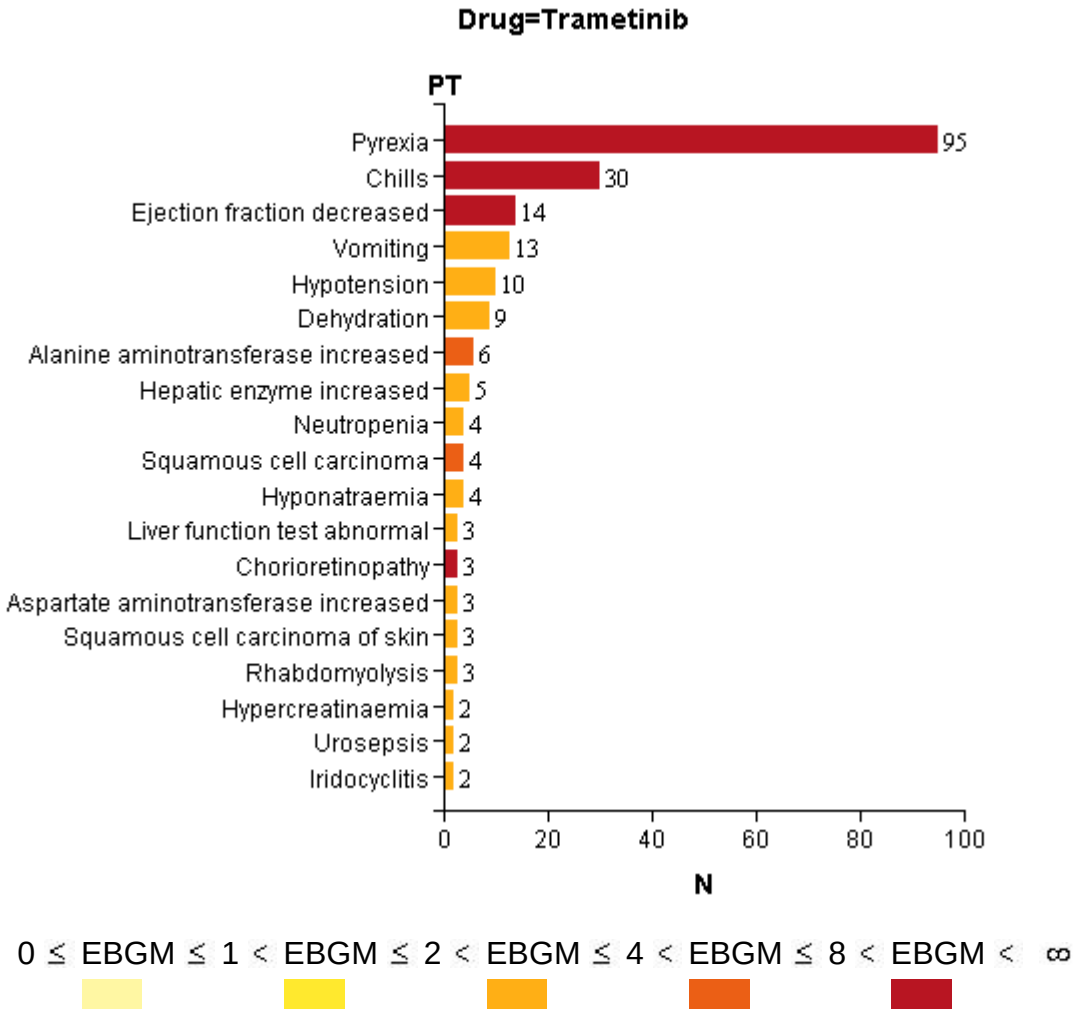
8 Postmarket Experience

An exploratory analysis of most common PTs in post-marketing reports is shown below for single-agent dabrafenib and trametinib.

Dabrafenib


Drug=Dabrafenib
PT
Pyrexia 93
Chills 31
Ejection fraction decreased 18
Hypotension 10
Dehydration 8
Basal cell carcinoma 6
Hyponatraemia 6
Alanine aminotransferase increased 6
Neutropenia 5
Febrile neutropenia 5
Liver function test abnormal 4
Hepatic enzyme increased 4
Chorioretinopathy 4
Squamous cell carcinoma of skin 4
Squamous cell carcinoma 4
Skin toxicity 4
Rhabdomyolysis 3
Radiation skin injury 3
Sudden death 2
Iridocyclitis 2
Melanoma recurrent 2
0 20 40 60 80 100
N
0 ≤ EBGM ≤ 1 < EBGM ≤ 2 < EBGM ≤ 4 < EBGM ≤ 8 < EBGM < ∞

Trametinib



Reviewer Comment:
Analysis of postmarketing data suggests that the benefit-risk of dabrafenib single-agent and trametinib single-agent remains positive. The overall safety profile of dabrafenib single-agent and trametinib single-agent is consistent with the current labeling information. Cardiomyopathy in trametinib patients is currently being assessed in a PMR.

9 Appendices

9.1 Literature Review/References

Bristow B, Casil J, Sorvillo F, Basurto-Davila D
Kuo T. Melanoma-related mortality and productivity losses in the USA, 1990-2008. Melanoma Res. 2013 Aug; 23(4):331-5.

Davies H, Bignell GR, Cox C et al.Mutations in BRAF gene in human cancer. Nature 2002; 417: 940-54

Gray-Schopfer V, Wellbrock C, Marais R. Melanoma biology and new targeted therapy. Nature 2007 22; 445(7130):851-7.

Hingorani SR, Jacobetz MA, Robertson GP. Suppression of BRAF (V599E) in human melanoma abrogates transformation. Cancer Res. 2003 Sep 1; 63(17):5198-202.

Howlader N, Noone AM, Krapcho M, Garshell J, Neyman N, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2010, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2010/, based on November 2012 SEER data submission, posted to the SEER web site, April 2013.

Mekinist, GlaxoSmithKline, USPI.

Proleukin, Prometheus Laboratories, Inc., USPI

Rubinstein JC, Sznol M, Pavlick AC, Ariyan S, Cheng E, Bacchiocchi A, Kluger HM, Narayan D, Halaban R. Incidence of the V600K mutation among melanoma patients with BRAF mutations, and potential therapeutic response to the specific BRAF inhibitor PLX4032. J Transl Med 2010 Jul 14;8:67.

Siegel R, Naishadham D, Jemal Al. Cancer statistics, 2013. CA Cancer J Clin. 2013 Jan; 63(1):11-30.

Tafinlar, GlaxoSmithKline, USPI.

Yervoy, Bristol-Myers Squibb Company, USPI.

Zelboraf, Hoffman-La Roche, USPI.

9.2 Labeling Recommendations

Refer to labeling of Tafinlar and Mekinist.

Reviewer Comment:
The Applicant has provided two separate labels, one for dabrafenib and the other for trametinib, and proposes adding the efficacy and safety results of the dabrafenib and trametinib combination treatment in both the labels. Labeling discussions are ongoing.

9.3 Advisory Committee Meeting

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

9.4 Financial Disclosure Template

Clinical Investigator Financial Disclosure
Review Template

Application Number: sNDA 202806, sNDA 204114
Submission Date(s): 07/08/2013, 07/09/2013
Applicant: GlaxoSmithKline
Product: Dabrafenib (Tafinlar) + Trametinib (Mekinist) combination

Reviewer: Maitreyee Hazarika, MD
Date of Review: 07/31/2013
Covered Clinical Study (Name and/or Number): BRF 1113220

Was a list of clinical investigators provided:	Yes ☐ X	No ☐ (Request list from Applicant)
Total number of investigators identified: 295		
Number of investigators who are sponsor employees (including both full-time and part-time employees): no reported cases		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: No disclosures. GSK states that they have a company policy and do not compensate clinical investigators in such a way that the total amount could vary with the outcome of the study		

Reference ID: 3422378

Significant payments of other sorts: 1. [redacted] (b) (6) Proprietary interest in the product tested held by investigator: None reported Significant equity interest held by investigator in sponsor of covered study: None reported		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ X	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ X	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) Not checked.		
Is an attachment provided with the reason:	Yes ☐ X	No ☐ (Request explanation from Applicant)

Discuss whether the Applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.[1] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

In accordance with 21 CFR 54.2, the Applicant submitted a list of the BRF113220 study investigators attached to FDA form 3454 certifying that the clinical 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.

The Applicant relied upon investigator financial interest information provided by the investigators through questionnaires. No investigator had a financial interest in the company at the time they started their participation in the covered study. The appropriate due diligence process as per the Applicant's SOPs, which is up to 3 documented attempts to collect, was carried out. It is the policy of the Applicant not to

[1] See [web address].

allow the participation of investigators in a clinical study if they, their spouse or dependent children have proprietary interest in the tested product, and not to compensate investigators in a way that the amount of compensation received could be affected by the outcome of the study.

Of 295 investigators (principal and sub-investigators) in the BRF113220 trial, 269 investigators had no disclosures, 25 investigators were listed by the Applicant on List (B) to Form 3454 and one investigator had received significant payments.

For the 25 investigators, the Applicant states that based on information available internally, none of the clinical investigators listed had disclosable interests of the type described in 21 CFR 54.2(a) (compensation potentially affected by the outcome of the study). In addition, based on whatever information may have been obtained at the threshold from some or all of the listed clinical investigators, no one listed had a disclosable interest of the type described in 21 CFR 54.2(b) (significant equity interest in the study sponsor) or 21 CFR 54.2(c) (proprietary interest in the tested product). However, the Applicant was unable to obtain timely information from them regarding updated equity interest, proprietary interest information and/or information about payments of other sorts.

One investigator, [redacted] (b) (6) was the Sub-Investigator for center [redacted] (b) (6), which recruited [redacted] (b) (6) subjects from a total of 422 Subjects, which was [redacted] (b) (6) of the total recruitment. This subinvestigator received a significant payment, i.e. > $25,000, consisting of grants to fund ongoing research ($65,632), honoraria ($1,750) and other ($263.61), a total payment of $67,645.61. The Applicant conducted analyses of the BRF113220 trial excluding the data from study site [redacted] (b) (6) on disposition, the most frequent AEs and Kaplan-Myer estimates of investigator-assessed PFS, results of which were consistent with the ITT population.

9.5 Specific Dose Modification Guidelines

Dose modification guidelines for specific adverse events provided in the protocol for Trial BRF113220 are included below.

Dose Modification Guidelines for Management of Neutropenia

Grade	ANC value /mm^3	Management of Neutropenia	GSK2118436 Dose Adjustment
1	1500-LLN	• Monitor per protocol time and events table	Continue at current dose
2	1000-<1500	• Re-check ANC in 1 week. If improvement to Grade 1, continue to monitor per protocol Time and Events Table. • If stable at Grade 2, monitor ANC every 2 weeks until resolution to Grade 1 or until stable for 4 weeks • If worsens to Grade 3 or 4 follow below.	Any occurrence: continue at current dose
3	500-<1000	• Re-check ANC at least weekly during dose interruption. • If resolved to Grade 1, re-check ANC 3 days after rechallenge with GSK2118436 and then 1 week later.	• Any occurrence: hold until return to Grade 1, then 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	<500	• Re-check ANC at least weekly • If resolved to Grade 1, re-check 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

Dose Modification Guidelines for Management of Fever

	Definition	Dose Modification Algorithms	GSK2118436 Dose Adjustment
Complicated fever. (≥38.5°C or 101.3°F)	Grade ≥3 or any Grade with signs and symptoms including: rigors, chills, dehydration, hypotension, dizziness or weakness	• Subject must be evaluated in clinic • Labs: Obtain blood sample to assess ANC, serum creatinine and BUN 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. • Re-check ANC 1 week after the start of fever; encourage subject to take oral temperature daily for 4 weeks after restarting GSK2118436.	• Interrupt GSK2118436 and GSK1120212 immediately and hold until fever resolves to <38.0°C or 100.4°F and accompanying symptoms resolve • At rechallenge, re-start dose of GSK2118436 and GSK1120212 at original dose level • Co-adminster oral steroids when GSK2118436 and GSK1120212 are re-started. Continue subject on course of steroids, as clinically indicated. • If steroids have been tapered and fever recurs, restarting the subject on steroids is recommended. However, Investigator may consider dose reducing GSK2118436 and/or GSK1120212, as clinically indicated.

	Definition	Dose Modification Algorithms	GSK2118436 Dose Adjustment
Uncomplicated Fever (≥38.5°C or 101.3°F)	defined as Grade≤ 2 without signs and symptoms as described above	• Encourage oral hydration. • If subject is seen in the clinic : Obtain blood sample to assess ANC, serum creatinine and BUN 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. • Re-check ANC 1 week after the start of fever; encourage subject to take oral temperature daily for 4 weeks after restarting GSK2118436.	• Hold until fever resolves to <38.0°C or 100.4°F • At rechallenge, re-start dose of GSK2118436 at original dose level. • When restarting drug, administer acetaminophen 500 mg or ibuprofen 400 mg (or suitable alternative) prophylactically BID with study drug for 2-3 days.[1] • If fever recurs after co-administration of acetaminophen or ibuprofen, switch to oral steroids when GSK2118436 is re-started. Continue subject on course of steroids, as clinically indicated. • If steroids have been tapered and fever recurs, restarting the subject on steroids is recommended. However, Investigator may consider dose reducing GSK2118436 and/or GSK1120212, as clinically indicated.

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

Dose Modification Guidelines for Skin Rash Management for Dabrafenib

Skin Toxicity Grade (CTCAE v 4.0)	Guideline for Management	Dose Reduction[a]
1	Topical corticosteroids (mometasone, betamethasone, or fluocinonide creams)	None
2	As for Grade 1, with the addition of, diphenhydramine oral prednisone (short course)[b]	None: if unacceptable to subject or medically concerning then hold until recovery to ≤Grade 1. Restart at same dose.
≥3		Hold until recovery to ≤Grade 1. Then reduce the dose by one dose level.

a. If no recovery after 2 weeks of holding drug, subjects 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 subject will experience clinical benefit from future treatment.
b. For subjects with Grade 3 or 4 extensive or symptomatic dermatologic event, or chronic, persistent or recurring lower grade skin events, dermatology consult is encouraged.

Dose Modification Guidelines For Skin Rash for Trametinib

Step	Rash grading	Rash severity	Management of Rash	GSK1120212 Dose Adjustment
1	Mild	Localized Minimally symptomatic No impact on ADL No sign of superinfection	Initiate prophylactic regimen if not already started. Consider using moderate strength topical steroid.* Reassess after 2 weeks; if rash worsens or does not improve, proceed to step 2	Continue current dose. Reassess after 2 weeks; if rash worsens or does not improve, proceed to step 2
2	Moderate	Generalized Mild symptoms (eg, pruritis, tenderness) Minimal impact on ADL No sign of superinfection	Initiate prophylactic regimen if not already started, using moderate strength topical steroid.* Reassess after 2 weeks; if rash worsens or does not improve, proceed to step 3	Reduce dose by at least one dose level or consider interrupting treatment until resolution to Grade 1. If toxicity resolves, can consider re-escalation to initial dose level. Reassess after 2 weeks; if rash worsens or does not improve, proceed to step 3
3	Severe	Generalized Severe symptoms (eg, pruritis, tenderness) Significant impact on ADL Sign of or potential for superinfection	Initiate prophylactic regimen if not already started, using moderate strength topical steroids PLUS methyprednisolone dose pack. Consider obtaining dermatology consultation. Manage rash per dermatologist's recommendation.	Interrupt treatment until rash improves (moderate, mild) or resolves, then follow steps outlined for the appropriate grading. Reassess after 2 weeks; if rash worsens or does not improve, permanently discontinue treatment with GSK1120212.

1. *eg, hydrocortisone 2.5% cream or fluticasone prioprionate 0.5% cream

Dose Modification Guidelines for Palmar-plantar Erythrodysesthesia [Hand Foot Skin reaction (HFSR)]

HFSR Grade	Occurrence	Dose Modification[a]
Grade 1: : Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Any occurrence.	Continue treatment with GSK2118436 and start topical therapy[b] for symptomatic relief.
Grade 2: : Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL	1st occurrence.	Continue treatment with GSK2118436 and start topical therapy[b] for symptomatic relief. Instruction on life-style modifications should also be given.[c] 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.[d] When resuming treatment, decrease GSK2118436 dose by one dose level. . Continue topical therapy[b] for symptomatic relief. Instruction on life-style modifications should also be given.[c]
	4th occurrence.	Discontinue GSK2118436 treatment.
Grade 3: or intolerable Grade 2: Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self care ADL	1st or 2nd occurrence.	Interrupt GSK2118436 treatment until toxicity resolves to Grade 0-1.[d] When resuming treatment, decrease GSK2118436 dose by one dose level. Continue topical therapy[b] for symptomatic relief. Instruction on life-style modifications should also be given.[c]
	3rd occurrence.	Discontinue GSK2118436 treatment.

a. No dose adjustment is required on the basis of subject age, gender, or body weight.
b. Topical therapy includes the following options; keratolytics (e.g. urea 40%), emollients, high potency corticosteroids, (fluocinonide, clobetasol)oral analgesia (non-steroidal antiinflammatories or narcotics)
c. Lifestyle modifications include; avoidance of excessive temperatures, exercise, and ill-fitting clothing/shoes. . Use of soft slippers (Tempurpedic or Crocs), friction-relieving measures (calfskin, gels).
d. HSFR usually resolves within 2-4 weeks of drug cessation.
[Lipworth, 2009]

Dose Modification Guidelines for Renal Insufficiency

Creatinine	Guidelines for Management
For subjects with serum creatinine increase >0.2 mg/dL (18 umol/L) but ≤0.5 mg/dL (44 umol/L) above baseline:	1. Continue GSK2118436 and re-check serum creatinine within 1 week 2. If subject has fever (T >/= 38.5C): treat pyrexia as per guidelines (please note NSAIDs can induce renal insufficiency, especially in subjects with dehydration); encourage oral fluids 3. If elevation in serum creatinine persists beyond 1 week, please contact Medical Monitor
For subjects with serum creatinineincrease >0.5 mg/dL (44 umol/L) above baseline or serum creatinine >2 mg/dL (> 177 umol/L)	1. Interrupt GSK2118436 2. If subject has fever (T >/= 38.5C): treat pyrexia as per guidelines (please note NSAIDs can induce renal insufficiency, especially in subjects with dehydration); consider IV hydration 3. Follow serum creatinine at least twice weekly (or consider hospitalization if serum creatinine cannot be monitored frequently) 4. Consider renal consultation 5. If serum creatinine returns to baseline, may restart study treatment 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 is required to re-initiate therapy if a. Subject's serum creatinine has not returned to baseline b. There is evidence of thrombotic microangiopathy

Left Ventricular Ejection Fraction Decrease Stopping Criteria

Subjects who have an asymptomatic, absolute decrease of > 10% in LVEF compared to baseline and the ejection fraction is below the institution's lower limit of normal (LLN) should temporarily discontinue GSK112012 and GSK2118436 and have a repeat evaluation of LVEF within 1 week. ECHO should be repeated every 1-2 weeks for 4 weeks or until LVEF recovery to above institutional lower limit of normal and within 10% of baseline.

- If the LVEF recovers (defined as ≥ LLN and absolute decrease ≤ 10% compared to baseline) at any time during the next 4 weeks, after consultation and approval of the GSK Medical Monitor, the subject may be restarted on GSK112012 and GSK2118436 at a reduced dose(s). For such subjects, monitoring of LVEF will then be performed 2 and 4 weeks after rechallenge, and every 4 weeks thereafter for 12 weeks and then per protocol.
- If repeat LVEF does not recover within 4 weeks, then the subject should permanently discontinue GSK112012 and GSK2118436. Ejection fraction should continue to be monitored every 4 weeks for 16 weeks or until resolution.

Subjects with a Grade 3 or 4 (symptomatic) left ventricular systolic dysfunction must discontinue GSK2118436. Ejection fraction should continue to be monitored every 4 weeks for 16 weeks or until resolution. If recovery occurs (LVEF to above institutional LLN and symptom resolution) within 4 weeks, the subject may restart GSK112012 and GSK2118436 at a reduced dose(s) in consultation with the GSK Medical Monitor.

Liver Chemistry Stopping Criteria

Immediately discontinue investigational product(s) when any of the liver chemistry sopping criteria below are met:

- Alanine aminotransferase (ALT) ≥3x upper limit of normal (ULN) **and** bilirubin ≥2xULN (>35% direct bilirubin) (or ALT≥3xULN and international normalized ratio [INR]>1.5, if INR measured)
- ALT ≥5xULN.
- 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 ≥3xULN persists for ≥4 weeks
- ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks

Visual Changes Stopping Criteria

Grade 1 visual changes:

- If the changes are clearly not due to retinal or retinal vein abnormalities or are clearly unrelated to study drug (e.g. conjunctivitis), GSK1120212 treatment may continue with close observation.
- If drug attribution or etiology is unclear, immediately refer the subject for ophthalmic exam; if an ophthalmic exam cannot be performed within 7 days, interrupt treatment with GSK1120212 until exam can be performed.
- If a retinal abnormality is noted, interrupt treatment with GSK1120212 immediately and consider referral to a retinal specialist, if available, for further evaluation
- If RVO is diagnosed, report as SAE and permanently discontinue treatment with GSK1120212
- If CSR is diagnosed, interrupt treatment with GSK1120212 until signs and symptoms have resolved. Resume treatment with GSK1120212 at reduced dose by one dose level.
- If there is no evidence of RVO or CSR, resume treatment with GSK1120212 at the same dose level.

Grade 2 or Grade 3 visual changes:

- Immediately interrupt treatment with GSK1120212 and refer subject to an ophthalmologist for evaluation with an ophthalmic exam.

- For all subjects with findings consistent with RVO or CSR based on the ophthalmic exam, referral to a retinal specialist, if available, should be considered for further evaluation.
- If RVO is diagnosed, permanently discontinue GSK1120212.
- If CSR is diagnosed, interrupt treatment with GSK1120212 until signs and symptoms have resolved and then resume treatment with GSK1120212 at reduced dose by at least one dose level.
- If there is no evidence of RVO or CSR, interrupt treatment with GSK1120212 until signs and symptoms have returned to Grade 1 or resolved. Resume treatment with GSK1120212 at reduced dose by one dose level. Treatment with GSK1120212 at the same dose level may be considered if visual changes are clearly unrelated to study drug.

Grade 4 visual changes require permanent discontinuation of treatment with GSK1120212.

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/s/

MAITREYEE HAZARIKA
12/15/2013

MARC R THEORET
12/16/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202806Orig1s002

CHEMISTRY REVIEW(S)

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I (Branch III)
Review of Chemistry, Manufacturing, and Controls

1. **NDA Supplement Number: NDA 202806 / S-002**

2. **Submission Being Reviewed**

Submission /Type	DARRTS SD Number	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
S- 002 (efficacy supplement)	104	08-Jul-2013	09-Jul-2013	01-Aug-2013	09-Jan-2014	15-Nov-2013

3. **Proposed Changes:** This efficacy supplement seeks approval for the use of Tafinlar® (dabrafenib) Capsules in combination with trametinib for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.

4. **Review #:** 1

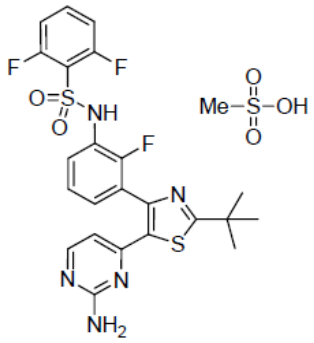
5. **Clinical Review Division:** Division of Oncology Products 2

6. **Name and Address of Applicant:**
   GlaxoSmithKline LLC
   c/o Eric Richards, M.S., M.P.H, Director, Global Regulatory Affairs GSK
   1250 South Collegeville Road, Mailstop UP4400
   Collegeville, PA 19426

7. **Drug Product:**

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC
Tafinlar® (dabrafenib) Capsules	capsule	50 mg, 75 mg	oral	Rx

8. **Chemical name and structure of drug substance:**

	USAN: Dabrafenib Mesylate Chemical name: N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzene sulfonamide, methanesulfonate salt Molecular formula: $C_{23}H_{20}F_3N_5O_2S_2 \cdot CH_4O_3S$ MW: 615.68

9. **Pharmacological Category/Indication:** Tafinlar is a kinase inhibitor currently approved as monotherapy (b) (4)

10. **Relating Document:** NDA 204114/S-001 (efficacy supplement for trametinib tablets)

11. **Consults: N/A**

12. **Summary/Remarks**

NDA 202806 was approved on May 29, 2013 for the use of Tafinlar® (dabrafenib) Capsules as monotherapy in the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation, as detected by an FDA-approved test.

This efficacy supplement seeks approval for the use of Tafinlar® (dabrafenib) Capsules in combination with trametinib for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.

This supplement does not propose CMC changes. All information related to Module 3 (Quality) is incorporated by cross-reference to the original NDA 202806 (for dabrafenib capsules) and NDA 204114 (for trametinib tablets).

A categorical exclusion from the preparation of an environmental assessment (EA) was requested under 21 CFR 25.31(b), which has been reviewed and found acceptable.

There are no changes to the container labels and carton labeling. Therefore, this supplement does not include container labels and carton labeling. There are no CMC-related changes to the package insert.

13. **Conclusions & Recommendations:**

This supplement is recommended for approval from the CMC perspective.

14. **Comments/Deficiencies to be Conveyed to Applicant:** None

15. **Primary Reviewer:** Sue-Ching Lin, CMC reviewer, ONDQA

Secondary Reviewer: Hasmukh Patel, Ph.D., Branch Chief, Branch III, Division of New Drug Quality Assessment I (DNDQA I), ONDQA

(See appended electronic signature page)

CMC Assessment

I. Background Information

NDA 202806 was approved on May 29, 2013 for the use of Tafinlar® (dabrafenib) Capsules as monotherapy in the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation, as detected by an FDA-approved test.

II. Proposed Changes

This efficacy supplement seeks approval for the use of Tafinlar® (dabrafenib) Capsules in combination with trametinib for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.

Note that this supplement does not propose CMC changes to either Tafinlar® (dabrafenib) Capsules or Mekinist® (trametinib) Tablets. Based on the labeling, the recommended dose for dabrafenib, for monotherapy or in combination with trametinib, is 150 mg orally twice daily. The recommended dose for trametinib, for monotherapy or in combination with dabrafenib, is 2 mg orally once daily. (b) (4)

III. Data Submitted to Support the Proposed Changes

The applicant states in the cover letter of this efficacy supplement that all information related to Module 3 (Quality) is incorporated by cross-reference to the original NDA 202806 and NDA 204114. An updated Module 3.2.P.3.1 is provided within this efficacy supplement to (b) (4)

Evaluation: Adequate. This is not a new change. During the review of the original NDA 202806, (b) (4)

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/s/

SUE CHING LIN
11/21/2013

LIANG ZHOU
11/21/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202806Orig1s002

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	202806 & 204114
Supporting document/s:	104 (NDA 202806) & 83 (NDA 204114)
Applicant's letter date:	July 8, 2013
CDER stamp date:	July 9, 2013
Product:	Dabrafenib (Tafinlar™) and Trametinib (Mekinist™) combination
Indication:	Treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutation as detected by an FDA-approved test
Applicant:	GlaxoSmithKline
Review Division:	Division of Hematology Oncology Toxicology
Reviewer:	Alexander H. Putman, Ph.D.
Supervisor/Team Leader:	Whitney S. Helms, Ph.D.
Division Director:	John Leighton, Ph.D.
Project Manager:	Norma S. Griffin

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1 Executive Summary

1.1 Introduction

GlaxoSmithKline submitted an efficacy supplement to support the use of dabrafenib (Tafinlar™), in combination with trametinib (Mekinist ™), for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.

1.2 Brief Discussion of Nonclinical Findings

Pharmacology studies demonstrated that the dabrafenib and trametinib combination results in greater growth inhibition of $BRAF^{V600}$ mutation-positive cell lines *in vitro* and *in vivo* xenograft models than with either drug alone. Specifically, in 9 of 11 $BRAF^{V600E}$ mutant positive melanoma cell lines, the dabrafenib and trametinib combination resulted in a synergistic enhancement of cell growth inhibition. In the $BRAF^{V600K}$ mutant positive melanoma lines, the dabrafenib and trametinib combination showed an approximately additive enhancement of cell growth inhibition. A synergistic effect from combination treatment was noted in the one $BRAF^{V600D}$ mutant positive melanoma cell line.

Using a $BRAF^{V600E}$ mutation positive melanoma xenograft model, female CD-1 nude mice were dosed orally with either dabrafenib, trametinib, or a combination of the two, for 90 days. All doses of dabrafenib, trametinib, and the combination, were tolerated and did not result in any significant effect on body weight. Administration of 10 and 30 mg/kg/day of dabrafenib resulted in 71 and 85% tumor growth inhibition, respectively, compared to the untreated control. Trametinib administration at doses of 0.1 and 0.3 mg/kg/day resulted in 66 and 95% tumor growth inhibition, respectively. Administration of the 10/0.1 mg/kg/day combination of dabrafenib and trametinib resulted in 95% tumor growth inhibition, suggestive of an additive effect. Other groups administered the dabrafenib and trametinib combination showed 100% tumor growth inhibition. The most pronounced effect of the dabrafenib and trametinib combination was seen following the 30/0.3 mg/kg/day combination dose and consisted of prolonged inhibition of tumor growth until the end of the 90-day dosing period (day 114 post-tumor implantation).

The toxicity of repeated oral dosing of the dabrafenib and trametinib combination was assessed by conducting a 4-week toxicity studies in dogs. The dog was considered a relevant species based on previously conducted pharmacology and toxicity studies of each drug separately. Single-agent toxicity studies of repeated oral dosing of dabrafenib or trametinib were previously reviewed under NDA 202806 and 204114, respectively. Target organs of toxicity for single-agent dabrafenib were the skin (lesions and papules), heart (hemorrhage of the atrioventricular valve), and male reproductive organs (degeneration in the testis and aspermia in the epididymis). Lymphoid depletion in the thymus was also noted. For single-agent trametinib, the primary target organ of toxicity was the skin (lesions and scabs). In the 4-week combination toxicity study, dogs were orally administered 0/0, 0.0075/5, or 0.0225/20 mg/kg/day of the trametinib/dabrafenib combination, respectively. Plasma exposure levels (AUC) were

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up to 0.5/9 times the exposure level in humans receiving the recommended dose of the trametinib/dabrafenib combination. Target organs of toxicity were the stomach (inflammation), thymus (decreased cellularity), and male reproductive organs (germ cell degeneration/oligospermia in epididymis and germinal epithelium degeneration in the testes).

The Applicant also submitted a study to assess the toxicity study of dabrafenib alone in juvenile rats. Rats were administered daily dabrafenib from Postnatal Day (PND) 7 to PND 35 at dose levels of 0, 1/3 (1 mg/kg/day from PND 7 to 21 with escalation to 3 mg/kg/day from PND 22 to 35), 10/20 (10 mg/kg/day from PND 7 to 21 then 20 mg/kg/day from PND 22 to 35), 0/20 (vehicle given from PND 7 to 21 then 20 mg/kg/day from PND 22-35), or 0/200 mg/kg/day (vehicle given from PND 7 to 21 then 200 mg/kg/day from PND 22 to 35). Doses were escalated on PND 22 in an effort to maintain consistent exposures across the duration of the dosing period. All doses of dabrafenib were tolerated. Target organs of toxicity were the kidneys, bone, stomach, and male reproductive organs. An increased incidence of cysts and tubular deposits was noted in the kidney following 1/3 and 10/20 mg/kg/day of dabrafenib. Macroscopic kidney cysts were also noted in 35% of 0/20 mg/kg/day animals. Bone toxicity consisted of an approximate 2, 5, 2.5, and 3.5% decrease in femur length and 3, 7, 2.5, and 4% decrease in tibia length following 1/3, 10/20, 0/20, and 0/200 mg/kg/day of dabrafenib, respectively. Kidney and bone toxicity occurred at doses approximately ≥ 0.23 times the human exposure at the recommended adult dose of dabrafenib based on AUC. Hyperplasia was noted in the stomach of ≥ 20% of 10/20 and 0/200 mg/kg/day animals (≥ 0.77 times the human exposure at the recommended adult dose of dabrafenib based on AUC). Male reproductive toxicity was noted following 10/20 and 0/200 mg/kg/day of dabrafenib (approximately ≥ human exposure at the recommended adult dose of dabrafenib based on AUC) and consisted of oligospermia in the epididymis and degeneration/atrophy and tubular dilatation in the testis. Female sexual maturation (day of vaginal opening) occurred approximately 4, 2, and 2 days earlier than controls in 10/20, 0/20, and 0/200 mg/kg/day females, respectively (approximately ≥ 2 times the human exposure at the recommended adult dose of dabrafenib based on AUC).

1.3 Recommendations

1.3.1 Approvability

From a Pharmacology/Toxicology perspective, approval of the dabrafenib (Tafinlar™), in combination with trametinib (Mekinist ™) is recommended.

1.3.2 Additional Non-Clinical Recommendations

None. From a Pharmacology/Toxicology perspective, no additional post-marketing commitments (PMCs) or post-marketing requirements (PMRs) are recommended for this indication.

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1.3.3 Labeling

See separate labeling review.

2 Drug Information

2.1 Drug

2.1.1 CAS Registry Number

Dabrafenib: 1195768-06-9
Trametinib: 871700-17-3

2.1.2 Generic Name

Dabrafenib
Trametinib

2.1.3 Code Name

Dabrafenib: GSK2118436B
Trametinib: GSK1120212B

2.1.4 Chemical Name

Dabrafenib: Benzenesulfonamide, *N*-[3-[5-(2-amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-4-thiazolyl]-2-fluorophenyl]-2,6-difluoro-, methanesulfonate (1:1)

Trametinib: Acetamide, N-[3-[3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]-3,4,6,7-tetrahydro-6,8-dimethyl-2,4,7-trioxopyrido[4,3-*d*]pyrimidin-1(2*H*)-yl]phenyl]-, compound with 1,1'-sulfinylbis[methane] (1:1)

2.1.5 Molecular Formula/Molecular Weight

Dabrafenib: $C_{23}H_{20}F_3N_5O_2S_2 \cdot CH_4O_3S$ / 615.68 g/mol
Trametinib: $C_{26}H_{23}FIN_5O_4 \cdot C_2H_6OS$ / 693.53 g/mol

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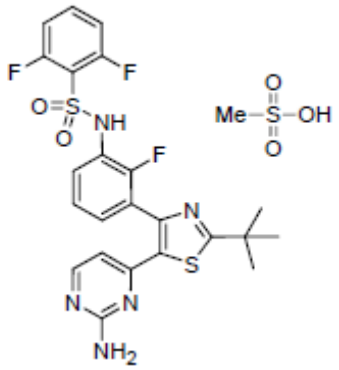
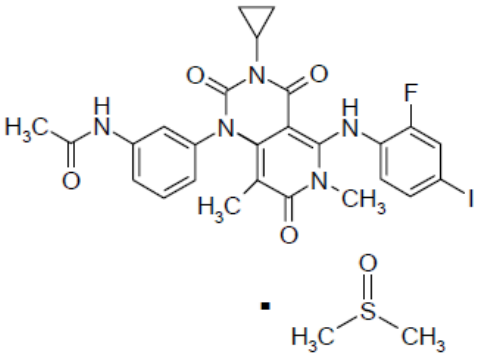
2.1.6 Structure

Dabrafenib:



(figure excerpted from Applicant's NDA)

Trametinib:



(figure excerpted from Applicant's NDA)

2.1.7 Pharmacologic class

Dabrafenib: BRAF kinase inhibitor
Trametinib: MEK kinase inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

Dabrafenib: IND 105032, NDA 202806
Trametinib: IND 102175, NDA 204114

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2.3 Drug Formulation

The composition of dabrafenib (50 and 75 mg) and trametinib (0.5, 1, and 75 mg) capsules are shown in the tables below.

Composition of Dabrafenib Capsules, 50 and 75 mg

Component	Quantity [mg/capsule]		Function	Reference to Standard
	50 mg	75 mg		
Dabrafenib Mesylate, Micronized[1]	59.25	88.88	Active	GSK[2]
Microcrystalline Cellulose	(b) (4)			USP/NF
Magnesium Stearate				USP/NF
Colloidal Silicon Dioxide				USP/NF
Total Unit Dose	(b) (4)		-	-
Hypromellose Capsules[3]	(b) (4)		Capsule shell	Supplier/GSK[2]

Note:

1. Dabrafenib Mesylate is the mesylate salt form of dabrafenib free base. Based on the molecular weights (mw), 1.185 mg of salt (mw 615.68) is equivalent to 1.00 mg of free base (mw 519.57).
2. Detail of the specification of the active ingredient is provided in Section S.4.1, details of the specification of the excipients are provided in Section P.4.
3. Information relating to Hypromellose Capsules is provided via (b) (4) (b) (4)

(table excerpted from Applicant's BLA)

Composition of Trametinib Capsules, 0.5, 1, and 75 mg

Component	Quantity (mg/tablet)			Function	Reference to Standard[1]
Strength	0.5	1	2		
Trametinib Dimethyl Sulfoxide[2]	0.5635	1.127	2.254	Active	GSK
Mannitol	(b) (4)				USP
Microcrystalline Cellulose					NF
Hypromellose (b) (4)					USP
Croscarmellose Sodium					NF
Sodium Lauryl Sulfate					NF
Colloidal Silicon Dioxide					NF
Magnesium Stearate[3]					NF
(b) (4) Yellow (b) (4)					Supplier
White (b) (4)					Supplier
Pink (b) (4)					Supplier
(b) (4)					USP
Total Tablet Weight	149.35	159.65	169.95	-	-

Note:

1. Details of the specification of the active ingredients are provided in S.4.1 Specification, details of the specifications of the excipients are provided in Section P.4 Control of Excipients.
2. The amount of trametinib dimethyl sulfoxide required to achieve the label claim is calculated utilizing the molecular conversion factor of 0.8873 for the ratio of trametinib (non-solvated parent) to trametinib dimethyl sulfoxide, and based on the purity value from the certificate of analysis.
3. Magnesium stearate is of vegetable origin.

(b) (4)

(table excerpted from Applicant's BLA)

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

None. No new impurities or degradants have been identified.

2.6 Proposed Clinical Population and Dosing Regimen

Dabrafenib (Tafinlar™) in combination with trametinib (Mekinist™) is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutation as detected by an FDA approved test. The recommended dose of dabrafenib (Tafinlar™) is 150 mg orally, twice daily. The recommended dose of trametinib is 2 mg orally, once daily.

2.7 Regulatory Background

On May 29, 2013, dabrafenib (Tafinlar™) was FDA-approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E as detected by an FDA-approved test.

On May 29, 2013, trametinib (Mekinist™) was FDA-approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutation as detected by an FDA approved test.

3 Studies Submitted

3.1 Studies Reviewed

Primary Pharmacology:

Study #	Study title
2011N116395	Cellular Assays with GSK2118436A, GSKI120212B, and GSK2126458A as Single Agents and in Combination with Each Other in BRAF$^{V600E/K/D}$ Mutant Melanoma Cell Lines
2012N139280	Efficacy of MEK Inhibitor GSK1120212B and BRAF Inhibitor GSK2118436A, Administered Separately or in Combination, in Mouse Tumor Xenograft Models of Human Melanoma

Repeat-dose Toxicology:

Study #	Study title
2011N112335	GSK1120212B and GSK2118436B: 4-Week Twice Daily Oral Toxicity Study in Dogs

Reproductive and Developmental Toxicology:

Study #	Study title
2012N148838	GSK2118436A: Oral Juvenile Toxicity Study in Rats (From Day 7 to 35 of Age) Followed by a 6-week Off-drug Period

3.3 Previous Reviews Referenced

The Pharmacology/Toxicology and other discipline reviews for NDA 202806 (dabrafenib) and 204114 (trametinib).

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4 Pharmacology

4.1 Primary Pharmacology

2011N116395: Cellular Assays with GSK2118436A, GSKI120212B, and GSK2126458A as Single Agents and in Combination with Each Other in $BRAF^{V600E/K/D}$ Mutant Melanoma Cell Lines.

In this study, a panel of $BRAF^{V600}$ mutant positive melanoma cell lines was treated with dabrafenib (GSK2118436A), trametinib (GSK1120212B), or a combination of dabrafenib and trametinib, to assess cell growth inhibition, apoptosis induction, and cell signaling changes.

Combination effects on potency of cell growth inhibition were evaluated using a Combination Index (CI), which was calculated with back-interpolated IC_{50} values and the equation ($CI = Da/IC_{50}(a) + Db/IC_{50}(b) + (Da \times Db)/(IC_{50}(a) \times IC_{50}(b))$) derived by Chou and Talalay [Chou, 1984]. $IC_{50}(a)$ is the IC_{50} of Compound A, $IC_{50}(b)$ is the IC_{50} for Compound B, Da is the concentration of Compound A in combination with Compound B that inhibited 50% of cell growth, and Db is the concentration of Compound B in combination with Compound A that inhibited 50% of cell growth. In general, a CI value <0.9, between 0.9-1.1, or >1.1 indicated synergy, additivity, or antagonism, respectively. In general, the smaller the CI number, the greater the synergy.

The combination effects on the response scale were quantified using the Excess Over Highest Single Agent (EOHSA) method [Liu, 2011]. EOHSA values were defined as increases in improvement (percentage points (ppts) difference) produced by the combination over the best single agent at its component dose level for the combination.

As shown in the following table, cell growth inhibition was induced by both single agents in 9 of 11 $BRAF^{V600E}$ mutant positive melanoma cell lines. In all 9 of these cell lines, the dabrafenib (GSK2118436A) and trametinib (GSK1120212B) combination resulted in a synergistic enhancement of cell growth inhibition. In the $BRAF^{V600K}$ mutant positive melanoma lines, the dabrafenib and trametinib combination showed an approximately additive enhancement of cell growth inhibition. A synergistic effect from combination treatment was noted in the one $BRAF^{V600D}$ mutant positive melanoma cell line.

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Effect on Cellular Proliferation of GSK2118436A, GSK1120212B, or the Combination of GSK2118436A and GSK1120212B on a Panel of BRAF$^{V600E/D/K}$ Mutant Positive Melanoma Cell Lines

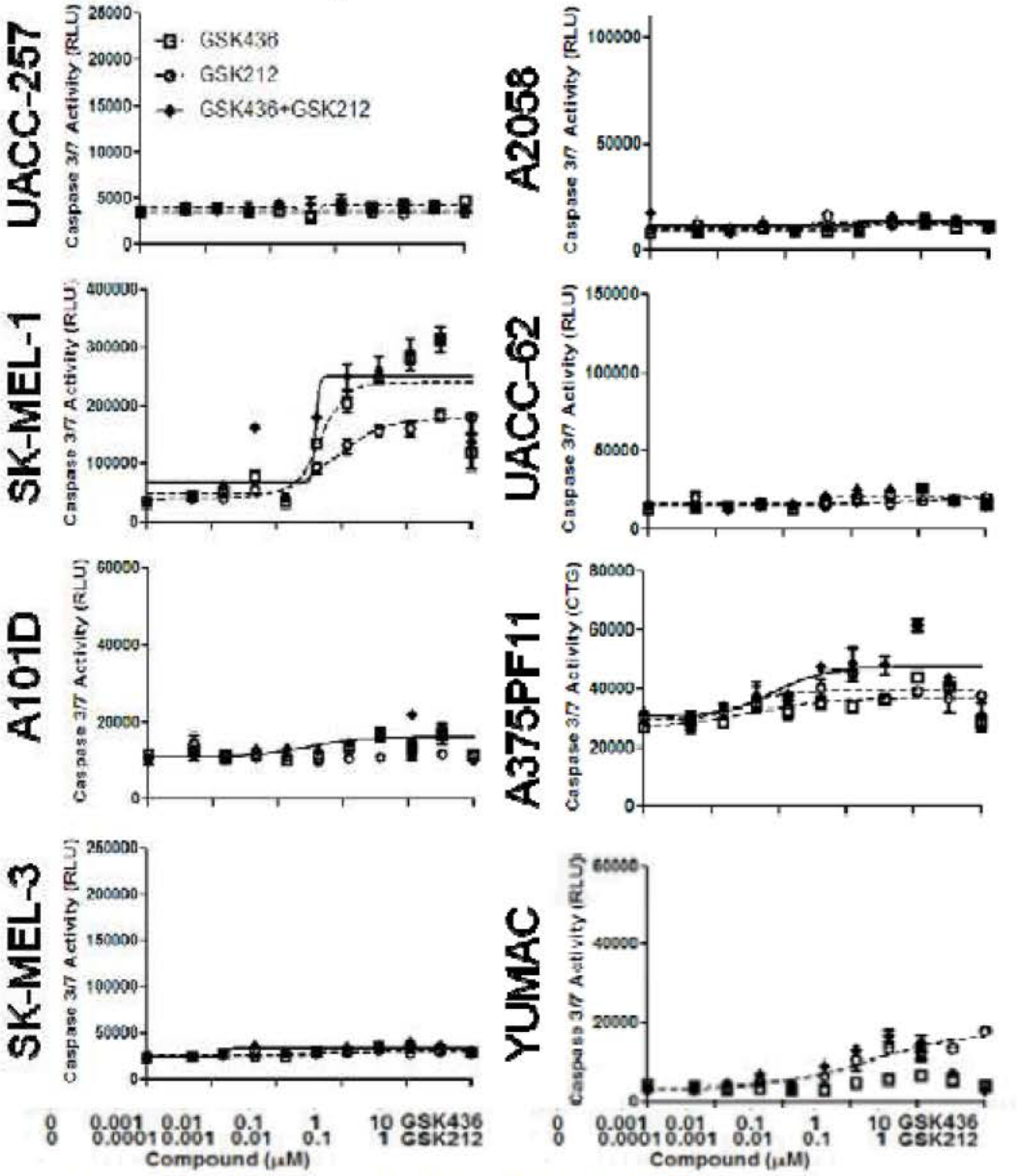
	Genetic Alterations		IC_{50} values (μM, mean ± std)				Combination Effect at IC_{50}	
			Single Agent Effect		10:1 Molar Combination			
CELL LINE	BRAF	PTEN	GSK2118436A	GSK1120212B	GSK2118436A	GSK1120212B	CI	EOHSA (ppt)
UACC-257	V600V/E	WT	0.011 ± 0.001	0.0041 ± 0.0065	0.005 ± 0.002	0.0005 ± 0.0002	0.75 ± 0.13	25.0 ± 9.5
SK-MEL-1	V600V/E	WT	0.018 ± 0.007	0.0023 ± 0.0006	0.005 ± 0.002	0.0005 ± 0.0002	0.53 ± 0.06	25.4 ± 4.0
COLO-829	V600V/E	NULL	0.026 ± 0.011	0.0043 ± 0.0014	0.009 ± 0.002	0.0009 ± 0.0002	0.66 ± 0.16	24.5 ± 4.5
A101D	V600V/E	NULL	0.033 ± 0.007	0.0053 ± 0.0012	0.010 ± 0.002	0.0010 ± 0.0002	0.56 ± 0.09	14.4 ± 1.5
SK-MEL-24	V600V/E	NULL	0.078 ± 0.072	0.0058 ± 0.0028	0.010 ± 0.003	0.0010 ± 0.0003	0.40 ± 0.20	15.5 ± 0.6
SK-MEL-5	V600V/E	WT	0.188 ± 0.174	0.0035 ± 0.0016	0.011 ± 0.004	0.0011 ± 0.0004	0.57 ± 0.37	18.8 ± 5.3
SK-MEL-3	V600V/E	WT	>10	>1	>10	>1	N/A	N/A
A2058	V600V/E	NULL	>10	>1	>10	>1	N/A	N/A
SK-MEL-28	V600E	T167A	0.010 ± 0.004	0.0014 ± 0.0005	0.004 ± 0.001	0.0004 ± 0.0001	0.76 ± 0.17	24.3 ± 9.4
UACC-62	V600E	NULL	0.011 ± 0.002	0.0026 ± 0.0026	0.005 ± 0.002	0.0005 ± 0.0002	0.87 ± 0.06	14.4 ± 3.9
A375PF11	V600E	WT	0.049 ± 0.003	0.0063 ± 0.0009	0.016 ± 0.003	0.0016 ± 0.0003	0.65 ± 0.11	14.1 ± 1.5
WW165	V600V/K	WT	0.005 ± 0.000	0.0003 ± 0.0000	0.002 ± 0.000	0.0002 ± 0.0000	1.18 ± 0.11	16.5 ± 0.9
IGR-1	V600V/K	WT	>10	0.0454 ± 0.0098	0.096 ± 0.075	0.0096 ± 0.0075	N/A	10.2 ± 5.9
YUMAC	V600K	WT	0.007 ± 0.001	0.0005 ± 0.0001	0.002 ± 0.000	0.0002 ± 0.0000	0.91 ± 0.22	29.6 ± 2.4
YULAC	V600K	WT	0.017 ± 0.014	0.0008 ± 0.0005	0.004 ± 0.002	0.0004 ± 0.0002	0.90 ± 0.20	29.6 ± 1.8
YUSIT1	V600K	WT	0.013 ± 0.001	0.0007 ± 0.0000	0.003 ± 0.001	0.0003 ± 0.0001	0.83 ± 0.21	22.2 ± 0.1
WM-115	V600V/D	NULL	0.041 ± 0.006	0.0064 ± 0.0041	0.014 ± 0.004	0.0014 ± 0.0004	0.64 ± 0.03	13.7 ± 4.1

CI, combination index
EOSHA, excess over highest single agent
NULL, no detectable protein and/or deletion mutation
N/A, not applicable

(table excerpted from Applicant's NDA)

The effect of the dabrafenib (GSK436) and trametinib (GSK212) combination on apoptosis, compared to each single agent alone, was assessed by measuring caspase 3/7 activity. As shown in the figure below, no difference in apoptosis induction was seen 24 hours post-treatment between the dabrafenib and trametinib combination and each single agent alone.

Apoptosis Induction after Treatment with GSK2118436A (GSK436), GSK1120212B (GSK212), or the Combination of GSK2118436A and GSK1120212B (GSK436+GSK212) in BRAF$^{V600E/K}$ Positive Mutant Cell Lines



(figure excerpted and slightly modified from Applicant's NDA)

In regard to cell signaling, A375PF11 cells (BRAF^{V600E}, PTEN wild-type) were treated with 0, 0.1, 0.3, or 1 μM dabrafenib (GSK2118436) without trametinib (GSK212), with 10 nM trametinib, or with 30 nM trametinib for 24 hours. Western blot analysis with the indicated antibody demonstrated that single agent dabrafenib and trametinib reduced ERK and S6P phosphorylation in A375 (see figure below). These inhibitors were sufficient to reduce cyclin D1 and increase p27^{kip1} protein levels. The dabrafenib and trametinib combination treatment reduced ERK and S6P phosphorylation greater than either single agent alone.

Effect of the Combination Treatment of GSK2118436A and GSK1120212B on MAPK and PI3K/AKT Pathway in the A375PF11, BRAF^{V600E} Mutant Positive Melanoma Line

(figure excerpted from Applicant's NDA)

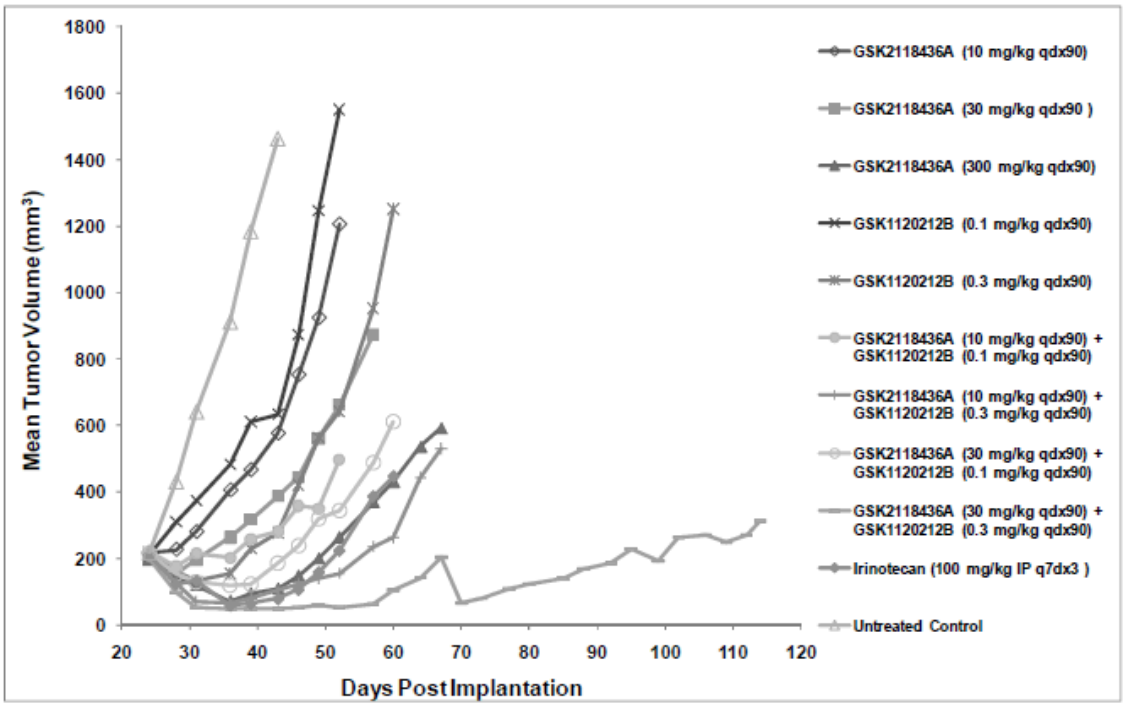
2012N139280: Efficacy of MEK Inhibitor GSK1120212B and BRAF Inhibitor GSK2118436A, Administered Separately or in Combination, in Mouse Tumor Xenograft Models of Human Melanoma.

The purpose of this study was to investigate the *in vivo* efficacy of the dabrafenib (GSK2118436A) and trametinib (GSK1120212B) combination in a xenograft model of human BRAFV600E melanoma in mice. The A375P F11s cell xenograft model consisted of subcutaneously injecting human A375P F11s cells encoding the BRAF^{V600E} mutation into female CD-1 nude mice. Tumors were established (~150-250 mm^3) approximately 4-weeks post injection. Mice were placed in groups of eight and daily dosed orally with either dabrafenib, trametinib, or a combination of the two, for 90 days. Doses of single agent dabrafenib were 10, 30, and 300 mg/kg/day. Doses of single agent trametinib were 0.1 and 0.3 mg/kg/day. Combination doses (dabrafenib/trametinib) consisted of 10/0.1, 10/0.3, 30/0.1, and 30/0.3 mg/kg/day, respectively. Irinotecan was administered intraperitoneally at 100 mg/kg, once per week for 3 weeks, as a positive control. Mice were assessed twice weekly for body weight and tumor growth measurements.

All doses of dabrafenib (GSK2118436A), trametinib (GSK1120212B), and the combination, were tolerated and did not result in any significant effect on body weight. Administration of 10 and 30 mg/kg/day of dabrafenib resulted in 71 and 85% tumor growth inhibition, respectively, compared to the untreated control. Trametinib administration at doses of 0.1 and 0.3 mg/kg/day resulted in 66 and 95% tumor growth inhibition, respectively. Administration of the 10/0.1 mg/kg/day combination of dabrafenib and trametinib resulted in 95% tumor growth inhibition, suggestive of an

additive effect. Other groups administered the dabrafenib and trametinib combination showed 100% tumor growth inhibition. As shown in the following table, the most pronounced effect of the dabrafenib and trametinib combination was seen following the 30/0.3 mg/kg/day combination dose and consisted of prolonged inhibition of tumor growth until the end of the 90-day dosing period (day 114 post-tumor implantation).

Study A375P D41-09KM Mean Tumor Volume Data



Note: Mean data shown only until any animal was removed from a group because of ulceration or large (>1500 mm^3) tumor volume.
(figure excerpted from Applicant's NDA)

6 General Toxicology

6.2 Repeat-Dose Toxicity

Study title: GSK1120212B and GSK2118436B: 4-Week Twice Daily Oral Toxicity Study in Dogs

Study no.:	2011N112335_00 (G10260)
Study report location:	4.2.3.2
Conducting laboratory and location:	GlaxoSmithKline 709 Swedeland Road King of Prussia, PA 19406 USA
Date of study initiation:	January 24, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	GSK1120212B, 091450, 99.8% GSK2118436B, 091220223, 99.4%

Key Study Findings:

- One 0.0225/20 mg/kg/day male was sacrificed in moribund condition on Day 11 due to body weight loss, decreased food consumption, dark red/black liquid feces, and increase body temperature.
- Target organs of toxicity were stomach, thymus, and male reproductive organs.
- Stomach toxicity was observed at all doses and consisted of inflammation, associated with increases in white blood cells, neutrophils, and monocyte counts, and decreased cellularity in the thymus.
- Male reproductive toxicity was seen predominately in 0.0225/20 mg/kg/day animals and consisted of germ cell degeneration/oligospermia in epididymis and germinal epithelium degeneration in the testes.
- Accumulation of GSK1120212B was noted at the end of the dosing period.

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Methods:

Doses:	The following low and high dose of each drug were given in combination. GSK1120212B (trametinib) – 0, 0.0075, and 0.0225 mg/kg GSK2118436B (dabrafenib) – 0, 5 (2.5 BID), and 20 (10 BID) mg/kg
Frequency of dosing:	GSK1120212B – daily GSK2118436B – daily (BID, ~ 8 hrs between doses)
Route of administration:	GSK1120212B – Oral gavage GSK2118436B – Oral capsules
Dose volume:	2 mL/kg for GSK1120212
Formulation/Vehicle:	GSK1120212B – 1.5% hydroxypropylmethylcellulose (HPMC, Pharmacoat 603), 5% D-mannitol, 0.2% sodium lauryl sulphate (SLS) GSK2118436B – mesylate salt form in gelatin capsule
Species/Strain:	Dog / Beagle
Number/Sex/Group:	3 - main group
Age:	18 to 19 months old
Weight:	Males – 9.6 to 11.5 kg; Females – 7.2 to 8.2 kg
Dose justification:	Given the maximum tolerated doses in 13 week dog studies of 0.0225 mg/kg/day (GSK1120212) and 20 mg/kg/day (GSK2118436), a high dose of .0225/20 mg/kg/day was selected for this study.

Observations and Results:

Mortality [observations made daily]

One 0.0225/20 mg/kg/day male was sacrificed in moribund condition on Day 11 due to body weight loss, decreased food consumption, dark red/black liquid feces, and increase body temperature (103.5 to 104.7°F). Microscopic findings were observed in the heart, colon, rectum, mesenteric lymph nodes, and thymus. In the heart, there was marked degeneration/necrosis of an extramural right coronary artery with transmural and perivascular neutrophilic and histiocytic inflammation. Mild neutrophilic inflammation was noted in the colonic and rectal mucosa, as well as in the mesenteric lymph nodes with mild sinus histiocytosis. In the thymus, there was marked decreased lymphoid cellularity.

Clinical Signs [daily]

Test article-related clinical observations included dose-dependent reductions in food consumption (canned food supplementation given to females given 0.0225/20

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mg/kg/day as early as Day 12 and 1 female given 0.0075/5 mg/kg/day), associated decreases in individual body weights and/or body weight gain at all doses, and fecal consistency changes. One male given 0.0225/20 mg/kg/day had a reddened muzzle and/or scab formation (ear/neck) by Day 26.

Body Weights [pre-dose; weekly]

In dogs given 0.0075/5 mg/kg/day, females exhibited a slight (~4%) decrease in body weights by Day 15 with subsequent gains to baseline by Day 26.

Dogs given 0.0225/20 mg/kg/day had a slight (~5%) decrease in mean body weight by Day 12 with moderate (~12%) body weight loss in one female by Day 12. This dog received canned food supplementation. On Day 15, the remaining female dogs given 0.0225/20 mg/kg/day and one female dog given 0.0075/5 mg/kg/day were also started on canned food supplementation for continued decreases in body weight.

Food Consumption [pre-dose; daily]

Decreased food consumption was consistent with body weight losses noted above. Food supplementation was administered to affected animals as early as Day 2 of dosing and reversed body weight losses.

Ophthalmoscopy [pre-dose; day 27]

Unremarkable

Electrocardiography [pre-dose; day 26 (1 hour post-dose)]

Unremarkable

Hematology [pre-dose; day 27]

At the end of the treatment period, an increase in white blood cells (+103%), neutrophils (+146%), and monocytes (+144%) was noted 0.0225/20 mg/kg/day females. Reversibility was not assessed. No treatment-related changes were seen in males at any dose.

Coagulation [pre-dose; day 27]

Unremarkable

Clinical Chemistry [pre-dose; day 27]

Reversibility was not assessed.

Day 27 - % change in clinical chemistry vs. control

	Males	Females

Reference ID: 3413290

	0.0225/20 mg/kg/day	0.0225/20 mg/kg/day
Alkaline phosphatase	+59	+164
Albumin	-9	-29

Urinalysis [pre-dose; day 27]

Unremarkable

Gross Pathology [at sacrifice]

Unremarkable

Organ Weights [at sacrifice]

At the end of the treatment period, a decrease in thymus weight was noted in males (13 and 40%) and females (19 and 35%) following 0.0075/5 and 0.0225/20 mg/kg/day, respectively. Reversibility was not assessed.

Histopathology [at sacrifice]

Adequate Battery: Yes
Peer Review: Yes

Reversibility was not assessed.

Treatment-related microscopic findings at the end of dosing period

Tissue and finding	Grade	Males 0.0075/5 mg/kg/day	Males 0.0225/20 mg/kg/day	Females 0.0075/5 mg/kg/day	Females 0.0225/20 mg/kg/day
Mesenteric Lymph Nodes					
-foreign material	1	0/3	2/2	2/3	0/3
-histiocytosis	1	1/3	0/2	0/3	1/3
Stomach					
-inflammation	1	2/3	2/2	3/3	3/3
Thymus					
-decreased cellularity	1-3	1/3	1/2	2/3	2/3
Epididymis					
-germ cell degeneration	2	0/3	2/2	-	-
-oligospermia	2	0/3	2/2	-	-
Testes					
-germinal epithelium degeneration	1-2	1/3	2/2	-	-

Grade 1, 2, 3, 4, 5 refers to minimal, slight, moderate, marked, severe, respectively.
The severity of findings was dose-dependent.

Reference ID: 3413290

Toxicokinetics [pre-dose, and 0.5, 1, 2, 4, 8, 8.5, 9, 10, 12, and 24 hrs post-dose on day 1 and 28]

- Exposure levels (AUC) were approximately dose proportional for GSK1120212B (trametinib) and less than dose proportional for GSK2118436 (dabrafenib).
- GSK1120212B (trametinib) accumulation was seen on Day 28.
- No significant sex differences were noted.
- Ratios of metabolite/dabrafenib AUC_{0-t} values ranged from 0.031 to 0.064 for M4, 0.25 to 0.35 for M7, and 0.0078 to 0.018 for M8.
- Details are shown in Applicant's tables below.

Mean Toxicokinetic Parameters on Day 1 and 28 following Daily Oral Administration of GSK1120212B (trametinib) to Dogs

Parameter [a]	Period	Daily Dose of GSK1120212B (mg/kg/day)			
		Male		Female	
		0.0075 (n=3) [b]	0.0225 (n=3) [c]	0.0075 (n=3) [b]	0.0225 (n=3) [c]
AUC_{0-t} (ng.h/mL)	Day 1	7.72 [5.65 – 9.14]	26.0 [24.4 – 26.9]	6.13 [4.86 – 7.29]	22.8 [17.8 – 30.5]
	Day 28	66.9 [60.9 – 72.8]	223 [d] [198, 248]	66.5 [42.6 – 99.5]	182 [119 – 231]
C_{max} (ng/mL)	Day 1	0.728 [0.463 – 0.901]	1.95 [1.30 – 2.97]	0.534 [0.301 – 0.989]	1.65 [1.35 – 1.88]
	Day 28	3.67 [3.37 – 4.22]	11.5 [d] [9.64, 13.4]	3.47 [2.04 – 5.68]	9.45 [6.24 – 11.6]
Median T_{max} (h)	Day 1	0.50 [0.50 – 1.00]	1.00 [0.50 – 1.00]	2.00 [0.50 – 8.00]	1.00 [1.00 – 4.00]
	Day 28	1.00 [0.50 – 12.00]	1.50 [d] [1.00 – 2.00]	1.00 [0.50 – 1.00]	2.00 [1.00 – 2.00]

a. Results are reported as mean unless stated otherwise and [range].
b. Dosed in combination with GSK2118436B at 5 mg/kg/day
c. Dosed in combination with GSK2118436B at 20 mg/kg/day
d. n = 2, one male killed on Day 11 due to declining clinical condition

(table excerpted from Applicant's NDA)

Mean Toxicokinetic Parameters on Day 1 and 28 following Daily Oral Administration of GSK2118436 (dabrafenib) to Dogs

Parameter [a]	Period	Daily Dose of GSK2118436 (mg/kg/day)			
		Male		Female	
		5 (n=3) [b]	20 (n=3) [c]	5 (n=3) [b]	20 (n=3) [c]
AUC_{0-t} (µg.h/mL)	Day 1	36.2 [20.8 – 44.9]	76.5 [58.4 – 87.6]	25.7 [17.8 – 35.3]	81.0 [24.9 – 132]
	Day 28	23.1 [12.6 – 34.6]	82.1 [d] [74.6, 89.6]	31.1 [19.1 – 46.5]	82.6 [48.6 – 121]
C_{max} (µg/mL)	Day 1	4.05 [2.04 – 5.46]	8.38 [7.44 – 10.1]	3.12 [1.72 – 4.62]	7.30 [3.10 – 14.1]
	Day 28	2.38 [1.93 – 3.19]	6.18 [d] [5.16, 7.19]	2.86 [1.89 – 4.04]	7.13 [3.72 – 12.5]
Median T_{max} (h)	Day 1	9.00 [2.00 – 10.00]	10.00 [2.00 – 10.00]	9.00 [4.00 – 10.00]	10.00 [2.00 – 12.00]
	Day 28	2.00 [2.00 – 9.00]	9.00 [d] [9.00]	9.00 [2.00 – 12.00]	12.00 [12.00]

a. Results are reported as mean unless stated otherwise and [range].
b. Dosed in combination with GSK1120212B at 0.0075 mg/kg/day
c. Dosed in combination with GSK1120212B at 0.0225 mg/kg/day
d. n = 2, one male killed on Day 11 due to declining clinical condition

(table excerpted from Applicant's NDA)

Mean Toxicokinetic Parameters on Day 1 and 28 for GSK2167542 (Metabolite 4 (M4)) following Daily Oral Administration of GSK2118436 to Dogs

Parameter [a]	Period	Daily Dose of GSK2118436 (mg/kg/day)			
		Male		Female	
		5 (n=3) [b]	20 (n=3) [c]	5 (n=3) [b]	20 (n=3) [c]
AUC_{0-t} (µg.h/mL)	Day 1	1.46 [1.19 – 1.62]	2.73 [1.74 – 3.68]	1.29 [1.03 – 1.67]	2.18 [1.85 – 2.47]
	Day 28	1.50 [1.37 – 1.67]	2.71 [d] [2.51, 2.91]	1.97 [1.50 – 2.24]	2.38 [1.84 – 2.99]
C_{max} (µg/mL)	Day 1	0.0947 [0.0834 – 0.115]	0.176 [0.119 – 0.215]	0.0956 [0.0696 – 0.129]	0.136 [0.110 – 0.152]
	Day 28	0.100 [0.0836 – 0.118]	0.143 [d] [0.138, 0.148]	0.108 [0.0878 – 0.122]	0.127 [0.0964 – 0.175]
Median T_{max} (h)	Day 1	10.00 [10.00 – 12.00]	12.00 [10.00 – 24.00]	12.00 [9.00 – 12.00]	12.00 [4.00 – 24.00]
	Day 28	4.00 [4.00 – 10.00]	16.50 [d] [9.00, 24.00]	12.00 [12.00]	4.00 [0.00 – 12.00]

a. Results are reported as mean unless stated otherwise and [range].
b. Dosed in combination with GSK1120212B at 0.0075 mg/kg/day
c. Dosed in combination with GSK1120212B at 0.0225 mg/kg/day
d. n = 2, one male was euthanized on Day 11 due to declining clinical condition.

(table excerpted from Applicant's NDA)

Mean Toxicokinetic Parameters on Day 1 and 28 for GSK2285403 (Metabolite 7 (M7)) following Daily Oral Administration of GSK2118436 to Dogs

Parameter [a]	Period	Daily Dose of GSK2118436 (mg/kg/day)			
		Male		Female	
		5 (n=3) [b]	20 (n=3) [c]	5 (n=3) [b]	20 (n=3) [c]
AUC_{0-t} (µg.h/mL)	Day 1	8.87 [5.30 – 13.2]	31.6 [14.8 – 50.1]	6.47 [5.97 – 6.85]	22.8 [11.5 – 33.2]
	Day 28	6.20 [4.06 – 8.38]	31.8 [d] [27.8, 35.7]	8.90 [7.36 – 11.7]	25.5 [22.7 – 27.4]
C_{max} (µg/mL)	Day 1	0.741 [0.415 – 1.04]	2.50 [1.06 – 3.70]	0.572 [0.485 – 0.726]	1.73 [1.06 – 2.71]
	Day 28	0.536 [0.397 – 0.616]	1.81 [d] [1.63, 1.99]	0.645 [0.485 – 0.761]	1.69 [1.27 – 2.23]
Median T_{max} (h)	Day 1	10.00 [10.00 – 12.00]	12.00 [10.00 – 24.00]	10.00 [8.00 – 10.00]	10.00 [4.00 – 24.00]
	Day 28	2.00 [2.00 – 10.00]	16.25 [d] [8.50, 24.00]	12.00 [10.00 – 12.00]	12.00 [12.00]

a. Results are reported as mean unless stated otherwise and [range].
b. Dosed in combination with GSK1120212B at 0.0075 mg/kg/day
c. Dosed in combination with GSK1120212B at 0.0225 mg/kg/day
d. n = 2, one male was euthanized on Day 11 due to declining clinical condition.

(table excerpted from Applicant's NDA)

Mean Toxicokinetic Parameters on Day 1 and 28 for GSK2167542 (Metabolite 8 (M8)) following Daily Oral Administration of GSK2118436 to Dogs

Parameter[a]	Period	Daily Dose of GSK2118436 (mg/kg/day)			
		Male		Female	
		5 (n=3) [b]	20 (n=3) [c]	5 (n=3) [b]	20 (n=3) [c]
AUC_{0-t} (µg.h/mL)	Day 1	0.506 [d] [NA]	1.19 [d] [NA]	NA [e]	0.324 [f] [0.0934, 0.554]
	Day 28	0.443 [0.243 – 0.611]	1.36 [f] [1.17, 1.55]	0.519 [0.426 – 0.630]	0.843 [0.511 – 1.10]
C_{max} (µg/mL)	Day 1	0.0356 [0.0162 – 0.0639]	0.0591 [0.0309 – 0.108]	0.0210 [0.0125 – 0.0256]	0.0304 [0.0232 - 0.0412]
	Day 28	0.0322 [0.0214 – 0.0389]	0.0803 [f] [0.0670, 0.0936]	0.0336 [0.0283 – 0.0403]	0.0593 [0.0266 – 0.0810]
Median T_{max} (h)	Day 1	24.00 [24.00]	24.00 [24.00]	24.00 [24.00]	24.00 [12.00 - 24.00]
	Day 28	0.50 [0.50 – 24.00]	16.00 [f] [8.00, 24.00]	24.00 [24.00]	12.00 [9.00 – 24.00]

NA = Not applicable
a. Results are reported as mean unless stated otherwise and [range].
b. Dosed in combination with GSK1120212B at 0.0075 mg/kg/day
c. Dosed in combination with GSK1120212B at 0.0225 mg/kg/day
d. n = 1, Insufficient quantifiable plasma concentration data from which to calculate AUC for the other 2 animals.
e. Insufficient quantifiable plasma concentration data from which to calculate AUC.
f. n = 2, Insufficient quantifiable plasma concentration data from which to calculate AUC for the other animal.

(table excerpted from Applicant's NDA)

9 Reproductive and Developmental Toxicology

Study title: GSK2118436A: Oral Juvenile Toxicity Study in Rats (From Day 7 to 35 of Age) Followed by a 6-week Off-drug Period

Study no:	2012N148838
Study report location:	4.2.3.5
Conducting laboratory and location:	(b) (4) [redacted]
Date of study initiation:	February 12, 2012
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	GSK2118436A, JW211647-142P, 99.5%

Key Study Findings:

- All doses were tolerated.
- Target organs of toxicity were kidneys, stomach, and male reproductive organs.
- Kidney toxicity (cysts and tubular deposits) was noted in 1/3 and 10/20 mg/kg/day animals. Macroscopic kidney cysts were also noted in 35% of 0/20 mg/kg/day animals.
- Hyperplasia was noted in the stomach of ≥ 20% of 10/20 and 0/200 mg/kg/day animals.
- Male reproductive toxicity was seen 10/20 and 0/200 mg/kg/day animals and consisted of oligospermia in the epididymis and degeneration/atrophy and tubular dilatation in the testis.
- A decrease in femur (2-6%) and tibia (2-8%) length was noted all animals administered GSK2118436A.
- Female sexual maturation (day of vaginal opening) occurred approximately 4, 2, and 2 days earlier than controls in 10/20, 0/20, and 0/200 mg/kg/day females, respectively. No changes in sexual maturation were noted in 1/3 mg/kg/day females.

Reference ID: 3413290

Methods:

Doses:	Dose levels of 0 (vehicle given from PND 7 to 35), 1/3 (1 mg/kg/day from PND 7 to 21 with escalation to 3 mg/kg/day from PND 22 to 35), 10/20 (10 mg/kg/day from PND 7 to 21 then 20 mg/kg/day from PND 22 to 35), 0/20 (vehicle given from PND 7 to 21 then 20 mg/kg/day from PND 22-35), or 0/200 mg/kg/day (vehicle given from PND 7 to 21 then 200 mg/kg/day from PND 22 to 35) were given to juvenile rats. Doses were escalated on PND 22 in an effort to maintain consistent exposures across the duration of the dosing period.
Frequency of dosing:	Daily from Postnatal Day (PND) 7 to PND 35
Route of administration:	Oral gavage
Dose volume:	5 mL/kg
Formulation/Vehicle:	0.5% (w/v) hydroxypropylmethlycellulose (HPMC) K15M and 0.1% (v/v) Tween® 80 in ultra pure water
Species/Strain:	Rats / Crl:CD™(SD)
Number/Sex/Group:	18
Age:	7 days
Weight:	Males – 13 to 21.7 g; Females – 12.4 to 21.1 g
Dose justification:	For the PND 7 to 35 age range, a high dose regimen of 10/20 mg/kg/day was chosen because higher doses prior to PND 21 were not tolerated in a previous conducted study. A low dose regimen of 1/3 mg/kg/day, dosed from PND 7 to 35 was chosen to explore a dose response relationship. For the PND 22 to 25 age range, a high dose of 200 mg/kg/day was chosen because significant decreases in body weight gain were seen at 300 mg/kg/day in a previously conducted study. A low dose of 20 mg/kg/day was chosen to explore a dose response relationship.

Observations and Results:

Mortality [observations made twice daily]

Unremarkable

Clinical Signs [daily]

Unremarkable

Reference ID: 3413290

Body Weights [pre-dose; weekly]

During the post-weaning dosing period (PND 21 to 35), statistically significant, test item related reductions in body weight gain were seen at all doses and durations (0.89X, 0.85X, 0.89X and 0.79X for males, 0.91X, 0.93X, 0.91X and 0.80X for females at doses of 1/3, 10/20, 0/20 and 0/200 mg/kg/day, respectively). Consequently, lower body weights were seen during both the dosing and off-drug periods for males. In contrast, the lower body weight seen in females was reversible.

Food Consumption [pre-dose; weekly]

Decreased food consumption was consistent with body weight losses noted above.

Sexual Maturation [Daily beginning on PND 26]

No adverse effects on sexual maturation were seen in males. In females, sexual maturation (day of vaginal opening) occurred approximately 4, 2, and 2 days earlier than controls in 10/20, 0/20, and 0/200 mg/kg/day females, respectively. No changes in sexual maturation were noted in 1/3 mg/kg/day females.

Ophthalmoscopy [PND 35 and PND 77]

Unremarkable

Behavioral Performance [PND 59 and 72]

Unremarkable.

Behavioral performance assessment consisted of learning and memory tests in a Cincinnati water maze. The maze consisted of two paths. On the first day of testing, each animal was tested twice by measuring the time to complete the first path (Path A). This was repeated on two additional consecutive days (second trial on the first day and first trial on the second day were approximately 25 hours apart) using the same path. The same paradigm (i.e., 3 days of testing) was repeated using a second path (Path B). Testing of the two paths was separated by two days. Any abnormality in swimming was recorded.

Urinalysis [PND 36 and PND 77]

Unremarkable

Hematology [PND 36 and PND 77]

Unremarkable

Reference ID: 3413290

Coagulation [PND 36]

Unremarkable

Clinical Chemistry [PND 36 and PND 77]

A reversible increase in urea levels was noted in males (20, 31, 20, and 26%) and females (21, 29, 18, and 18%) following 1/3, 10/20, 0/20, and 0/200 mg/kg/day, respectively.

Organ Weights [at sacrifice]

A decrease in thymus weight (relative to body weight) was noted in males (12, 10, 12, and 10%) and females (0, 3, 5, and 4%) following 1/3, 10/20, 0/20, and 0/200 mg/kg/day, respectively. No differences in organ weights were noted at the end of the recovery period.

Bone Measurements [at sacrifice]

A decrease in femur length was noted in males (2, 4, 2, and 4%) and females (2, 6, 3, and 3%) following 1/3, 10/20, 0/20, and 0/200 mg/kg/day, respectively. A decrease in tibia length was also noted in males (2, 6, 2, and 5%) and females (4, 8, 3, and 3%) following 1/3, 10/20, 0/20, and 0/200 mg/kg/day, respectively. Changes in femur and tibia length were generally irreversible by the end of the recovery period in males and partially reversible in females.

Gross Pathology [at sacrifice]

Kidney cysts were noted in 30% and 40% of males and females administered 0/20 mg/kg/day, respectively. This was reversible by the end of the recovery period. Small epididymis that was irreversible by the end of the recovery period was observed in 20% of 0/200 mg/kg/day males.

Histopathology [at sacrifice]

Histopathological findings in 1/3 and 0/20 mg/kg/day were unremarkable. Findings noted at the end of the dosing period in 10/20 and 0/20 mg/kg/day animals were reversible or on a trend of reversibility by the end of the recovery period. Additional adverse findings of male reproductive organs were noted at the end of the recovery period, as detailed below.

Reference ID: 3413290

Incidence and grade of histopathology at end of dosing period

Tissue and finding	Grade	Males 10/20 mg/kg	Males 0/200 mg/kg	Females 10/20 mg/kg	Females 0/200 mg/kg
Kidney*					
-cyst	1-2	8/10	0/10	8/10	0/10
-tubular deposits	1-2	9/10	0/10	10/10	0/10
Stomach					
-hyperplasia	1	2/10	4/10	2/10	2/10

Grade 1, 2, 3, 4, 5 refers to minimal, slight, moderate, marked, severe, respectively.
**Kidney cysts and tubular deposits also noted in approximately 20% of 1/3 mg/kg/day animals.*
Severity of findings was generally dose-dependent.

Incidence and grade of histopathology at end of recovery period

Tissue and finding	Grade	Males 10/20 mg/kg	Males 0/200 mg/kg	Females 10/20 mg/kg	Females 0/200 mg/kg
Epididymis					
-oligospermia	1-5	3/10	3/10	-	-
Testis					
-degeneration/atrophy of seminiferous epithelium	1-4	4/10	4/10	-	-
-tubular dilatation	1-3	4/10	4/10	-	-

Grade 1, 2, 3, 4, 5 refers to minimal, slight, moderate, marked, severe, respectively.
Severity of findings was generally dose-dependent..

Toxicokinetics [pre-dose, and 0.5, 1, 2, 4, 8, and 24 hrs post-dose on PND 13, 22, and 35]

- Exposure levels (AUC) were less than dose proportional for GSK2118436.
- No significant sex differences in GSK2118436 exposure levels (AUC) were noted.
- Ratios of metabolite/dabrafenib AUC_{0-t} values ranged from 1.79 to 11.5 for M4, 1.31 to 3.83 for M7, and 0.02 to 0.2 for M8.
- Details are shown in Applicant's tables below.

Mean Toxicokinetic Parameters on PND 13, 22, and 35 Following Oral Administration of GSK2118436 to Rats

Composite Toxicokinetic Parameters for GSK2118436 (parent) from Male and Female Rats Following Oral Administration of GSK2118436A					
Parameter	Period	Dose (mg/kg/day)[a]			
		1/3	10/20	0/20	0/200
Male (n=2 or 3/timepoint)					
AUC_{0-t} (µg.h/mL)	PND 13[b]	5.10	12.9	NA	
	PND 22[c]	3.99	22.3	21.8	63.7
	PND 35[d]	2.14	7.11	7.40	11.0
C_{max} (µg/mL)	PND 13[b]	0.724	2.51	NA	
	PND 22[c]	0.870	2.84	3.85	7.98
	PND 35[d]	0.591	1.45	1.47	1.93
T_{max} (hour)	PND 13[b]	2.0	1.0	NA	
	PND 22[c]	2.0	4.0	2.0	4.0
	PND 35[d]	1.0	1.0	4.0	4.0
Female (n=2 or 3/timepoint)					
AUC_{0-t} (µg.h/mL)	PND 13[b]	3.29	13.1	NA	
	PND 22[c]	4.71	17.8	17.1	92.6
	PND 35[d]	1.92	6.21	7.89	15.9
C_{max} (µg/mL)	PND 13[b]	0.664	2.51	NA	
	PND 22[c]	1.07	3.30	4.39	7.26
	PND 35[d]	0.579	1.28	1.63	2.27
T_{max} (h)	PND 13[b]	2.0	2.0	NA	
	PND 22[c]	1.0	2.0	2.0	4.0
	PND 35[d]	1.0	4.0	2.0	2.0

NA = Not applicable, toxicokinetic samples were not taken on PND 13 in 0/20 and 0/200 mg/kg/day dose groups as these groups were given vehicle during PND 7 to 21.

a. Doses were escalated/initiated on PND 22, e.g., 1/3 indicates 1 mg/kg/day GSK2118436A given from PND 7-21 followed by 3 mg/kg/day from PND 22-35; 0/20 indicates vehicle given from PND 7-21 and GSK2118436A given from PND 22-35.

b. For groups given 1/3 or 10/20 mg/kg/day, PND 13 was Dosing Day 7.

c. For groups given 1/3 or 10/20 mg/kg/day, PND 22 was Dosing Day 16, the day of dose escalation; for groups given 0/20 or 0/200 mg/kg/day, PND 22 was the first day of administration of GSK2118436.

d. For groups given 1/3 or 10/20 mg/kg/day, PND 35 was Dosing Day 29; for groups given 0/20 or 0/200 mg/kg/day, PND 35 was the 14th day of administration of GSK2118436.

(table excerpted from Applicant's NDA)

Mean Toxicokinetic Parameters on PND 13, 22, and 35 for GSK2167542 (Metabolite 4 (M4)) Following Oral Administration of GSK2118436 to Rats

Parameter	Period	Dose (mg/kg/day)[a]			
		1/3	10/20	0/20	0/200
		Male (n=2 or 3/timepoint)			
AUC_{0-t} (µg.h/mL)	PND 13[b]	25.6	148	NA	
	PND 22[c]	20.2	97.8	86.0	120
	PND 35[d]	10.2	31.2	28.0	60.7
C_{max} (µg/mL)	PND 13[b]	1.22	7.41	NA	
	PND 22[c]	1.74	8.44	6.65	6.01
	PND 35[d]	1.44	3.03	3.44	5.87
T_{max} (h)	PND 13[b]	8.0	8.0	NA	
	PND 22[c]	8.0	8.0	8.0	8.0
	PND 35[d]	4.0	4.0	4.0	4.0
		Female (n=2 or 3/timepoint)			
AUC_{0-t} (µg.h/mL)	PND 13[b]	25.8	129	NA	
	PND 22[c]	11.8	67.0	63.1	171
	PND 35[d]	3.44	17.9	20.0	38.1
C_{max} (µg/mL)	PND 13[b]	1.41	6.56	NA	
	PND 22[c]	1.08	6.08	5.06	11.3
	PND 35[d]	0.424	1.46	1.49	2.82
T_{max} (h)	PND 13[b]	8.0	8.0	NA	
	PND 22[c]	8.0	8.0	8.0	24.0
	PND 35[d]	4.0	4.0	8.0	4.0

NA = Not applicable, toxicokinetic samples were not taken on PND 13 in 0/20 and 0/200 mg/kg/day dose groups

a. Doses were escalated/initiated on PND 22, e.g., 1/3 indicates 1 mg/kg/day GSK2118436A given from PND 7-21 followed by 3 mg/kg/day from PND 22-35; 0/20 indicates vehicle given from PND 7-21 and GSK2118436A given from PND 22-35.

b. For groups given 1/3 or 10/20 mg/kg/day, PND 13 was Dosing Day 7.

c. For groups given 1/3 or 10/20 mg/kg/day, PND 22 was Dosing Day 16, the day of dose escalation; for groups given 0/20 or 0/200 mg/kg/day, PND 22 was the first day of administration of GSK2118436.

d. For groups given 1/3 or 10/20 mg/kg/day, PND 35 was Dosing Day 29; for groups given 0/20 or 0/200 mg/kg/day, PND 35 was the 14th day of administration of GSK2118436.

(table excerpted from Applicant's NDA)

Mean Toxicokinetic Parameters on PND 13, 22, and 35 for GSK2167542 (Metabolite 7 (M7)) Following Oral Administration of GSK2118436 to Rats

Parameter	Period	Dose (mg/kg/day)[a]			
		1/3	10/20	0/20	0/200
		Male (n=2 or 3/timepoint)			
AUC_{0-t} (µg.h/mL)	PND 13[b]	13.5	46.9	NA	
	PND 22[c]	9.30	47.0	46.3	86.8
	PND 35[d]	2.92	9.32	11.4	14.8
C_{max} (µg/mL)	PND 13[b]	0.829	3.86	NA	
	PND 22[c]	1.54	4.56	4.60	9.08
	PND 35[d]	0.497	1.55	1.53	2.26
T_{max} (hour)	PND 13[b]	8.0	4.0	NA	
	PND 22[c]	4.0	4.0	4.0	8.0
	PND 35[d]	2.0	4.0	4.0	4.0
		Female (n=2 or 3/timepoint)			
AUC_{0-t} (µg.h/mL)	PND 13[b]	12.6	43.1	NA	
	PND 22[c]	9.35	42.2	39.1	160
	PND 35[d]	5.76	18.1	22.9	30.8
C_{max} (µg/mL)	PND 13[b]	0.835	4.01	NA	
	PND 22[c]	1.19	5.59	4.85	12.4
	PND 35[d]	0.764	3.12	2.76	2.71
T_{max} (hour)	PND 13[b]	8.0	4.0	NA	
	PND 22[c]	2.0	4.0	4.0	8.0
	PND 35[d]	2.0	4.0	4.0	2.0

NA = Not applicable, toxicokinetic samples were not taken on PND 13 in 0/20 and 0/200 mg/kg/day dose groups

a. Doses were escalated/initiated on PND 22, e.g., 1/3 indicates 1 mg/kg/day GSK2118436A given from PND 7-21 followed by 3 mg/kg/day from PND 22-35; 0/20 indicates vehicle given from PND 7-21 and GSK2118436A given from PND 22-35.

b. For groups given 1/3 or 10/20 mg/kg/day, PND 13 was Dosing Day 7.

c. For groups given 1/3 or 10/20 mg/kg/day, PND 22 was Dosing Day 16, the day of dose escalation; for groups given 0/20 or 0/200 mg/kg/day, PND 22 was the first day of administration of GSK2118436.

d. For groups given 1/3 or 10/20 mg/kg/day, PND 35 was Dosing Day 29; for groups given 0/20 or 0/200 mg/kg/day, PND 35 was the 14th day of administration of GSK2118436.

(table excerpted from Applicant's NDA)

Mean Toxicokinetic Parameters on PND 13, 22, and 35 for GSK2167542 (Metabolite 8 (M8)) Following Oral Administration of GSK2118436 to Rats

Parameter	Period	Dose (mg/kg/day)[a]			
		1/3	10/20	0/20	0/200
		Male (n=2 or 3/timepoint)			
AUC_{0-t} (µg.h/mL)	PND 13[b]	0.262	2.57	NA	
	PND 22[c]	ND	3.05	ND	1.23
	PND 35[d]	ND	0.495	0.153	1.41
C_{max} (µg/mL)	PND 13[b]	0.0178	0.157	NA	
	PND 22[c]	0.0303	0.244	0.0469	0.0676
	PND 35[d]	0.0129	0.0318	0.0403	0.120
T_{max} (hour)	PND 13[b]	4.0	4.0	NA	
	PND 22[c]	8.0	8.0	8.0	24.0
	PND 35[d]	4.0	4.0	4.0	2.0
		Female (n=2 or 3/timepoint)			
AUC_{0-t} (µg.h/mL)	PND 13[b]	0.440	2.37	NA	
	PND 22[c]	ND	2.23	ND	1.70
	PND 35[d]	ND	ND	ND	0.718
C_{max} (µg/mL)	PND 13[b]	0.0217	0.111	NA	
	PND 22[c]	0.0182	0.216	0.0283	0.126
	PND 35[d]	ND	0.0126	0.0136	0.0451
T_{max} (hour)	PND 13[b]	8.0	8.0	NA	
	PND 22[c]	8.0	8.0	8.0	24.0
	PND 35[d]	ND	4.0	2.0	4.0

NA = Not applicable, toxicokinetic samples were not taken on PND 13 in 0/20 and 0/200 mg/kg/day dose groups as these groups were given vehicle during PND 7 to 21

ND = Not determined, insufficient data to calculate AUC

a. Doses were escalated/initiated on PND 22, e.g., 1/3 indicates 1 mg/kg/day GSK2118436A given from PND 7-21 followed by 3 mg/kg/day from PND 22-35; 0/20 indicates vehicle given from PND 7-21 and GSK2118436A given from PND 22-35.

b. For groups given 1/3 or 10/20 mg/kg/day, PND 13 was Dosing Day 7.

c. For groups given 1/3 or 10/20 mg/kg/day, PND 22 was Dosing Day 16, the day of dose escalation; for groups given 0/20 or 0/200 mg/kg/day, PND 22 was the first day of administration of GSK2118436.

d. For groups given 1/3 or 10/20 mg/kg/day, PND 35 was Dosing Day 29; for groups given 0/20 or 0/200 mg/kg/day, PND 35 was the 14th day of administration of GSK2118436.

(table excerpted from Applicant's NDA)

11 Integrated Summary and Safety Evaluation

GlaxoSmithKline submitted an efficacy supplement to support the use of dabrafenib (Tafinlar™), in combination with trametinib (Mekinist™), for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test.

Reference ID: 3413290

Pharmacology studies demonstrated that the dabrafenib and trametinib combination results in greater growth inhibition of $BRAF^{V600}$ mutation-positive cell lines *in vitro* and *in vivo* xenograft models than with either drug alone, as conveyed in the Taflinar™ and Mekinist™ label (see separate labeling review).

The toxicity of repeated oral dosing of the dabrafenib and trametinib combination was assessed by conducting a 4-week toxicity studies in dogs. The dog was considered a relevant species based on previously conducted pharmacology and toxicity studies of each drug separately. Single-agent toxicity studies of repeated oral dosing of dabrafenib or trametinib were previously reviewed under NDA 202806 and 204114, respectively. Target organs of toxicity for single-agent dabrafenib were the skin (lesions and papules), heart (hemorrhage of the atrioventricular valve), and male reproductive organs (degeneration in the testis and aspermia in the epididymis). Lymphoid depletion in the thymus was also noted. For single-agent trametinib, the primary target organ of toxicity was the skin (lesions and scabs). In the 4-week combination toxicity study, dogs were orally administered 0/0, 0.0075/5, or 0.0225/20 mg/kg/day of the trametinib/dabrafenib combination, respectively. Plasma exposure levels (AUC) were up to 0.5/9 times the exposure level in humans receiving the recommended dose of the trametinib/dabrafenib combination. Target organs of toxicity were the stomach (inflammation), thymus (decreased cellularity), and male reproductive organs (germ cell degeneration/oligospermia in epididymis and germinal epithelium degeneration in the testes). Since these toxicities were not unique to the dabrafenib and trametinib combination, changes to their respective labels were not warranted.

The Applicant also submitted a study to assess the toxicity study of dabrafenib alone in juvenile rats. Rats were administered daily dabrafenib from Postnatal Day (PND) 7 to PND 35 at dose levels of 0, 1/3 (1 mg/kg/day from PND 7 to 21 with escalation to 3 mg/kg/day from PND 22 to 35), 10/20 (10 mg/kg/day from PND 7 to 21 then 20 mg/kg/day from PND 22 to 35), 0/20 (vehicle given from PND 7 to 21 then 20 mg/kg/day from PND 22-35), or 0/200 mg/kg/day (vehicle given from PND 7 to 21 then 200 mg/kg/day from PND 22 to 35). Doses were escalated on PND 22 in an effort to maintain consistent exposures across the duration of the dosing period. All doses of dabrafenib were tolerated. Target organs of toxicity were the kidneys, bone, stomach, and male reproductive organs. An increased incidence of cysts and tubular deposits was noted in the kidney following 1/3 and 10/20 mg/kg/day of dabrafenib. Macroscopic kidney cysts were also noted in 35% of 0/20 mg/kg/day animals. Bone toxicity consisted of an approximate 2, 5, 2.5, and 3.5% decrease in femur length and 3, 7, 2.5, and 4% decrease in tibia length following 1/3, 10/20, 0/20, and 0/200 mg/kg/day of dabrafenib, respectively. Kidney and bone toxicity occurred at doses approximately ≥ 0.23 times the human exposure at the recommended adult dose of dabrafenib based on AUC. Hyperplasia was noted in the stomach of ≥ 20% of 10/20 and 0/200 mg/kg/day animals (≥ 0.77 times the human exposure at the recommended adult dose of dabrafenib based on AUC). Male reproductive toxicity was noted following 10/20 and 0/200 mg/kg/day of dabrafenib (approximately ≥ human exposure at the recommended adult dose of dabrafenib based on AUC) and consisted of oligospermia in the epididymis and degeneration/atrophy and tubular dilatation in the testis. Female sexual

Reference ID: 3413290

maturation (day of vaginal opening) occurred approximately 4, 2, and 2 days earlier than controls in 10/20, 0/20, and 0/200 mg/kg/day females, respectively (approximately ≥ 2 times the human exposure at the recommended adult dose of dabrafenib based on AUC). Adverse changes in kidney, bone, and female sexual maturation were considered clinically relevant and resulted in changes to the Taflinar™ label (see separate labeling review). Adverse changes to male reproductive organs were also considered clinically relevant but did not necessitate changes to the Taflinar™ label since these findings were already reflected in the current Taflinar™ labeling.

In conclusion, the non-clinical studies support the use of dabrafenib (Tafinlar™), in combination with trametinib (Mekinist ™), for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. From a Pharmacology/Toxicology perspective, approval of dabrafenib (Tafinlar™), in combination with trametinib (Mekinist ™) is recommended.

Reference ID: 3413290

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/s/

ALEXANDER H PUTMAN
11/26/2013

WHITNEY S HELMS
11/26/2013

The major nonclinical data required to support the approval of the combination of dabrafenib and trametinib were submitted previously under NDAs 202806 and 204114. The combination toxicology data submitted with the current supplements supports the use of the two drugs together. Relevant data from the studies submitted with the current supplements will be added to the labels for the individual drugs. I concur with Dr. Putman's conclusions that the available nonclinical data support the approval of the combination of dabrafenib and trametinib for the treatment of V600E or V600K positive metastatic melanoma.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202806Orig1s002

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

BLA Serial Number:	202806/ 02, 204114/01
Drug Name:	Tafinlar® (Dabrafenib), Mekinist® (Trametinib)
Indication(s):	unresectable or metastatic melanoma [redacted] (b) (4)
Applicant:	GlaxoSmithKline (GSK)
Receipt Date	07/08/2013
PDUFA Goal Date	12/20/2013
Review Priority:	Priority
Biometrics Division:	V
Statistical Reviewer:	Weishi Yuan
Concurring Reviewers:	Kun He, Team Leader Rajeshwari Sridhara, Division Director
Medical Division:	Division of Oncology Products 2
Clinical Team:	Maitreyee Hazarika, Clinical Reviewer Marc Theoret, Team Leader Patricia Keegan, Division Director
Project Manager:	Norma Griffin

Keywords: Objective Response Rate (ORR), Progression Free Survival (PFS), Overall Survival (OS), Exact Confidence Intervals, Melanoma

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1. EXECUTIVE SUMMARY

The applicant submitted data and final study reports of a Phase 1/2 study to support accelerated approval for combination of dabrafenib and trametinib indicated for the treatment of patients with unresectable or metastatic melanoma (b) (4)

This application was based on a single trial, Study BRF113220 (Study 113220), titled "An Open-Label, Dose-Escalation, Phase IB/II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of the BRAF Inhibitor GSK2118436 in Combination with the MEK Inhibitor GSK1120212 in Subjects with BRAF Mutant Metastatic Melanoma". The study comprised four parts, of which Part C was a randomized Phase 2 portion. This review focuses on the Part C of Study 113220 which supports the efficacy findings.

For Part C of Study 113220, the original primary endpoint was the occurrence rate of squamous cell carcinoma (SCC), a safety endpoint. Objective response rate (ORR) and progression free survival (PFS) were also listed as primary objectives. Secondary endpoint was overall survival (OS). The efficacy endpoints were not formally tested. A total of 162 patients were randomized in a 1:1:1 allocation with 54 in each of the three arms: dabrafenib 150 mg (150) arm, dabrafenib 150 mg / trametinib 1 mg (150/1) arm, and dabrafenib 150 mg / trametinib 2 mg (150/2) arm.

The data and analyses from current submission showed that the ORR of patients in the dabrafenib/trametinib 150 mg / 2 mg arm was higher than that of patients in the dabrafenib 150 mg arm. Based on investigator's assessment, ORR was 76% with 95% confidence interval (CI) (62.4%, 86.5%) in the 150/2 combination arm compared with 54% with 95% CI (39.6%, 67.4%) in the dabrafenib 150 mg monotherapy arm, and the difference between the two arms was 22% with 95% CI (2.5%, 40.7%). FDA re-evaluated the outcome of the BIRC assessment. Based on FDA's evaluation of BICR assessment, ORR was 57% with 95% CI (43.2%, 70.8%) in the 150/2 combination arm compared with 46% with 95% CI (32.6%, 60.4%) in the dabrafenib 150 mg monotherapy arm, and the difference between the two arms was 11% with 95% CI (-8.6%, 30.2%).

Also based on investigator's assessment, the median PFS was 9.4 months in the 150/2 combination arm compared with 5.8 months in the 150 monotherapy arm. The estimated hazard ratio (HR) based on a stratified Pike estimator was 0.39 with 95% CI (0.25, 0.62). The results of blinded independent central review (BICR) assessed ORR and PFS were similar to those assessed by investigators.

There was no difference in OS between the 150/2 combination arm and 150 monotherapy arm. With a total of 33 deaths, the median survivals in the two study arms were not estimable. The estimated hazard ratio (HR) based on pike estimator was 0.67 with 95% CI (0.34, 1.34).

The incidence rate of Cutaneous Squamous Cell Carcinoma (SCC) was the original primary endpoint of Study 113220 Part C. A total of 15 patients experienced SCC in the randomization phase of Part C, with 4 in the 150 arm, 1 in the dabrafenib 150/1 arm and 4 in the 150/2 arm. Based on the ITT population, the difference between the 150 arm and 150/1 arm was -17% with 95% CI (-35.5%, 3.1%), and the two-sided p-value from Fisher's Exact test was 0.008; and the difference between the 150 arm and 150/2 arm was -11% with 95% CI (-30.2%, 8.6%), and the two-sided p-value from Fisher's Exact test was 0.15. The results based on the safety population were similar.

Based on the data and analyses, the study results showed that dabrafenib 150 mg / trametinib 2 mg combination observed a higher ORR compared with dabrafenib 150 mg monotherapy. Whether the data and analyses provided in this submission showed a favorable benefit/risk profile in supporting a regulatory approval will be a clinical decision.

2. INTRODUCTION

The applicant submitted data and final study reports of a Phase 1/2 study to seek an accelerated approval for the combination of dabrafenib 150 mg and trametinib 2 mg. This application was based on Study BRF113220 (Study 113220), an open-label, dose-escalation, Phase 1/2 study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of the BRAF inhibitor dabrafenib in combination with the MEK Inhibitor trametinib in subjects with BRAF mutant metastatic melanoma.

2.1 Overview

2.1.1. Class and Indication

Dabrafenib was reported to be a potent and selective inhibitor of B-RAF kinase activity with a mode of action consistent with adenosine triphosphatecompetitive inhibition. Trametinib was reported to be a potent and selective allosteric non competitive inhibitor of MEK1/MEK2 activation and kinase activity.

The indication sought for the combination therapy was the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutation as detected by an FDA approved test.

2.1.2. Regulatory History

Both dabrafenib and trametinib were approved as monotherapy [redacted] (b) (4) in May 2012.

The combination therapy was studied under IND113557. In the January 2012 meeting, the applicant proposed the development plan for the combination therapy which included Study 113220 and two proposed Phase 3 studies MEK115306 and MEK116513, and the potential for submission under the accelerated approval program based on results of Study 113220. Two pre-NDA meetings were held for this submission on September 12 and December 6, 2012. The data package was converted to CDISC format after the first pre-NDA meeting to facilitate FDA review [redacted] (b) (4).

The orphan drug exclusivity was granted on January 12, 2011 for dabrafenib and on December 20, 2010 for trametinib.

2.1.3. Study Reviewed

Study 113220 was an open-label, dose-escalation, Phase 1/2 study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of the BRAF inhibitor dabrafenib in combination with the MEK Inhibitor trametinib in

subjects with BRAF mutant metastatic melanoma. The study comprised four parts, designated as Part A to D, of which Part C was the three-arm randomized Phase 2 portion of the study. Part A was to determine the pharmacokinetics (PK) of single dose dabrafenib alone and with repeat dose trametinib. Part B was to determine the safety, tolerability and range of tolerated doses of dabrafenib and trametinib in combination in the targeted patient population. Part D was to determine PK of dabrafenib hydoxypropyl-methylcellulose (HPMC) capsules alone and in combination with trametinib, since Part A, B and C were conducted using gelatin capsules but the commercial formulation will be HPMC capsules.

In Part C, patients were randomized in a 1:1:1 ratio to receive oral dabrafenib 150 mg twice daily, either alone or in combination with trametinib 1 mg daily or 2 mg daily. Patients in the dabrafenib monotherapy arm had the option to cross over to the 150/2 combination arm upon disease progression.

The primary objective of Part C was to compare the rate of squamous cell carcinoma (SCC) between the dabrafenib monotherapy arm and the two combination therapy arms. Efficacy endpoints ORR and PFS were also listed as primary objectives. OS was added as a secondary endpoint in a protocol amendment. There was no formal statistical test or multiplicity adjustment plan proposed for the efficacy endpoints. The sample size calculation was based on the assumptions on the SCC rate.

2.2 Data Sources

Data used for review is from the electronic submission received from July 8, 2013. The network paths for these submissions are:

- \\Cdsesub1\evsprod\NDA202806\0063.

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data and reports of this submission were submitted electronically. The applicant submitted data as well as the related SAS programs for analysis.

The applicant submitted datasets using CDISC format. The data were properly organized and adequate documentations were provided.

The reviewer was able to perform the analyses using the submitted data.

3.2 Evaluation of Efficacy

3.2.1. Study Design and Endpoints

Part C of Study 113220 was a three-arm, open-label, randomized Phase II study comparing dabrafenib monotherapy with 2 doses of dabrafenib and trametinib combination in patients with BRAF V600 mutation metastatic melanoma.

Patients were randomized in a 1:1:1 ratio to receive oral dabrafenib 150 mg twice daily alone (150 arm), oral dabrafenib 150 mg twice daily combined with oral trametinib 1 mg once daily (150/1 arm), or oral dabrafenib 150 mg twice daily combined with oral trametinib 2 mg once daily (150/2 arm). Randomization was not stratified. Patients in the dabrafenib monotherapy arm had the option to cross over to the 150/2 combination therapy arm upon disease progression.

The primary endpoint was a safety endpoint, the incidence rate of SCC. The primary efficacy endpoints were progression free survival (PFS), overall response rate (ORR), and duration of response. OS was a secondary efficacy endpoint.

An interim analysis of Part C safety and efficacy data by treatment arm was conducted, which was pre-specified in protocol Amendment 3. The results of the interim analysis were shared with health authorities including the FDA but not with study investigators. Based on the discussion of the results of the interim analysis with health authorities, the protocol was amended to eliminate additional interim analysis for efficacy data, and Blinded Independent Central Review (BICR) was introduced.

Reviewer's Comments:

Though PFS and ORR were listed as the primary efficacy endpoints of Part C, the formal hypothesis testing was only set up for the safety endpoint SCC. Power analysis was not conducted for any efficacy endpoint. No adjustment for multiplicity, or interim analysis were proposed or made.

3.2.2. Efficacy Measures

In the applicant's analysis plan the primary efficacy endpoints were PFS and ORR, and secondary efficacy endpoint was OS. Disease assessments were performed using radiographic imaging (e.g., CT, MRI, bone scan, plain radiograph) and physical examination, and were recorded as CR, PR, stable disease (SD), or progressive disease (PD) according to RECIST v1.1 criteria. All imaging results were assessed by the investigator. Subjects whose disease responded (either CR or PR) had a confirmatory disease assessment performed at least 4 weeks after the date of the assessment during which response was demonstrated. Post-baseline response evaluations were made every 4 weeks.

ORR was defined as the percentage of subjects achieving either a CR or PR per RECIST 1.1. Duration of Response (DoR) was defined as the time from first documented evidence of CR or PR until first documented disease progression or death due to any cause.

PFS was defined as the interval of time between the date of randomization and the earlier of date of disease progression or date of death due to any cause. In general the applicant's analysis plan followed the FDA's Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics.

ORR and PFS were also assessed by a blinded independent central review (BICR). According to the BICR Charter, the independent review was composed of three sequential stages of review: 1.) the pre-selection of the target skin lesions by the independent oncologist prior to the Independent Radiology Review; 2.) the Independent Radiology Review, a central blinded assessment of medical imaging data by one qualified radiologist; and 3.) the Independent Oncology Review, in which one independent qualified oncologist will assess the skin lesion photographs in addition to the independent radiology findings to make a final determination for the case, if applicable.

For the independent review, the primary radiologist will assess study imaging to determine overall radiographic tumor response at each time point using modified RECIST 1.1. If applicable, with guidance of the oncologist, the radiologist will include target skin lesions in the time point assessments. The oncologist will assess any additional skin lesions and determine relevant endpoints based on a combined assessment of radiologic and skin lesions.

For the secondary endpoint, OS was defined as the time from randomization to death by any cause. For patients who had not died, duration of survival was censored at the date the patient was last contacted. The OS included all deaths, including those following crossover.

Final analyses were to be conducted when, for all three treatment arms combined, at least 70% subjects have either progressed or died.

Reviewer's Comments:

1. While in the final clinical study report, investigator assessed ORR and PFS were considered as the primary efficacy endpoints, the study protocol did not explicitly state that the investigator assessments were primary outcomes.
2. In this review ORR, DoR and PFS assessed by the BICR are reported.

3.2.3. Sample Size Consideration

A total of 150 patients were planned for this study with 50 in each of the three arms. Assuming the SCC rate was 20% in the dabrafenib monotherapy arm and 3% in a combination therapy arm, the study would have 82% power to detect an absolute 17% decrease with 0.05% type I error rate using a Fisher's exact test.

A total of 162 patients were randomized with 54 in each of the three arms.

Reviewer's Comments:

The study was initially designed to demonstrate a superior safety profile of the combination therapy. The initial sample size for each arm was 20, and it was increased to 50 patients per arm in a protocol amendment.

3.2.4. Statistical Methodologies

The Intent-to-Treat (ITT) population was used for the efficacy analysis. The ITT population comprises all randomized patients regardless of whether or not treatment was administered.

Both PFS and OS were summarized using the Kaplan-Meier estimates and the differences between the monotherapy arm and one of the two combination therapy arms were analyzed using a log-rank test. The hazard ratio (HR) was estimated by the Pike estimator.

ORR was analyzed using the exact methods. Exact 95% confidence intervals (CIs) for ORR in each arm and the difference between the two arms were calculated. The differences between the monotherapy arm and one of the two combination therapy arms were analyzed using a Fisher's exact test. DoR was analyzed similar to PFS.

For all efficacy endpoints, a statistical procedure to adjust multiple endpoints was not proposed.

Reviewer's Comments:

1. Since the primary hypothesis testing was only established for the safety endpoint SCC in the protocol and statistical analysis plan, and multiplicity adjustment was not proposed, although the p-values obtained from testing procedure for all efficacy endpoints, including ORR, PFS and OS, were used as nominal to evaluate the findings, the p-values are not interpretable.
2. The DoR analysis is limited to responders. Therefore regardless of the previous issue no comparison can be made in the responder analysis.

3.2.5. Patient Disposition, Demographic and Baseline Characteristics

A total of 162 patients were randomized to one of three treatment arms using a 1:1:1 randomization ratio with 54 patients in each arm. A total of 16 study centers enrolled patients, with 2 centers in Australia and 14 centers in the USA.

The study was initiated on December 14, 2010 and primary analysis data cut-off date was May 31, 2012. The median follow up time was 14 months.

As of the primary analysis cut-off date, 66% of patients were still ongoing in the study, with 65% in the 150 monotherapy arm, 59% in the 150/1 combination arm, and 74% in the 150/2 combination arm. Forty three (81%) patients randomized to the 150 monotherapy arm received 150/2 combination therapy in the crossover phase. A total of 51 subjects across the three arms died at or prior to the time of the data cut-off. The patient disposition is summarized in Table 1.

Table 1. Patient Disposition

Dabrafenib **Trametinib**	150 mg BID -- N (%)	150 mg BID 1 mg QD N (%)	150 mg BID 2 mg QD N (%)
Randomized	54 (100)	54 (100)	54 (100)
Subject Status			
Died	19 (35)	18 (33)	14 (26)
Ongoing in Study	35 (65)	32 (59)	40 (74)
On Treatment	16 (30)	23 (43)	23 (43)
In Follow-up	19 (35)	9 (17)	17 (31)
Withdrawl from Study	0	4 (7)	0
Withdrawl Consent	0	4 (7)	0

Demographic characteristics at baseline are summarized in Table 2.

Table 2. Patient Demographics

Dabrafenib	150 mg BID	150 mg BID	150 mg BID
Trametinib	--	1 mg QD	2 mg QD
	N (%)	N (%)	N (%)
Randomized	54 (100)	54 (100)	54 (100)
Gender			
Male	29 (54)	30 (56)	34 (63)
Female	25 (46)	24 (44)	20 (37)
Race			
Caucasian	52 (96)	54 (100)	53 (98)
Asian	0	0	1 (2)
Missing	2 (4)	0	0
Age			
< 65	42 (78)	46 (85)	43 (80)
≥ 65	12 (22)	8 (15)	11 (20)
Country			
USA	49 (91)	50 (93)	44 (81)
Australia	5 (9)	4 (7)	10 (19)

Disease characteristics at baseline are summarized in Table 3.

Table 3. Disease Characteristics at Baseline

Dabrafenib **Trametinib**	150 mg BID -- N (%)	150 mg BID 1 mg QD N (%)	150 mg BID 2 mg QD N (%)
Randomized	54 (100)	54 (100)	54 (100)
ECOG baseline			
0	34 (63)	38 (70)	35 (65)
≥1	20 (37)	16 (30)	19 (35)
BRAF status			
V600E	45 (83)	45 (83)	47 (87)
V600K	9 (17)	9 (17)	7 (13)
Primary Tumor at Diagnosis			
Melanoma	53 (98)	53 (98)	54 (100)
Unknown	1 (2)	1 (2)	0
Baseline Disease Stage			
IIIcM0, IVm1a, IVM1B	17 (31)	21 (39)	16 (30)
IVM1c	37 (69)	33 (61)	38 (70)
LDH at Baseline			
≤ULN	27 (50)	29 (54)	32 (59)
>ULN	27 (50)	25 (46)	22 (41)
Prior Brian Met			
Yes	4 (7)	7 (13)	2 (4)
No	50 (93)	47 (87)	52 (96)

Reviewer's comments:

The demographic and baseline characteristics of the ITT population are generally balanced over the two arms.

3.2.6. Results and Conclusions

Primary Endpoint Analysis: ORR

The observed ORRs in the combination therapy arms were higher than that of the monotherapy arm. The results of ORR analyses, along with corresponding DoR, by the investigator's assessment and BICR are summarized in the following table.

Table 4. Primary ORR Analyses

Dabrafenib	150 mg BID	150 mg BID	150 mg BID
Trametinib	--	1 mg QD	2 mg QD
	N=54	N=54	N=54
Investigator			
CR+PR (%)	29 (54%)	27 (50%)	41 (76%)
95% CI	(39.6%, 67.4%)	(36.1%, 63.9%)	(62.4%, 86.5%)
CR	2 (4)	3 (6%)	5 (9%)
PR	27 (50%)	24 (44%)	36 (67%)
Difference (95% CI)	--	-4% (-23.1%, 15.9%)	22% (2.5%, 40.7%)
Median DoR (95% CI)	5.6 (4.1, 7.4)	9.5 (7.4, NE)	10.5 (7.4, 14.9)
BICR			
CR+PR (%)	25 (46%)	21 (39%)	33 (61%)
95% CI	(32.6%, 60.4%)	(25.9%, 53.1%)	(46.9%, 74.1%)
CR	4 (7%)	4 (7%)	7 (13%)
PR	21 (39%)	17 (31%)	26 (48%)
Difference (95% CI)	--	-7% (-26.7%, 12.3%)	15% (-5.0%, 33.7%)
Median DoR (95% CI)	7.6 (4.7, NE)	11.3 (5.8, NE)	7.6 (6.7, NE)

Reviewer's comments:

1. As discussed in Section 3.2.4, the p-values from the Fisher's exact test for ORR are considered nominal and therefore not presented in this review. The 95% confidence intervals are presented for ORR using the exact method and for median DoR using the Kaplan-Meier estimates.
2. The results by investigator and BICR are consistent with each other.
3. An efficacy interim analysis was performed by the Internal Data Review Committee on November 9, 2011 which included data through November 8, 2011. All patients were enrolled at that time. The results of the interim analysis were consistent with those of the final analysis, and the nominal p-value for the interim analysis was less than 0.05.

4. The clinical reviewer also reevaluated the data and produced a dataset for ORR and DoR. Patients with no measurable disease at baseline were considered not evaluable and not included as responders (Patient (b) (6) and (b) (6)). The following table summarizes the ORR results based on FDA's assessment. The results of FDA-evaluated investigator-assessed ORR are the same as those reported by the applicant. The results of FDA-evaluated BICR ORR are similar to those reported by the applicant.

Table 5. ORR Results Based on FDA Assessment

Dabrafenib	150 mg BID	150 mg BID	150 mg BID
Trametinib	--	1 mg QD	2 mg QD
FDA_Investigator	N=54	N=54	N=54
CR+PR (%)	29 (54%)	27 (50%)	41 (76%)
95% CI	(39.6%, 67.4%)	(36.1%, 63.9%)	(62.4%, 86.5%)
CR	2 (4)	3 (6%)	5 (9%)
PR	27 (50%)	24 (44%)	36 (67%)
Difference (95% CI)	--	-4% (-23.1%, 15.9%)	22% (2.5%, 40.7%)
Median DoR (95% CI)	5.6 (4.1, 7.4)	9.5 (7.4, NE)	10.5 (7.4, 14.9)
FDA_BICR	N=54	N=54	N=54
CR+PR (%)	25 (46%)	20 (37%)	31 (57%)
95% CI	(32.6%, 60.4%)	(24.3%, 51.3%)	(43.2%, 70.8%)
CR	4 (7%)	3 (6%)	5 (9%)
PR	21 (39%)	17 (31%)	26 (48%)
Difference (95% CI)	--	-9% (-28.5%, 10.5%)	11% (-8.6%, 30.2%)
Median DoR (95% CI)	7.6 (4.7, NE)	9.5 (5.6, NE)	7.6 (6.7, NE)

5. For subgroup analyses of ORR please refer to Section 4.

Primary Endpoint Analysis: PFS

Based on investigator's assessment, there were a total of 117 patients who progressed or died at time of the primary analysis, of which 47 were in the 150 arm, 39 were in the 150/1 arm and 41 in the 150/2 arm.

Table 6 summarizes the main efficacy analysis results for PFS. PFS in the combination arms was longer than that of the monotherapy arm. Per investigator's assessment, the median PFS was 5.8 months for the 150 arm, 9.2 months for the 150/1 arm and 9.4 months for the 150/2 arm. The estimated HR was 0.39 with 95% CI (0.25, 0.62) between the 150/2 arm and the 150 arm based on a Pike estimator stratified by disease staging at randomization. The results by the BIRC were similar.

Table 6. Results of PFS

Dabrafenib	150 mg BID	150 mg BID	150 mg BID
Trametinib	--	1 mg QD	2 mg QD
Investigator	N=54	N=54	N=54
Number of Events (%)	47 (87.0%)	39 (72.2%)	31 (57.4%)
Median PFS (95% CI)	5.8 (4.3, 7.4)	9.2 (5.7, 11.0)	9.4 (7.6, 16.7)
HR (95% CI) by Pike		0.56 (0.37, 0.87)	0.39 (0.25, 0.62)
HR (95% CI) by Cox		0.54 (0.35, 0.84)	0.37 (0.23, 0.60)
BICR	N=54	N=54	N=54
Number of Events (%)	32 (59.3%)	36 (66.7%)	28 (51.9%)
Median PFS (95% CI)	7.3 (5.5, 9.4)	8.3 (5.6, 11.1)	9.2 (7.4, NE)
HR (95% CI) by Pike		0.73 (0.45, 1.19)	0.54 (0.32, 0.91)
HR (95% CI) by Cox		0.70 (0.43, 1.14)	0.53 (0.31, 0.88)

Figure 1 shows the estimated Kaplan-Meier curves for the distribution of PFS assessed by investigator.

Figure 1. K-M Curves of PFS by Investigator

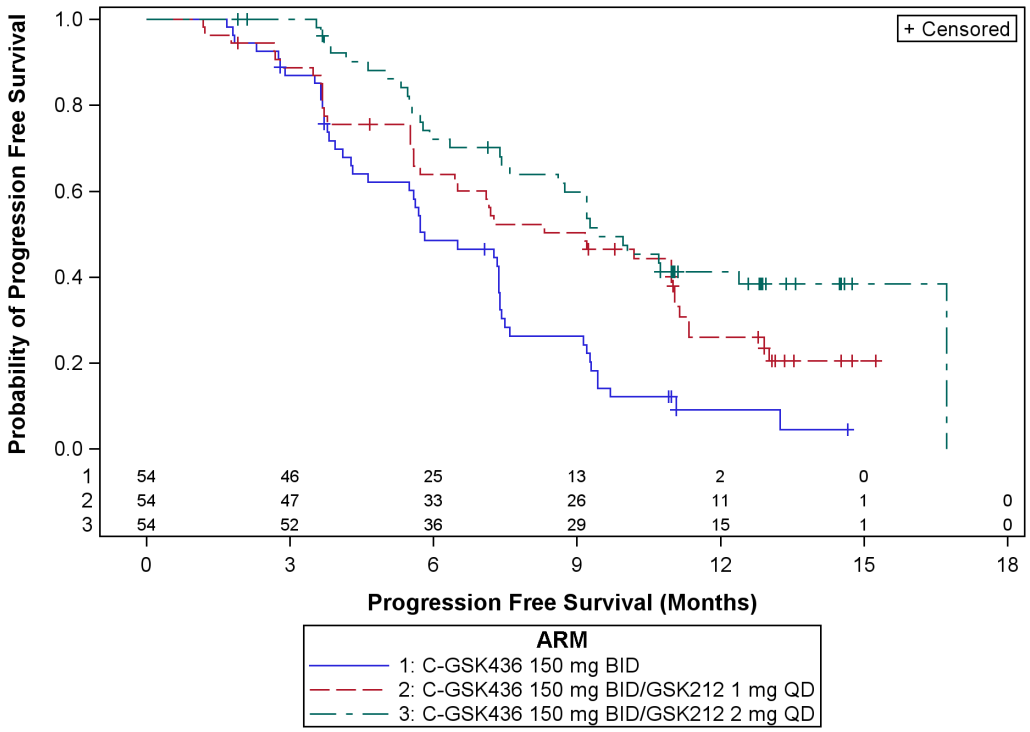
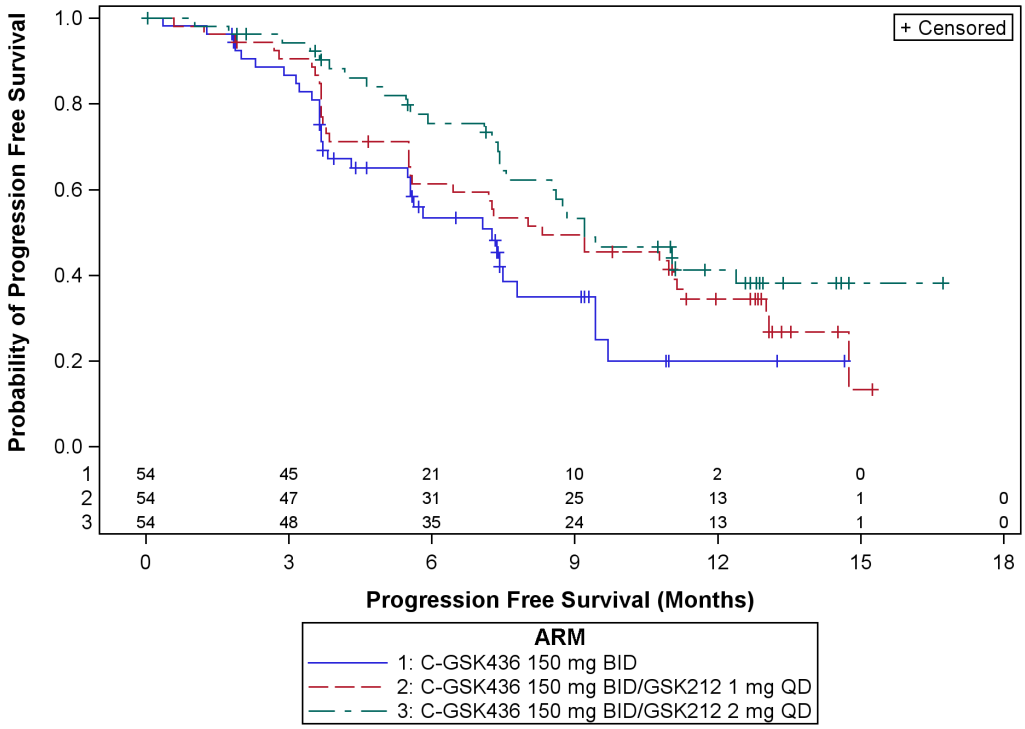


Figure 2 shows the estimated Kaplan-Meier curves for the distribution of PFS assessed by BICR.

Figure 2. K-M Curves of PFS by BICR

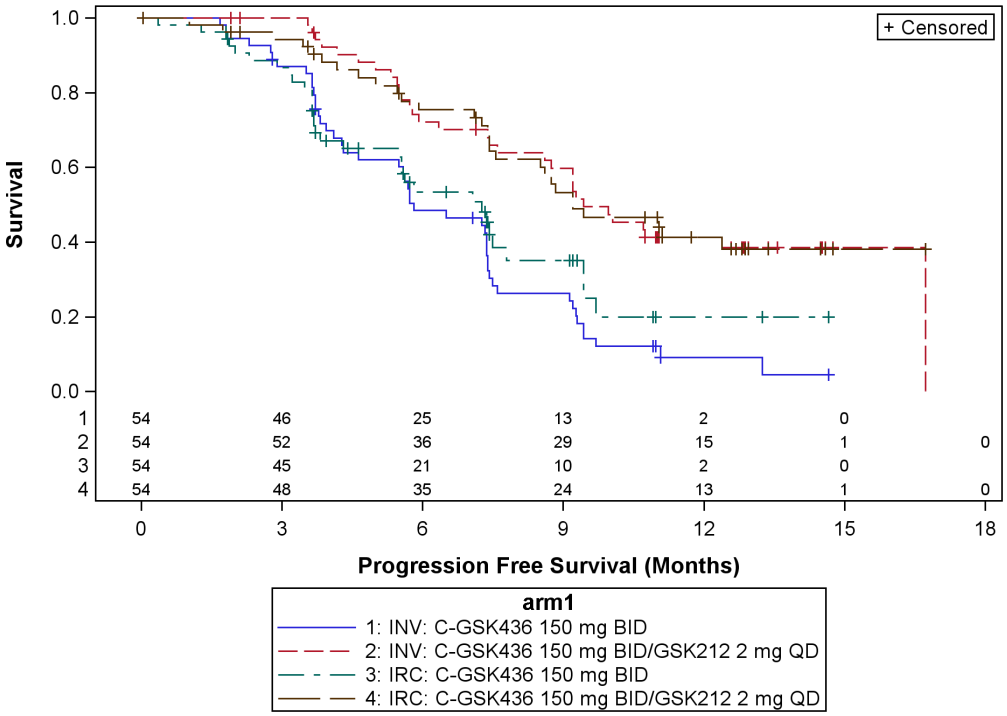


Reviewer's comments:

1. Similar to ORR, the p-values are not presented because formal statistical tests were not pre-specified for PFS.

2. The following figure combines the PFS results by both investigator and BICR for the 150 arm and 150/2 arm.

Figure 3. K-M Curves for PFS Combining Investigator's Assessment and BICR



The curves by the investigator's assessment and the BICR are superimposed on each other. However the design of the study may have led to informative censoring between the treatment arms. According to the protocol, patients could continue the randomized treatment beyond investigator assessed disease progression, while 81% of the monotherapy patients crossed over to the 150/2 arm. Therefore a larger proportion of monotherapy subjects who were censored (17 subjects) by the BICR assessment.

3. Various sensitivity analyses and subgroups analyses were conducted for PFS. The results of these analyses are consistent with the main analyses results presented above.

<u>Secondary Endpoints Analyses: OS</u>

The analysis for OS included data throughout the study from the randomized phase to crossover phase.

There were a total of 51 patients who had died at time of the primary analysis, of which 19 were in the 150 arm, 18 were in the 150/1 arm and 14 in the 150/2 arm.

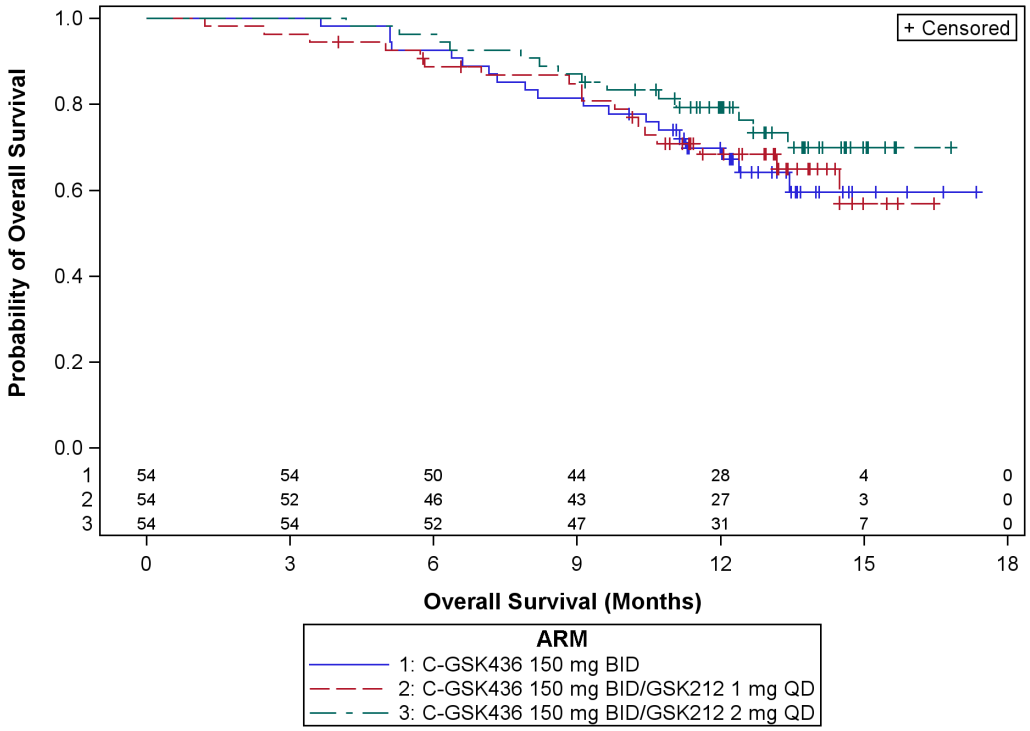
Table 7 summarizes the main efficacy analysis results for OS. None of the three treatments arms reached median OS at the data cut-off. The OS data are not mature.

Table 7. Results of OS Analysis

Dabrafenib	150 mg BID	150 mg BID	150 mg BID
Trametinib	--	1 mg QD	2 mg QD
	N=54	N=54	N=54
Number of Deaths (%)	19 (35.2%)	18 (33.3%)	14 (25.9%)
Median OS (95% CI)	NE (12.4, NE)	NE (13.2, NE)	NE (NE, NE)
HR (95% CI) by Pike		0.98 (0.51, 1.87)	0.67 (0.34, 1.34)
HR (95% CI) by Cox		0.97 (0.51, 1.86)	0.67 (0.34, 1.34)

Figure 4 shows the estimated Kaplan-Meier curves for the distribution of OS.

Figure 4. K-M Cures of OS



Reviewer's comments:

The results from the OS analysis are not considered robust due to the small number of deaths.

3.3 Evaluation of Safety

The original primary end of Study 113220 Part C was the incidence rate of the Cutaneous Squamous Cell Carcinoma (SCC).

There were a total of 15 patients experienced SCC in the randomization phase of Part C. The results of the SCC analyses, based on the ITT population (i.e. planned treatment) and the safety population (i.e. actual treatment) are summarized in the following table. The p-values are based on the Fisher's Exact test.

Table 8. Primary SCC Analyses

Dabrafenib	150 mg BID	150 mg BID	150 mg BID
Trametinib	--	1 mg QD	2 mg QD
Acutal Treatment	N=53	N=54	N=55
SCC Rate (%)	10 (19%)	1 (2%)	4 (7%)
95% CI	(9.4%, 32.0%)	(0.1%, 9.9%)	(2.0%, 17.6%)
Difference (95% CI)		-17% (-34.9%, 2.1%)	-12% (-30.3%, 6.9%)
p-value, left-sided		0.004	0.065
p-value, two-sided		0.004	0.09
Planned Treatment	N=54	N=54	N=54
SCC Rate (%)	10 (19%)	1 (2%)	4 (7%)
95% CI	(9.3%, 31.4%)	(0.1%, 9.9%)	(2.1%, 17.9%)
Difference (95% CI)		-17% (-35.5%, 3.1%)	-11% (-30.2%, 8.6%)
p-value, left-sided		0.004	0.075
p-value, two-sided		0.008	0.15

Reviewer's comments:

1. The original protocol did not specify multiplicity adjustment for the two sets of comparisons. Assuming that each of the two comparisons between a combination arm and the monotherapy arm is based on 2.5% type one error rate, the difference between the 150/1 arm and the 150 arm were statistically significant while the different between the 150/2 arm and the 150 arm were not statistically significant. However they showed the same trend that the SCC rate in the combination therapy arms is lower.
2. One patient assigned to the dabrafenib monotherapy arm actually received the 150/2 combination therapy. But this patient did not have an SCC event.

Please refer to the clinical review of this application for details of other safety evaluations.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender, Race, and Geographic Region

Since 98% of the patients were Caucasians, the subgroup analysis on race was not performed.

The results reported in this sub-section are based on investigator's assessment.

Table 9 summarizes the subgroup analysis of ORR by age.

Table 9. Subgroup Analysis of ORR by Age

Dabrafenib	150 mg BID	150 mg BID	150 mg BID
Trametinib	--	1 mg QD	2 mg QD
Age <65	N=42	N=46	N=43
CR+PR (%)	22 (52%)	26 (57%)	32 (74%)
95% CI	(36.4%, 68.0%)	(41.1%, 71.1%)	(58.9%, 86.5%)
Median DoR (95% CI)	5.6 (4.5, 7.4)	9.5 (7.4, NE)	14.9 (7.6, 14.9)
Age ≥ 65	N=12	N=8	N=11
CR+PR (%)	7 (58%)	1 (13%)	9 (82%)
95% CI	(27.7%, 84.8%)	(0.3%, 52.7%)	(48.2%, 97.7%)
Median DoR (95% CI)	4.1 (2.8, 7.6)	NE	7.4 (2.4, NE)

Table 10 summarizes the subgroup analysis of ORR by gender.

Table 10. Subgroup Analysis of ORR by Gender

Dabrafenib	150 mg BID	150 mg BID	150 mg BID
Trametinib	--	1 mg QD	2 mg QD
Female	N=25	N=24	N=20
CR+PR (%)	15 (60%)	11 (46%)	15 (75%)
95% CI	(38.7%, 78.9%)	(25.6%, 67.2%)	(50.9%, 91.3%)
Median DoR (95% CI)	5.6 (4.1, 7.4)	NE (3.7, NE)	NE (7.0, NE)
Male	N=29	N=30	N=34
CR+PR (%)	14 (48%)	16 (53%)	26 (76%)
95% CI	(29.4%, 67.5%)	(34.3%, 71.7%)	(58.8%, 89.3%)
Median DoR (95% CI)	5.5 (3.7, 11.3)	9.5 (5.5, NE)	9.1 (5.7, 14.9)

Table 11 summarizes the subgroup analysis of ORR by region.

Table 11. Subgroup Analysis of ORR by Region

Dabrafenib	150 mg BID	150 mg BID	150 mg BID
Trametinib	--	1 mg QD	2 mg QD
USA	N=49	N=50	N=44
CR+PR (%)	27 (55%)	24 (48%)	33 (75%)
95% CI	(40.2%, 69.3%)	(33.7%, 62.6%)	(59.7%, 86.8%)
Median DoR (95% CI)	5.6 (4.1, 7.4)	9.5 (7.4, NE)	14.9 (7.4, 14.9)
Australia	N=5	N=4	N=10
CR+PR (%)	2 (40%)	3 (75%)	8 (80%)
95% CI	(5.3%, 85.3%)	(19.4%, 99.4%)	(44.4%, 97.5%)
Median DoR (95% CI)	4.7 (2.0, 7.4)	NE (3.7, NE)	8.1 (3.7, NE)

Reviewer's comments:

The analyses showed that the analysis results for subgroups of ORR were consistent with the primary analysis.

4.2 Other Subgroup Analysis

The follow tables summarize subgroup analysis of ORR by BRAF V600 mutation type, per investigator's assessment and BICR, respectively.

Table 12. Investigator Subgroup Analysis of ORR by BRAF V600 Type

Dabrafenib	150 mg BID	150 mg BID	150 mg BID
Trametinib	--	1 mg QD	2 mg QD
V600E	N=45	N=45	N=47
CR+PR (%)	26 (58%)	24 (53%)	36 (77%)
95% CI	(42.2%, 72.3%)	(37.9%, 68.3%)	(62.0%, 87.7%)
Median DoR (95% CI)	5.6 (4.1, 7.4)	9.2 (5.5, NE)	10.5 (7.4, 14.9)
V600K	N=9	N=9	N=7
CR+PR (%)	3 (33%)	3 (33%)	5 (71%)
95% CI	(7.5%, 70.1%)	(7.5%, 70.1%)	(29.0%, 96.3%)
Median DoR (95% CI)	5.5 (3.7, 5.8)	NE (9.5, NE)	NE (7.4, NE)

Table 13. BICR Subgroup Analysis of ORR by BRAF V600 Type

Dabrafenib	150 mg BID	150 mg BID	150 mg BID
Trametinib	--	1 mg QD	2 mg QD
V600E	N=45	N=45	N=47
CR+PR (%)	23 (51%)	19 (42%)	29 (62%)
95% CI	(35.8%, 66.3%)	(27.7%, 57.9%)	(46.4%, 75.5%)
Median DoR (95% CI)	7.6 (4.1, NE)	11.3 (5.6, NE)	NE (6.7, NE)
V600K	N=9	N=9	N=7
CR+PR (%)	2 (22%)	2 (22%)	4 (57%)
95% CI	(2.8%, 60.0%)	(2.8%, 60.0%)	(18.4%, 90.1%)
Median DoR (95% CI)	5.5 (NE, NE)	NE (9.5, NE)	NE (7.4, NE)

The following tables summarize subgroup analysis of ORR by BRAF V600 mutation type, per investigator's assessment and BICR and based on FDA clinical reviewer's evaluation, respectively.

Table 14. Investigator Subgroup Analysis of ORR by BRAF V600 Type Based on FDA Evaluation

Dabrafenib	150 mg BID	150 mg BID	150 mg BID
Trametinib	--	1 mg QD	2 mg QD
V600E	N=45	N=45	N=47
CR+PR (%)	26 (58%)	24 (53%)	36 (77%)
95% CI	(42.2%, 72.3%)	(37.9%, 68.3%)	(62.0%, 87.7%)
Median DoR (95% CI)	5.6 (4.1, 7.4)	9.2 (5.5, NE)	10.5 (7.4, 14.9)
V600K	N=9	N=9	N=7
CR+PR (%)	3 (33%)	3 (33%)	5 (71%)
95% CI	(7.5%, 70.1%)	(7.5%, 70.1%)	(29.0%, 96.3%)
Median DoR (95% CI)	5.5 (3.7, 5.8)	NE (9.5, NE)	NE (7.4, NE)

Table 15. BICR Subgroup Analysis of ORR by BRAF V600 Type Based on FDA Evaluation

Dabrafenib	150 mg BID	150 mg BID	150 mg BID
Trametinib	--	1 mg QD	2 mg QD
V600E	N=45	N=45	N=47
CR+PR (%)	23 (51%)	18 (40%)	27 (57%)
95% CI	(35.8%, 66.3%)	(25.7%, 55.7%)	(42.2%, 71.7%)
Median DoR (95% CI)	7.6 (4.1, NE)	9.4 (5.6, NE)	7.6 (5.6, NE)
V600K	N=9	N=9	N=7
CR+PR (%)	2 (22%)	2 (22%)	4 (57%)
95% CI	(2.8%, 60.0%)	(2.8%, 60.0%)	(18.4%, 90.1%)
Median DoR (95% CI)	5.5 (NE, NE)	NE (9.5, NE)	NE (7.4, NE)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The major statistical of this application is the lack of pre-specified statistically testing procedures for the efficacy endpoints. The original protocol stated the primary objective of Study 113220 Part C was to identify a superior safety profile for the combination therapy compared with the monotherapy. In addition, multiplicity adjustments were not pre-specified for multiple primary endpoints including SCC rate, PFS and ORR.

The data and analyses from current submission showed that the ORR of patients in the dabrafenib/trametinib 150 mg / 2 mg arm was higher than that of patients in the dabrafenib 150 mg arm. Based on investigator's assessment, ORR was 76% with 95% confidence interval (CI) (62.4%, 86.5%) in the 150/2 combination arm compared with 54% with 95% CI (39.6%, 67.4%) in the dabrafenib 150 mg monotherapy arm, and the difference between the two arms was 22% with 95% CI (2.5%, 40.7%). FDA re-evaluated the outcome of the BIRC assessment. Based on FDA's evaluation of BIRC assessment, ORR was 57% with 95% CI (43.2%, 70.8%) in the 150/2 combination arm compared with 46% with 95% CI (32.6%, 60.4%) in the dabrafenib 150 mg monotherapy arm, and the difference between the two arms was 11% with 95% CI (-8.6%, 30.2%).

Also based on investigator's assessment, the median PFS was 9.4 months in the 150/2 combination arm compared with 5.8 months in the 150 monotherapy arm. The estimated hazard ratio (HR), based on a stratified Pike estimator, was 0.39 with 95% CI (0.25, 0.62). The results of blinded independent central review (BICR) assessed ORR and PFS were similar.

There was no difference in OS between the 150/2 combination arm and 150 monotherapy arm. With a total of 33 deaths, the median survivals in the two study arms were not estimable. The estimated hazard ratio (HR) was 0.67 with 95% CI (0.34, 1.34).

The incidence rate of Cutaneous Squamous Cell Carcinoma (SCC) was the original primary endpoint of Study 113220 Part C. A total of 15 patients experienced SCC in the randomization phase of Part C, with 4 in the 150 arm, 1 in the dabrafenib 150/1 arm and 4 in the 150/2 arm. Based on the ITT population, the difference between the 150 arm and 150/1 arm was -17% with 95% CI (-35.5%, 3.1%), and the two-sided p-value from Fisher's Exact test was 0.008; and the difference between the 150 arm and 150/2 arm was -11% with 95% CI (-30.2%, 8.6%), and the two-sided p-value from Fisher's Exact test was 0.15. The results based on the safety population were similar.

5.2 Conclusions and Recommendations

Based on the data and analyses, the study results showed that dabrafenib 150 mg / trametinib 2 mg combination observed a higher ORR compared with dabrafenib 150 mg monotherapy. Whether the data and analyses provided in this submission showed a favorable benefit/risk profile in supporting a regulatory approval will be a clinical decision.

5.3 Labeling Recommendations

1. The primary analysis set for the efficacy results are the ITT population.
2. The primary analysis of ORR should be reported as the main efficacy results since this application is seeking accelerated approval based on the ORR results. Both investigator-assessed results and BIRC-assessed (based on FDA's re-evaluation) results should be reported.
3. [redacted] (b) (4)
4. The p-values should be excluded for the efficacy endpoints because no testing procedures were pre-specified for these endpoints.

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/s/

WEISHI YUAN
11/25/2013

KUN HE
11/25/2013

RAJESHWARI SRIDHARA
11/26/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202806Orig1s002

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NDA Clinical Pharmacology Review

NDA/SDN/eCTD Sequence No.	NDA 202806/104/0063
Type/Category	Efficacy supplement; Priority
Brand Name	TAFINLAR
Generic Name	Dabrafenib (GSK2118436)
Receipt Date	July 9, 2013
PDUFA Date	January 9, 2014
Proposed Indication	TAFINLAR in combination with trametinib is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutation as detected by an FDA-approved test.
Dosage Form	50 and 75 mg capsules
Route of Administration	Oral
Dosing Regimen and Strength	150 mg twice daily (BID)
Applicant	GlaxoSmithKline
OCP Division	Division of Clinical Pharmacology V (DCPV)
OND Division	Division of Oncology Products 2 (DOP2)
Clinical Pharmacology Reviewer	Ruby Leong, Pharm.D.
Clinical Pharmacology Team Leader	Hong Zhao, Ph.D.
Pharmacometrics Reviewer	Jingyu (Jerry) Yu, Ph.D.
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1 EXECUTIVE SUMMARY

TAFINLAR (dabrafenib) is a BRAF kinase inhibitor that was approved on May 29, 2013 as a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test. The recommended dose for dabrafenib as a single agent is 150 mg orally twice daily (BID) taken at least 1 hour before or 2 hours after a meal.

MEKINIST (trametinib) is a MEK kinase inhibitor that was approved on May 29, 2013 as a single agent for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. The recommended dose for trametinib as a single agent is 2 mg orally once daily (QD) taken at least 1 hour before or 2 hours after a meal.

TAFINLAR and MEKINIST [redacted] (b) (4) The Applicant's proposed indication is:

> TAFINLAR in combination with trametinib is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutation as detected by an FDA-approved test. This indication is based on the demonstration of durable response rate. [redacted] (b) (4)

TAFINLAR, as a single agent or in combination with trametinib, is not indicated for treatment of patients with wild-type BRAF melanoma. The proposed dose for dabrafenib in combination with trametinib is 150 mg orally BID taken at least 1 hour before or 2 hours after a meal.

To support registration, Part C of Study BRF113220 was conducted in patients with BRAF inhibitor-naïve BRAF V600 mutation-positive metastatic melanoma who were randomized 1:1:1 to receive dabrafenib 150 mg BID plus trametinib 2 mg QD (150/2 combination) (n=54), dabrafenib 150 mg BID plus trametinib 1 mg QD (150/1 combination) (n=54), or dabrafenib 150 mg BID as a single agent (n=54). The investigator-assessed objective response rate (ORR) was 76% (95% CI: 62%, 87%) in the dabrafenib 150 mg BID plus trametinib 2 mg QD arm as compared to 54% (95% CI: 40%, 67%) in the dabrafenib 150 mg BID arm. The most common adverse reactions (≥ 20%) in patients treated with the combination of dabrafenib and trametinib included pyrexia, chills, fatigue, nausea, vomiting, diarrhea, cough, headache, peripheral edema, rash, arthralgia, night sweats, decreased appetite, constipation, and myalgia.

The Clinical Pharmacology Section of the supplemental NDA is supported by Study BRF113220 Part A to assess drug interaction potential between dabrafenib and trametinib, Part B dose escalation, and Part D to assess differences in pharmacokinetics (PK) and safety with the marketed HPMC formulation and gelatin clinical trial formulation of dabrafenib. In Part C, 104 patients (64%) received both gelatin and HPMC capsule formulations. Although exposures were higher with the HPMC capsule as compared to the gelatin capsule formulation, there were no apparent increased safety issues or incidence of adverse events with the use of the HPMC capsule formulation. Population pharmacokinetic (popPK) and exposure-response (E-R) analyses using PK data from Part C of Study BRF113220 did not identify clinically important covariates influencing dabrafenib or trametinib PK. There appears to be an E-R relationship for efficacy (ORR) with trametinib, which is consistent with the higher ORR observed with the 2 mg versus 1 mg daily dose of trametinib in combination with 150 mg BID dabrafenib. There is evidence for a relationship between safety (pyrexia) and hydroxy-dabrafenib, supporting the proposed dose reduction to manage pyrexia in the labeling.

1.1 RECOMMENDATIONS

This efficacy supplement is acceptable from a clinical pharmacology perspective provided that the Applicant and the Agency come to an agreement regarding the labeling language. For labeling recommendations for TAFINLAR, please refer to **Section 3**.

1.2 PHASE 4 REQUIREMENTS AND COMMITMENTS

There are no clinical pharmacology requested Postmarketing Requirements or Commitments (PMRs or PMCs).

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1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

Drug Interactions: After administration of dabrafenib 150 mg BID in combination with trametinib 2 mg QD, the exposure ($AUC_{0-\tau}$) of dabrafenib increased by 23% for the parent drug and by 33% for its metabolite desmethyl-dabrafenib; trametinib exposures were similar as compared to previously reported trametinib single agent PK data.

Relative Bioavailability: TAFINLAR has been approved and marketed as 50 and 75 mg HPMC capsules. Prior to development of the HPMC capsule formulation, a gelatin capsule formulation was used in earlier clinical studies. The bioavailability of dabrafenib is higher following single dose administration as HPMC capsules as compared to gelatin capsules, with a geometric mean ratio (90% CI) of 1.8 (1.3, 2.5) for AUC_{0-inf} and 2.0 (1.4, 2.9) for C_{max}. A popPK analysis showed that dabrafenib AUC increased by 42% (single agent) and 33% (combination) following administration of dabrafenib as HPMC capsules. In Part C of Study BRF113220 that is intended to support registration of dabrafenib in combination with trametinib, 104 patients (64%) received both gelatin and HPMC capsule formulations. Although exposures were higher with the HPMC capsule as compared to the gelatin capsule formulation, there were no apparent increased safety issues or incidence of adverse events with the use of the HPMC capsule formulation. Patients in the proposed confirmatory trial (Study MEK115306) of dabrafenib in combination with trametinib have received only HPMC capsules.

Population PK and Exposure-Response Analyses: The popPK analysis did not identify clinically meaningful effects of body weight, age, gender, mild and moderate renal impairment, or mild hepatic impairment as covariates on clearance or volume of distribution of dabrafenib and trametinib when used in combination. Using PK, efficacy, and safety data from the

registration trial (Part C of Study BRF113220), there appears to be an E-R relationship for efficacy (ORR) with trametinib, which is consistent with the higher ORR observed with the 2 mg versus 1 mg daily dose of trametinib in combination with 150 mg BID dabrafenib. There is evidence for a relationship between safety (pyrexia) and hydroxy-dabrafenib, supporting the proposed dose reduction to manage pyrexia in the labeling.

2 QUESTION-BASED REVIEW

For brevity, only QBR questions related to the current submission for the dabrafenib and trametinib combination are addressed below. For additional details, please refer to the original NDA 202806 submission (eCTD SN 0003, SDN 3, receipt date of 7/30/2012) and the corresponding clinical pharmacology review in DAARTS (Reference ID: 3287747) for dabrafenib as a single agent; and the original NDA 204114 submission (eCTD SN 0002, SDN 2, receipt date of 8/3/2012) and the corresponding clinical pharmacology review in DAARTS (Reference ID: 3289560) for trametinib as a single agent.

2.1 GENERAL CLINICAL PHARMACOLOGY

2.1.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Table 1 includes a summary description of Study BRF113220. Part C is intended to support registration.

Table 1. Summary of Study BRF113220

Part	Study Design	Objectives	Dosing Regimen	PK Sampling
A	Drug-drug interaction (n=8)	*Primary:* PK of single dose of dabrafenib and metabolites with and without repeat doses of trametinib *Secondary:* Steady state PK of trametinib	Day 1: Single dose of dabrafenib 75 mg Days 2-15: Trametinib 2 mg QD Day 15: Single dose of dabrafenib 75 mg plus trametinib 2 mg	*Dabrafenib and metabolites*:* Pre-dose, 1, 2, 3, 4, 6, 8, 10, 24 h post-dose on days 1 and 15 *Trametinib:* Pre-dose and 24 h post-dose on day 15
B	Phase 1, 3+3 dose escalation with expansion phase *Cohort B-1:* (n=6) *Cohort B-2:* (n=23) *Cohort B-3:* (n=27) *Cohort B-4:* (patients with BRAF V600 mutation-positive melanoma and prior treatment with a BRAF inhibitor (n=26) or no prior treatment with a BRAF inhibitor (n=24); patients with BRAF V600 mutation-positive colorectal cancer (n=28);	*Primary:* Safety of dabrafenib in combination with trametinib *Secondary:* Steady state PK of dabrafenib and its metabolites and trametinib; clinical activity of the dabrafenib and trametinib combination	*Cohort B-1*: Dabrafenib 75 mg BID + trametinib 1 mg QD *Cohort B-2*: Dabrafenib 150 mg BID + trametinib 1 mg QD *Cohort B-3*: Dabrafenib 150 mg BID + trametinib 1.5 mg QD *Cohort B-4*: Dabrafenib 150 mg BID + trametinib 2 mg QD	*Dabrafenib and metabolites* and trametinib:* Pre-dose on day 15 and pre-dose, 1, 2, 4, 6, and 8 h post-dose on day 21

Part	Study Design	Objectives	Dosing Regimen	PK Sampling
	patient with neuroendocrine carcinoma (n=1)			
C	Phase 2, randomized, open label in patients with BRAF V600 mutation-positive melanoma and no prior treatment with a BRAF inhibitor *Single agent:* (n=54) *150/1 combination:* (n=54) *150/2 combination:* (n=54)	*Primary:* Clinical activity, safety, dose ranging of dabrafenib and trametinib combination *Secondary:* PopPK, duration of response	*Single agent:* Dabrafenib 150 mg BID *Combination dose level 1:* Dabrafenib 150 mg BID + trametinib 1 mg QD *Combination dose level 2:* Dabrafenib 150 mg BID + trametinib 2 mg QD	*Dabrafenib and metabolites* and trametinib:* Pre-dose on day 15 and every 8 weeks until week 48
D	Comparison of PK and safety of dabrafenib as gelatin and HPMC capsules *Cohort D-1:* (n=12) *Cohort D-2:* (n=16) *Cohort D-3:* (n=43) *Cohort D-4:* (n=39)	*Primary:* Single and steady-state PK of dabrafenib HPMC capsules alone and in combination, safety *Secondary:* Clinical activity of the dabrafenib and trametinib combination	*Cohort D-1:* Dabrafenib 75 mg BID *Cohort D-2:* Dabrafenib 150 mg BID *Cohort D-3:* Dabrafenib 75 mg BID + trametinib 2 mg QD *Cohort D-4:* Dabrafenib 150 mg BID + trametinib 2 mg QD	*Dabrafenib and metabolites* and trametinib:* Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 24 h post-dose on day 1; Pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 10 h post-dose on day 21; Pre-dose every 8 weeks until week 24

Abbreviations: BID: Twice daily; HPMC: Hydroxypropyl-methylcellulose; PK: Pharmacokinetics; PopPK: Population pharmacokinetics; QD: Once daily
*Dabrafenib metabolites include GSK2285403 (hydroxy-dabrafenib), GSK2298683 (carboxy-dabrafenib), and GSK2167542 (desmethyl-dabrafenib)

2.1.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

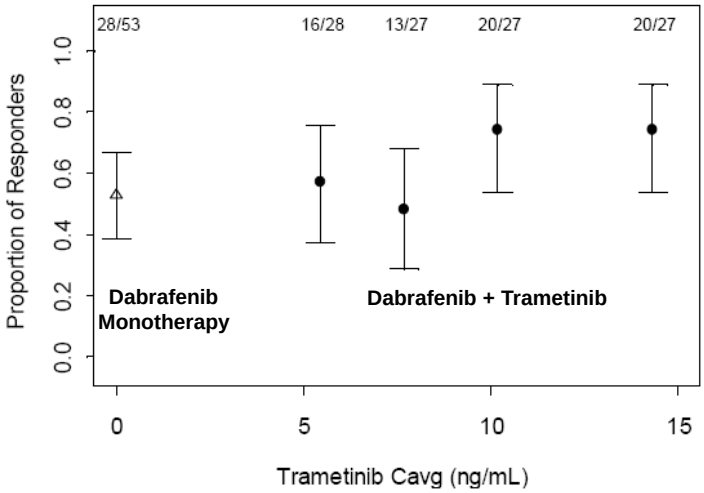
The major efficacy outcome measure of the registration trial BRF113220 was investigator-assessed ORR.

2.1.3 Exposure-response

2.1.3.1 *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?*

The Applicant's exposure-response (E-R) analyses using data from Part C of Study BRF113220, verified by our pharmacometrics review, showed that there is no evident relationship between ORR and exposures of dabrafenib and its metabolites for dabrafenib as a single agent and in combination with trametinib at the dose of 150 mg BID. There appears to be a higher response rate with increased exposures (C_{avg}) of trametinib (dose levels of 1 and 2 mg QD) administered in combination with dabrafenib (**Figure 1**). E-R analyses for the efficacy endpoint of PFS were not conducted due to the small sample size of patients with available PK data.

Figure 1. Proportion of responders by average trametinib concentration (C_{avg}) in Part C of Study BRF113220

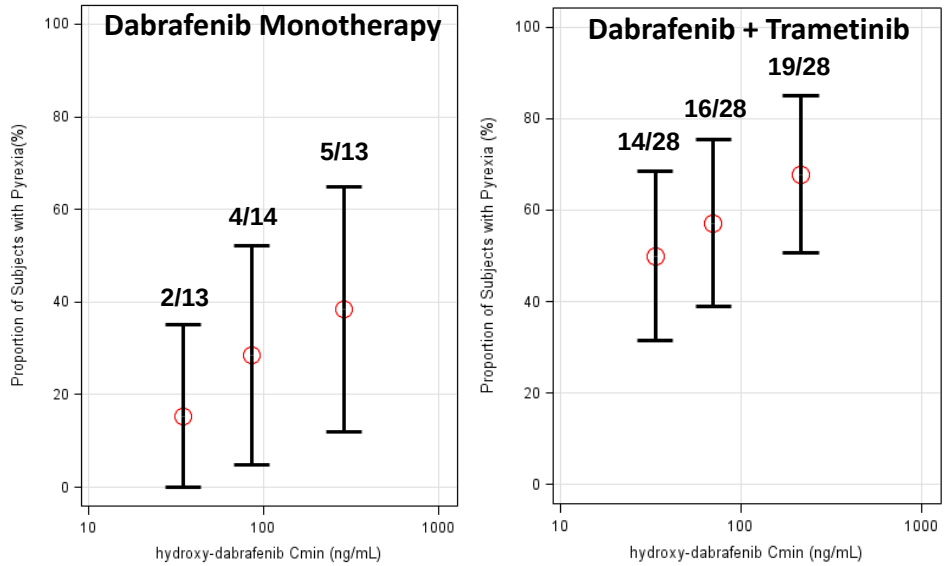


In the original NDA 204114 submission, there was no evident E-R relationship for trametinib as a single agent and ORR given that only one dose level of 2 mg QD was evaluated in the Phase 2 and 3 trials and the range of exposure was narrow (Reference ID: 3289560).

2.1.3.2 *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?*

An E-R relationship between pyrexia and hydroxy-dabrafenib trough concentration (C_{min}) was identified (**Figure 2**).

Figure 2. Proportion of patients with pyrexia by hydroxy-dabrafenib C_{min} in Part C of Study BRF113220



An increase in the proportion of patients who experienced pyrexia was observed with administration of dabrafenib in combination with trametinib compared to dabrafenib as a single agent, possibly due to observed increased exposures of dabrafenib after repeat doses of the combination (see **Section 2.3.1.2**) and pharmacodynamic interactions between dabrafenib and trametinib that are currently unknown. This E-R relationship supports the recommended dose modifications in the proposed labeling for dabrafenib as a single agent and in combination with trametinib in the event of febrile drug reactions.

2.1.3.3 *Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and is there any unresolved dosing or administration issue?*

The Applicant's rationale for the proposed dosing regimen of dabrafenib 150 mg BID in combination with trametinib 2 mg QD is based on the following:

- Recommended single agent dosing regimens of dabrafenib 150 mg BID and trametinib 2 mg QD
- Objective response rate of 76% with 150 mg BID in combination with trametinib 2 mg QD as compared to 50% with 150 mg BID in combination with trametinib 1 mg QD.
- Median duration of response was 10.5 months with 150 mg BID in combination with trametinib 2 mg QD as compared to 9.5 months with 150 mg BID in combination with trametinib 1 mg QD.

Based on the dose-response and E-R relationships observed for trametinib and dose modifications of dabrafenib for management of pyrexia in the proposed labeling, the proposed dosing regimen of dabrafenib 150 mg BID in combination with trametinib 2 mg QD appears acceptable and there are no unresolved dosing or administration issues.

2.1.4 What are the PK characteristics of the drug?

2.1.4.1 *What are the single dose and multiple dose PK parameters?*

In Part D of Study BRF113220, PK samples were collected at pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 24 hours post-dose on day 1; pre-dose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 10 hours post-dose on day 21; and pre-dose every 8 weeks until week 24. PK parameters of dabrafenib and its metabolites following administration of dabrafenib 150 mg BID (as HPMC capsules) in combination with trametinib 2 mg QD are summarized in **Table 2**.

Table 2. Summary of PK parameters on days 1 and 21 of repeat doses of dabrafenib 150 mg BID (as HPMC capsules) with trametinib 2 mg QD in Part D of Study BRF113220

	Geometric Mean (%CV)			
	Dabrafenib	**Hydroxy-dabrafenib**	**Desmethyl-dabrafenib**	**Carboxy-dabrafenib**
Day 1 (n=15)				
$AUC_{0\text{-}tau}$ (ng·hr/mL)	7331 (61.6%)	6524 (74.3%)	354 (78.2%)	20935 (105%)
$AUC_{0\text{-}inf}$ (ng·hr/mL)	8152 (62.2%)	7907 (72.5%)	NA	NA
C_{max} (ng/mL)	2289 (68.8%)	1363 (87.0%)	86.3 (143%)	2551 (75.9%)
T_{max} (h)	1.5 (1.0-10.0)	2.1 (1.5-10.0)	24.0 (10.0-24.3)	8.0 (4.1-24.0)
$t_{1/2}$ (h)	3.6 (36.4%)	4.0 (17.7%)	NA	NA
Day 21 (n=12)				
$AUC_{0\text{-}tau}$ (ng·hr/mL)	5886 (40.0%)	4216 (58.5%)	3632 (61.9%)	52712 (45.2%)
C_{max} (ng/mL)	2052 (56.0%)	1120 (77.3%)	440 (63.9%)	6319 (48.3%)
T_{max} (h)	1.5 (1.0-3.0)	2.0 (1.0-4.0)	1.8 (0.0-9.9)	4.0 (3.0-6.1)
C_{τ} (ng/mL)	72.1 (106%)	83.3 (101%)	333 (61.6%)	2764 (39.6%)

2.1.4.2 *What are the characteristics of drug metabolism?*

According to the original NDA clinical pharmacology review (Reference ID: 3287747), 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 PK 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.

According to the original NDA clinical pharmacology review (Reference ID: 3289560), trametinib is metabolized via deacetylation to form M5; deacetylation in combination with hydroxylation to form M7; glucuronidation of M5 to form M6, and glucuronidation of M7 to form M9. Trametinib was the major component (≥75%), with M5 and M7 each constituting

approximately 10% of drug-related material in plasma.

2.2 INTRINSIC FACTORS

2.2.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

No formal studies have been conducted to assess the effect of age, race, weight, height, or organ dysfunction on exposure and response to dabrafenib in combination with trametinib. The Applicant's popPK analysis, verified by our pharmacometrics review, did not identify clinically meaningful effects of body weight, age, gender, mild and moderate renal impairment, and mild hepatic impairment as covariates on clearance or volume of distribution of dabrafenib and trametinib when used in combination, which is consistent with the findings for dabrafenib and trametinib as single agents. For additional details, please refer to the original NDA 202806 submission (eCTD SN 0003, SDN 3, receipt date of 7/30/2012) and the corresponding clinical pharmacology review in DAARTS (Reference ID: 3287747) for dabrafenib as a single agent; and the original NDA 204114 submission (eCTD SN 0002, SDN 2, receipt date of 8/3/2012) and the corresponding clinical pharmacology review in DAARTS (Reference ID: 3289560) for trametinib as a single agent.

2.2.1.1 *Genetics*

BRAF and MEK are mediators of the MAPK pathway, which is activated in the majority of patients with advanced or metastatic melanoma. Pathway activation typically occurs through somatic activating mutations in BRAF (40-50%) or NRAS (15–20% cutaneous melanomas) [PMID: 22945644]. Most of BRAF mutations in melanoma correspond to substitutions at position V600 of BRAF. Among these, V600E accounts for approximately 80-90% of all V600 mutations, while V600K (the second most common) accounts for approximately 5-12% of cases [My Cancer Genome, www.mycancergenome.org]. Other V600 mutations are less common.

In the original phase 3 trial that supported trametinib approval (MEK114267), clinical activity was observed across BRAF V600E and V600K mutation subgroups based on the applicant's and FDA analyses [NDA204114]. The favorable benefit risk profile led to FDA approval of trametinib for the treatment of patients with BRAF V600E or V600K mutant melanoma. However, in case of dabrafenib, the phase 3 registration trial (BRF113683) was limited to patients with BRAF V600E melanoma, (b) (4) dabrafenib is approved for the treatment of patients with BRAF V600E (b) (4) mutant melanoma.

The applicant's rationale for the combination included the following: (a) a more complete inhibition of the MAPK pathway can be achieved with the combination leading to a more pronounced initial response to therapy, (b) (4)

The trial BRF113220 was an open-label, dose-escalation, phase 1/2 trial to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of dabrafenib in combination with trametinib in subjects with BRAF mutant metastatic melanoma. This trial had 4 parts: part C is

relevant for this review. Part C (N=162) was a randomized (1:1:1) open-label multicenter phase 2 trial of trametinib (1 or 2 mg QD) in combination with dabrafenib (150 mg BID) versus dabrafenib alone (150 mg BID). All patients were positive for BRAF V600E or V600K mutations. The presence of BRAF mutations for eligibility was determined based on local testing. The BRAF mutation status was subsequently confirmed using an analytically validated IUO allele-specific PCR assay and the FDA-approved companion diagnostic test (bMxTHxID cDx assay).

With respect to efficacy, three primary endpoints were specified: overall response rate (ORR), duration of response (DoR) and progression free survival (PFS). With respect to safety, the primary goal was to identify at least one combination dose of dabrafenib and trametinib with a superior safety profile in terms of occurrence of cuSCC compared to dabrafenib alone.

Key results are collectively discussed below based on the applicant analyses.

- Pre-clinical models (including BRAF mutant melanoma cell lines with V600E or V600K mutations) support the combination compared to monotherapy.

- Higher investigator-assessed confirmed ORRs and longer duration of responses were observed in the 150/2 combination therapy group (N=54) compared with the dabrafenib monotherapy group (N=54). The ORR was 76% (95% CI: 62, 87) in the combination group and 54% (95% CI: 40, 67) in the dabrafenib group. The ORR for BRAF V600E mutant melanoma patients was 77% (95% CI: 62, 88) in the combination (N=47) and 58% (95% CI: 42, 72) in the dabrafenib group (N=45) and the ORR for BRAF V600K mutant melanoma patients was 71% (95% CI: 29, 96) in the combination (N=7) and 33% (95% CI: 8, 70) in the dabrafenib group (N=9). Although based on a small subset of melanoma patients with BRAF V600K mutations, it appears that patients with BRAF V600K mutant melanoma, for which limited activity has been observed for BRAF inhibition alone, respond to combination therapy. The median duration of confirmed response (investigator assessment) was 10.5 months (95% CI: 7.4, 14.9) in the 150/2 combination group compared with 5.6 months (95% CI: 4.5, 7.4) in the dabrafenib group. For the BRAF V600E mutant melanoma patients, the median duration was 10.5 months (95% CI: 7.6, 14.9) in the 150/2 combination group and 5.6 months (95% CI: 4.5, 7.4) in the dabrafenib group. Response durations were not calculated for BRAF V600K mutant melanoma patients because of the small sample size.

- A lower incidence rate of cuSCC was observed in the combination therapy group compared with the dabrafenib monotherapy group. In the BRF113683 trial, cuSCCs (including keratoacanthomas) occurred in 7% (14/187) of patients treated with dabrafenib and in none of the patients treated with dacarbazine. Also, the incidence of new primary malignant melanomas was 2% (3/187) for patients receiving dabrafenib, whereas no new primary malignant melanoma was diagnosed in dacarbazine-treated patients by the cutoff date (dabrafenib labeling/FDA Medical Review). The development of these secondary tumors has mostly been attributed to paradoxical MAPK activation in the presence of mutated RAS (PMID: 23712190). In the BRF113220 trial (Part C), cuSCCs (including keratoacanthomas) occurred in 7% (4/55) of patients receiving dabrafenib in combination with trametinib (150/2) compared with 19% (10/53) of patients receiving dabrafenib

monotherapy. One case of new primary malignant melanoma was reported by the applicant in the dabrafenib monotherapy group. The impact of simultaneous administration of BRAF and MEK inhibitors on other potential treatment-related secondary malignancies is yet unclear.

Based on the above, the proposed indication of dabrafenib in combination with trametinib for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA approved test is acceptable from the OCP Genomics and Targeted Therapy Group perspective, provided clinical and statistical reviews concur with demonstration of a favorable risk-benefit profile. No labeling or post approval actions are proposed at this time.

2.3 EXTRINSIC FACTORS

2.3.1 Drug-Drug Interactions

2.3.1.1 *Is there an in vitro basis to suspect in vivo drug-drug interactions?*

An in vitro basis for a drug-drug interaction between dabrafenib and trametinib exists. The metabolism of dabrafenib is mediated by CYP2C8 (56%) and CYP3A4 (23%) to form hydroxy-dabrafenib, which is further oxidized via CYP3A4 to form carboxy-dabrafenib. Trametinib is an inhibitor of CYP2C8 in vitro (R_1 value of 1.2), and may affect the PK of dabrafenib. Trametinib is metabolized predominantly by deacetylation alone or with mono-oxygenation or in combination with glucuronidation; therefore, dabrafenib is not expected to affect trametinib PK via CYP enzyme-mediated interactions. Refer to **Section 2.3.1.2** below for results of in vivo evaluation of potential drug-drug interaction between dabrafenib and trametinib.

2.3.1.2 *Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?*

Dabrafenib is labeled to be coadministered with trametinib for this marketing application. The evaluation of potential drug-drug interaction between dabrafenib and trametinib in Part A of Study BRF113220 showed that multiple doses of 2 mg trametinib (administered on days 2-15) had no effect on the PK of a single 75 mg dose of dabrafenib (administered alone on day 1 and in combination with trametinib on day 15) (**Table 3**). In Part D of Study BRF113220, the AUC of dabrafenib after repeat doses was 23% higher and that of desmethyl-dabrafenib was 33% higher in patients administered 150 mg BID dabrafenib in combination with 2 mg QD trametinib as compared to 150 mg BID dabrafenib as a single agent (**Table 4**). The popPK analysis showed that dabrafenib AUC increased by 19% in combination with trametinib, as consistent with observed results. As mentioned in **Section 2.1.3.2**, an increase in the proportion of patients who experienced pyrexia was observed with administration of dabrafenib in combination with trametinib compared to dabrafenib as a single agent. This E-R relationship supports the recommended dose modifications in the proposed labeling for dabrafenib as a single agent and in combination with trametinib in the event of febrile drug reactions.

Table 3. Comparative analysis of PK parameters of a single dose of dabrafenib with and without trametinib in Part A of Study BRF113220

	Geometric Mean Ratio of Combination/Single Agent * (90% CI)			
	Dabrafenib	**Hydroxy-dabrafenib**	**Desmethyl-dabrafenib**	**Carboxy-dabrafenib**
$AUC_{0\text{-}tau}$ (ng·hr/mL)	1.01 (0.85, 1.19)	1.02 (0.84, 1.25)	1.02 (0.76, 1.37)	1.02 (0.81, 1.29)
$AUC_{0\text{-}inf}$ (ng·hr/mL)	0.94 (0.82, 1.08)	0.92 (0.81, 1.03)	NA	NA
C_{max} (ng/mL)	1.03 (0.79, 1.34)	0.99 (0.78, 1.25)	0.98 (0.66, 1.45)	1.03 (0.84, 1.27)

* Single dose of 75 mg dabrafenib (as gelatin capsules) on day 1 (single agent) vs. day 15 (combination with 2 mg trametinib); n=8

Table 4. Comparative analysis of PK parameters on day 1 and 21 of repeat doses of dabrafenib with and without trametinib in Part D of Study BRF113220

	Geometric Mean Ratio of Combination/Single Agent * (90% CI)			
	Dabrafenib	**Hydroxy-dabrafenib**	**Desmethyl-dabrafenib**	**Carboxy-dabrafenib**
Day 1				
$AUC_{0\text{-}tau}$ (ng·hr/mL)	1.10 (0.82, 1.49)	1.08 (0.79, 1.48)	1.84 (1.14, 2.98)	1.27 (0.89, 1.82)
C_{max} (ng/mL)	1.35 (0.96, 1.90)	1.28 (0.92, 1.77)	1.25 (0.77, 2.03)	1.11 (0.83, 1.48)
Day 21				
$AUC_{0\text{-}tau}$ (ng·hr/mL)	1.23 (0.89, 1.69)	0.97 (0.69, 1.37)	1.33 (0.81, 2.17)	0.81 (0.55, 1.18)
C_{max} (ng/mL)	1.16 (0.80, 1.68)	0.94 (0.65, 1.35)	1.23 (0.72, 2.11)	0.92 (0.67, 1.27)

* 150 mg BID dabrafenib (as HPMC capsules) single agent vs. 150 mg BID plus 2 mg QD trametinib combination arm; n=15

Dabrafenib has no effect on the PK of trametinib. Following administration of repeat doses of trametinib 2 mg QD in combination with dabrafenib 150 mg BID, the geometric mean (%CV) for $AUC_{0\text{-}\tau}$ is 394 ng·hr/mL (35%), C_{max} is 22.4 ng/mL (30%), and C_{τ} is 12.4 ng/mL (42%). Based on historical trametinib single agent data [FIH Study MEK111054], the geometric mean (%CV) for $AUC_{0\text{-}\tau}$ is 370 ng·hr/mL (22%), C_{max} is 22.2 ng/mL (28%), and C_{τ} is 12.1 ng/mL (19%), which are similar to the PK parameters following trametinib 2 mg QD in combination with 150 mg BID dabrafenib.

2.3.1.3 *What other co-medications are likely to be administered to the target population?*

Concomitant medications used by ≥ 20% of patients treated with the 150/2 combination in the registration trial included ibuprofen (62%), paracetamol (56%), ondansetron (31%), prednisone (29%), acetylsalicylic acid (29%), and oxycodone hydrochloride (20%).

(b) (4)

A potential drug-drug interaction between dabrafenib and oral corticosteroids exists. Dexamethasone is a strong CYP3A4 inducer; high doses of dexamethasone (16-24 mg/day) promote CYP3A4 transcription (PMID: 15634032). Prednisone is a weak CYP3A4 inducer (20-50% decrease in AUC as defined in the 2012 FDA Drug Interaction draft Guidance for Industry) and methylprednisolone (8 mg QD) does not induce CYP3A4 in healthy volunteers (PMID: 15634032). The $AUC_{0-\tau}$ was 32% lower for dabrafenib, 27% lower for hydroxy-dabrafenib, and 23% higher for desmethyl-dabrafenib in patients who received concomitant oral corticosteroids (mostly prednisone) for the management of pyrexia as compared to that in patients who did not receive concomitant oral corticosteroids (**Table 5**). These results suggest that strong CYP3A4 inducers (e.g., dexamethasone) should be avoided and alternative oral corticosteroids (e.g., prednisone) can be administered if needed for management of pyrexia. Further information on the effect of rifampin (strong CYP3A4 inducer) on the repeat dose PK of dabrafenib will be available as part of a drug-drug interaction trial to fulfill PMR 2044-7.

Table 5. Comparative analysis of repeat dose PK parameters with and without oral corticosteroids in patients administered dabrafenib 150 mg BID in combination with trametinib 2 mg QD (Parts B and D of Study BRF113220)

	Geometric Mean (%CV)			
	Dabrafenib	**Hydroxy-dabrafenib**	**Desmethyl-dabrafenib**	**Carboxy-dabrafenib**
With corticosteroid (n=10)				
$AUC_{0\text{-}tau}$ (ng·hr/mL)	3279 (62%)	2551 (55%)	3984 (66%)	52913 (61%)
C_{max} (ng/mL)	1200 (63%)	700 (58%)	542 (67%)	6410 (79%)
T_{max} (h)	1.2 (1.0-2.0)	1.8 (1.0-2.1)	1.7 (1.0-4.0)	4.0 (1.0-8.1)
C_{τ} (ng/mL)	59.0 (196%)	66 (52%)	357 (99%)	2943 (62%)
Without corticosteroid (n=74)				
$AUC_{0\text{-}tau}$ (ng·hr/mL)	4796 (37%)	3484 (54%)	3240 (65%)	51857 (39%)
C_{max} (ng/mL)	1411 (47%)	801 (72%)	397 (70%)	5723 (36%)
T_{max} (h)	2.0 (1.0-6.0)	2.0 (1.0-8.0)	2.0 (0.5-10.0)	4.0 (1.0-8.0)
C_{τ} (ng/mL)	84.1 (109%)	90 (102%)	250 (73%)	3176 (50%)

2.4 GENERAL BIOPHARMACEUTICS

2.4.1 What is the relative bioavailability of the proposed to-be-marketed formulation to the clinical trial formulation?

TAFINLAR has been approved and marketed as 50 and 75 mg HPMC capsules. Prior to development of the HPMC capsule formulation, a gelatin capsule formulation was used in earlier clinical studies. According to the clinical pharmacology review of the original NDA (Reference ID: 3287747), the bioavailability of dabrafenib is higher following single dose administration of HPMC capsules as compared to gelatin capsules, with a geometric mean ratio (90% CI) of 1.8 (1.3, 2.5) for $AUC_{0\text{-}inf}$ and 2.0 (1.4, 2.9) for C_{max} [Study BRF113468]. The popPK analysis for dabrafenib as a single agent showed that dabrafenib AUC increased by 42% with the administration of dabrafenib as HPMC capsules.

In patients administered repeat doses of dabrafenib 150 mg BID in combination with trametinib 2 mg QD, the bioavailability of dabrafenib is higher following administration of HPMC capsules (Part D) as compared to gelatin capsules (Part B), with a geometric mean ratio (90% CI) of 1.1 (0.8, 1.4) for $AUC_{0\text{-}\tau}$ and 1.5 (1.1, 2.1) for C_{max} (**Table 6**). The popPK analysis for dabrafenib combination therapy showed that dabrafenib AUC increased by 33% with the administration of

dabrafenib as HPMC capsules.

Table 6. Comparative analysis of day 21 PK parameters of 150 mg BID dabrafenib administered as HPMC (Part D) versus gelatin capsules (Part B)

	Geometric Mean Ratio of HPMC*/Gelatin† (90% CI)			
	Dabrafenib	**Hydroxy-dabrafenib**	**Desmethyl-dabrafenib**	**Carboxy-dabrafenib**
$AUC_{0\text{-}tau}$ (ng·hr/mL)	1.10 (0.84, 1.44)	1.20 (0.91, 1.59)	0.97 (0.67, 1.42)	0.88 (0.68, 1.15)
C_{max} (ng/mL)	1.51 (1.10, 2.08)	1.59 (1.15, 2.19)	1.05 (0.70, 1.58)	1.00 (0.77, 1.29)
C_{τ} (ng/mL)	1.02 (0.50, 2.10)	1.16 (0.64, 2.10)	0.97 (0.63, 1.50)	0.78 (0.57, 1.06)
* n=23; † n=42				

In Part C of Study BRF113220 that is intended to support registration of dabrafenib in combination with trametinib, 104 patients (64% of all patients; n=35 patients in dabrafenib single agent arm, n=33 patients in the 150/1 combination arm, n=36 patients in the 150/2 combination arm) received both gelatin and HPMC capsule formulations. Although dabrafenib exposures were higher with the HPMC capsule as compared to the gelatin capsule formulations, there were no apparent increased safety issues or incidence of adverse events with the use of the HPMC capsule formulation (**Table 7**). Refer to the Clinical review for more details. Patients in the confirmatory trial (Study MEK115306) of dabrafenib in combination with trametinib have received only HPMC capsules.

Table 7. Comparison of adverse events (>20%) in patients administered dabrafenib as HPMC or gelatin capsules

	Dabrafenib 150 mg BID / Trametinib 2 mg QD		
	Dabrafenib -Gelatin		Dabrafenib -HPMC
Preferred Term	Part C (N=55)	Part B (N=24)	Part D (N=39)
Any AE, n (%)	**55 (100)**	**24 (100)**	**38 (97)**
Pyrexia	39 (71)	21 (88)	22 (56)
Chills	32 (58)	18 (75)	20 (51)
Fatigue	29 (53)	13 (54)	13 (33)
Nausea	24 (44)	10 (42)	19 (49)
Vomiting	22 (40)	9 (38)	17 (44)
Diarrhea	20 (36)	9 (38)	7 (18)
Cough	16 (29)	10 (42)	11 (28)
Headache	16 (29)	11 (46)	14 (36)
Edema peripheral	16 (29)	6 (25)	7 (18)
Arthralgia	15 (27)	9 (38)	14 (36)
Rash	15 (27)	10 (42)	15 (38)
Night sweats	13 (24)	7 (29)	8 (21)
Constipation	12 (22)	6 (25)	3 (8)
Decreased appetite	12 (22)	6 (25)	9 (23)
Myalgia	12 (22)	3 (13)	7 (18)
Dermatitis acneiform	9 (16)	8 (33)	4 (10)
Dizziness	9 (16)	7 (29)	5 (13)
Pain in extremity	9 (16)	5 (21)	2 (5)
Anemia	7 (13)	5 (21)	7 (18)
Oropharyngeal pain	7 (13)	5 (21)	4 (10)
Ejection fraction decreased	5 (9)	5 (21)	2 (5)

Source: Applicant's Summary of Clinical Safety, page 122

2.5 ANALYTICAL SECTION

2.5.1 How are the active moieties identified and measured in the plasma and other matrices?

Plasma concentrations of dabrafenib and its metabolites including the hydroxy-, carboxy- and desmethyl-metabolites, were measured using validated UHPLC-MS/MS methods. Plasma concentrations of trametinib were measured using a validated HPLC-MS/MS assay method.

2.5.2 Which metabolites have been selected for analysis and why?

Dabrafenib and its major metabolites including hydroxy-dabrafenib (GSK2285403, M7), desmethyl-dabrafenib (GSK2167542; M8) and carboxy-dabrafenib (GSK2298683; M4) were measured. Metabolites were not measured for trametinib as M5 was not considered to be a major circulating metabolite at steady-state.

2.5.3 What bioanalytical methods are used to assess concentrations?

Dabrafenib and its metabolites, hydroxy-dabrafenib and desmethyl-dabrafenib, were measured using a validated UHPLC-MS/MS assay method over the range of 1 to 1000 ng/mL [Report No. CD2010/00018/01]. The within-run precision (%CV) for dabrafenib and desmethyl-dabrafenib is corrected in this version and smaller than that in the version reviewed as part of the original NDA that was found to be acceptable [Report No. CD2010/00018/00]. Carboxy-dabrafenib was measured using a validated UHPLC-MS/MS assay method over the range of 5 to 5000 ng/mL [Report No. CD2010/00125/00] reviewed as part of the original NDA that was found to be acceptable. Refer to the clinical pharmacology review of the original NDA 202806 (Reference ID: 3287747) for details on the validated assay methods. Accuracy (%RE) and precision (%CV) of the quality controls (QCs) for the runs used in measuring dabrafenib and metabolite concentrations in Study BRF113220 were ≤ 15%, which are acceptable based on the current FDA Guidance for Industry *Bioanalytical Method Validation*.

Trametinib was measured using a validated HPLC-MS/MS assay method (Report No. CD2008/00957, 2010N108094) reviewed as part of the original NDA, and was found to be acceptable. Refer to the clinical pharmacology review of the original NDA 204114 submission (Reference ID: 3289560) for details on the validated assay method. Accuracy (%RE) and precision (%CV) of the quality controls (QCs) for the runs used in measuring trametinib concentrations in Study BRF113220 were ≤ 15%, which are acceptable based on the current FDA Guidance for Industry *Bioanalytical Method Validation*.

3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included. The Applicant's proposed TAFINLAR labeling changes are in BLUE and modifications made by the Agency are in RED. Of note, the Agency's labeling modifications have not been agreed upon by the Applicant as of the date of this review.

(b) (4)

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/s/

RUBY LEONG
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11/26/2013

NITIN MEHROTRA
11/26/2013

CHRISTIAN GRIMSTEIN
11/26/2013

ROSANE CHARLAB ORBACH
11/26/2013
concur with genomics

HONG ZHAO
11/26/2013
I concur.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202806Orig1s002

<u>OTHER REVIEW(S)</u>

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	January 7, 2014
To:	Patricia Keegan, MD Director **Division of Oncology Products 2 (DOP2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Nathan Caulk, MS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Quynh-Van Tran, PharmD, BCPP Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	TAFINLAR (dabrafenib)
Dosage Form and Route:	Capsules, for oral use
Application Type/Number:	NDA 202-806
Supplement Number:	S-002
Applicant:	GlaxoSmithKline, LLC

1 INTRODUCTION

On July 9, 2013, GlaxoSmithKline LLC submitted for the Agency's review a Prior Approval Supplement (PAS)- Efficacy, to their New Drug Application (NDA) 202-806/S-002 for TAFINLAR (dabrafenib) Capsules. TAFINLAR (dabrafenib) Capsules was originally approved on May 29, 2013, and is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E as detected by an FDA-approved test. In this submission, the Applicant proposes a new indication for TAFINLAR (dabrafenib) Capsules, in combination with trametinib, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 E or V600K mutations, as detected by an FDA-approved test.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 2 (DOP2) on August 1, 2013, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TAFINLAR (dabrafenib) capsules.

2 MATERIAL REVIEWED

- Draft TAFINLAR (dabrafenib) Capsules MG received on July 9, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 3, 2014.
- Draft TAFINLAR (dabrafenib) capsules Prescribing Information (PI) received on July 9, 2013, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 3, 2014.
- Approved MEKINIST (trametinib) tablets comparator labeling dated May 29, 2013.
- MEKINIST (trametinib) Tablets, Review of Patient Labeling: Patient Package Insert (PPI) dated December 20, 2013.
- Approved ZELBORAF (vemurafenib) tablet comparator labeling dated July 3, 2013.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the MG document using the Verdana font, size 11.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

NATHAN P CAULK
01/07/2014

QUYNH-VAN TRAN
01/07/2014

SHARON R MILLS
01/07/2014

LASHAWN M GRIFFITHS
01/07/2014

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 3, 2014

To: Norma Griffin
Regulatory Project Manager
Division of Oncology Products 2 (DOP2)

From: Quynh-Van Tran, PharmD, BCPP
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **TAFINLAR (dabrafenib) Capsules, for oral use (Tafinlar)**
NDA 202806/Supplement 002
OPDP Review of Prescribing Information (PI)

In response to the August 1, 2013 consult request from DOP 2, OPDP has reviewed the proposed PI (FDA version sent via email to OPDP on January 3, 2014), and offers the following comments for Tafinlar. Please see the attached PI with our comments incorporated therein (e.g., "OPDP QVT . . .").

Thank you for the opportunity to provide comments on the proposed PI. If you have any questions, please contact Quynh-Van Tran at (301) 796-0185, or quynh-van.tran@fda.hhs.gov.

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/s/

QUYNH-VAN TRAN
01/03/2014

Food and Drug Administration
Center for Devices and Radiological Health

MEMORANDUM

Date: December 10, 2013

To: Marc Theoret MD, Clinical Team Leader CDER/OHOP/DOP2
through Norma Griffin Senior Regulatory Health Project Manager

From: Donna Roscoe, Ph.D., Associate Director CDRH/OIR/DIHD/IHGB
Through Reena Philip, Ph.D., Deputy Director CDRH/OIR/DIHD
and Robert Becker, MD, PhD, Chief Medical Officer CDRH/OIR

Subject: CDRH Review of Bridging Study for bioMérieux THxID –BRAF Kit in support of sNDA 202806_002 (SDN 104) – TAFINLAR and sNDA 204114_001 (SDN 83) – MEKINIST

I. Summary

The GSK study BRF113220 study is a phase I/II study that evaluates the clinical utility of TAFINLAR in combination with MEKINIST. Patients whose melanoma tumors were BRAF V600E or K positive were enrolled to the clinical study BRF113220. GlaxoSmithKline (GSK) submitted on July 8, 2013 two NDA supplements (sNDA 204114 and sNDA 202806) to support safety and efficacy claims for the approved melanoma monotherapies, tramatenib (MEKINIST) and dabrafenib (TAFINLAR) when used in combination (administered simultaneously) to treat melanoma patients whose tumors are BRAF V600E and V600K positive and revise the monotherapy labels accordingly. CDRH is providing consult to CDER about the effectiveness of the companion diagnostic (bioMerieux THxID™ BRAF Kit) to aid in the selection of patients receiving the combination therapy. (Consult receipt date August 1, 2013).

II. Background

Therapeutics:

GSK received approval for two therapeutics TAFINLAR (dabrafenib) NDA 202806 and MEKINIST (trametinib) NDA 204114 on May 28, 2013. The approved indications are as follows:

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

- ***MEKINIST*** *is a kinase inhibitor indicated as monotherapy for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. Limitation of use: MEKINIST as monotherapy is not indicated for treatment of patients who have received prior BRAF-inhibitor therapy.*

Reference ID: 3429229

New Indications under Review:
Data are intended to support the following proposed indications to each therapeutic label as follows:

- ***MEKINIST*** *in combination with dabrafenib is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. This indication is based on the demonstration of durable response rate.* (b) (4)

- ***TAFINLAR*** *in combination with trametinib is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutation as detected by an FDA-approved test. This indication is based on the demonstration of durable response rate.* (b) (4)

Companion Diagnostic:

The companion diagnostic sponsor, bioMérieux, Inc., received PMA (P120014) approval for the THxID –BRAF Kit as a safe and effective companion diagnostic on May 28, 2013. The approved indication is as follows:

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

Per current CDRH policy, the new therapeutic indications do not warrant revisions to the indications-for-use or labeling changes to the THxID -BRAF Kit device label since the use of the device in this trial and the associated therapeutic labeling updates, is consistent with device approval. However, because this study did not use the associated FDA approved test to screen patients for accrual to the trial, a bridging study to the approved device is needed. The bridging study is the basis for the consult request.

Prior Submissions Related to this Indication:

Discussions regarding the companion diagnostic development projects for GSK combination therapy claims were initiated as consults to CDER under IND 113557 (ICC 1200144, ICC1200032, and GEN1101092). Additional discussions were held under pre-submission numbers: I100245 (b) (4) The diagnostic manufacturer, bioMérieux SA (bMx), has an approved

Reference ID: 3429229

IDE (G120011) for the THxID™ -BRAF Assay Kit to select patients for the GlaxoSmithKline (GSK) MEK115306 trial which is a phase III, randomized, double-blinded study comparing the combination of the BRAF inhibitor Dabrafenib and the MEK inhibitor Tramatenib to Dabrafenib alone. Specifically, patients with BRAF V600E/K mutation positive are selected with the THxID- BRAF kit to determine for V600E, V600K or V600E/K mutation [redacted] (b) (4)

III. Clinical Study

1. **BRF113220 Clinical Study** was a multicenter open-label, phase I/II study conducted in four parts to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of the BRAF Inhibitor dabrafenib in combination with the MEK Inhibitor tramatenib in subjects with BRAF mutant metastatic melanoma. The 4 parts of the study were as follows:
   - Part A: to investigate the effect of repeat doses of tramatenib on the pharmacokinetics of single dose dabrafenib
   - Part B: to identify the range of tolerated dose combinations using a dose escalation procedure
   - Part C: to evaluate dose combination of dabrafenib and tramatenib based on results from the dose escalation cohorts
   - Part D: to evaluate dose combinations of dabrafenib administered as HPMC capsules alone and in combination with tramatenib

   Study centers: Two sites in Australia and 14 sites in the USA.

   Investigators: Multicenter study.

   Study period: May 25, 2010 to September 25, 2012.

   Study Design: A total of 415 subjects were enrolled across all 4 parts of the study. In Part A, the first subject was dosed with both therapeutics for safety and tolerability. As the results of Part A showed that trametinib did not have a clinically significant effect on the PK of dabrafenib, the study advanced to Part B. The first subject in Part B started treatment in the initial dose escalation cohort with dabrafenib and trametinib and continued until reaching the full recommended monotherapy doses. Subsequently, Cohort B was expanded by 20 BRAF-naive subjects (study B-4). In addition, enrollment to the BRAF-failure melanoma cohort and BRAF-mutant colorectal cohort in Cohort B-4 commenced. The colorectal expansion cohort of Part B currently remains open to enrollment. In parallel with enrollment into the Cohort B-4 expansion cohorts, the randomized Phase II Part C of the study was initiated. The first subject in Part C was dosed on 14 December 2010. Enrollment into Part C was completed on 7 July 2011. The fourth and final part of the study, Part D, started dosing subjects on 27 July 2011. Once the initial 4 cohorts in Part D had enrolled 15 subjects each, the 2 cohorts that started with combination treatment (Cohorts D-3 and D-4), were expanded to enroll 30 more subjects in each cohort from 13 January 2012 to 25 May 2012.

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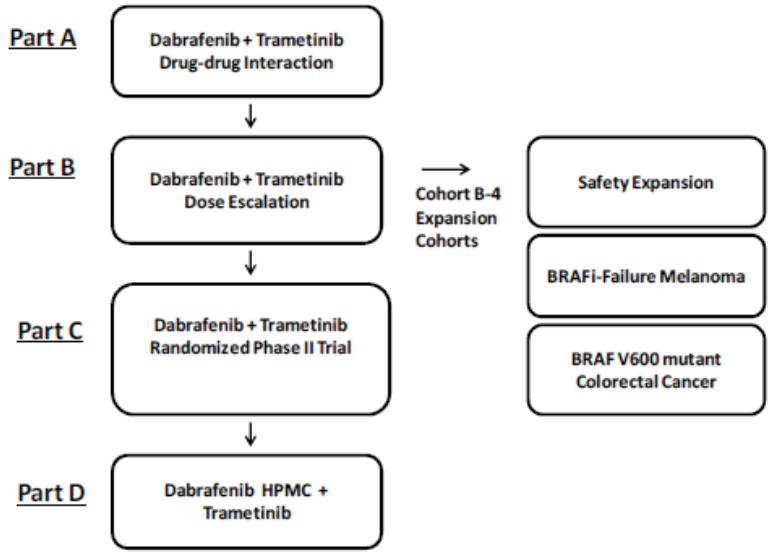
Figure 1 illustrates the phase I components of the study (A, B, and D) and the phase II component (C).

Figure 1 BRF113220 Study Design



Tumor specific Inclusion Criteria/Exclusion Criteria:

1. Male or female age ≥ 18 years of age.
2. BRAF mutation-positive melanoma (i.e., V600E, V600K or V600D) as determined via relevant genetic testing (in Parts A and B, other BRAF mutation-positive tumor types may be enrolled with approval of the GSK medical monitor). Testing with the GSK BRAF mutation assay may be required for enrollment.
   a. Part A: No archived tissue required, but must have known BRAF mutation (i.e., V600E, V600K or V600D);
   b. Part B: Must have archived tissue requested, must have BRAF mutation (i.e., V600E, V600K or V600D);
   c. Part C and D: Archived tissue required, need fresh biopsy if archived tissue is not available, must have BRAF mutation (must be V600E, V600K or V600D). Only melanoma patients can be enrolled.

BRAF Testing: Patients were eligible based on a tumor BRAF mutation status that was conducted by a local testing laboratory rather than a single, centralized laboratory. For many subjects, eligibility into the study was based on previously obtained tumor BRAF mutation results generated by local laboratories as part of a routine diagnostic work up for melanoma. As a result of local BRAF mutation testing, tumors from BRAF mutation positive subjects enrolled into the study were analyzed by 27 local laboratories using 11 different assay platforms. Specimens were subject to further confirmation by one of the local laboratories (Response Genetics, Inc). A comparison of the platforms and estimated analytical sensitivity was submitted by GSK. The laboratory information included comparison of test platforms, ability of test to distinguish BRAF V600E and V60)K mutations, tissue processing, DNA extraction method, DNA quantity required, claimed limit of detection (LOD) and the

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protocol for LOD determination, frequency of melanoma BRAF testing, and breakdown of BRAF positive vs. BRAF negative results for melanoma testing. The data was reviewed to assess the similarity in test methods and thus the assumption that test selection would be generally considered to be uniform across platforms. The data demonstrated a range of claimed performance across platforms.

Populations

A total of 415 subjects were enrolled across all 4 parts of the study as of the first clinical cut-off date (25May2012).

Part A: 8 subjects enrolled and analyzed.

Part B: 135 subjects enrolled and analyzed.

Part C: 162 subjects enrolled

Part D: 110 subjects enrolled and analyzed.

Demography and Baseline Disease Characteristics:

Subjects were not stratified for prognostic variables. The demographics and baseline disease characteristics for the ITT population were generally well-balanced between the ITT populations across treatment arms and compared to the population available for retest by the THxID -BRAF test. Most subjects were white (>99%). There were more female than male. Most (All subjects in Part C) had melanoma as their primary tumor type at baseline and the majority (83-87%) harbored the V600E mutation. The incidence of V600K mutation in Part C subjects (15%) is consistent with the reported frequency of this mutation in the overall melanoma population (~10-20%).

Objectives and Endpoints- Part C

	Objective	Endpoints
Primary	To determine clinical activity of dabrafenib and trametinib in subjects with BRAF mutant metastatic melanoma. To determine the safety, tolerability and range of tolerated doses of dabrafenib and trametinib dosed orally in combination in subjects with BRAF mutant metastatic melanoma.	Response rate (CR + PR) of dabrafenib and trametinib in BRAF mutant metastatic melanoma. Duration of response. Progression-free survival AEs (including rate of squamous cell carcinoma) and changes in laboratory values and vital signs

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Secondary	To characterize the population PK parameters of dabrafenib and trametinib when administered daily in subjects with BRAF mutant metastatic melanoma. To characterize the durability of response in subjects achieving clinical benefit.	Population PK parameters, such as oral clearance and oral volume of distribution of dabrafenib and trametinib will be determined. Additional PK parameters may also be estimated. Overall survival

Table 3 Key Efficacy Data from Part C of Study BRF113220 (ITT Population)

Endpoints/ assessment	Dabrafenib monotherapy N=54	150/1 Combination N=54	150/2 Combination N=54
Progression-free survival			
Investigator-assessed, median, months (95% CI)	5.8 (4.6, 7.4)	9.2 (6.4, 11.0)	9.4 (8.6, 16.7)
HR (95% CI)	--	0.56 (0.37, 0.87)	0.39 (0.25, 0.62)
p-value	--	0.0057	<0.0001
BICR-assessed, median, months (95% CI)	7.3 (5.5, 9.4)	8.3 (5.6, 11.3)	9.2 (7.6, -)
HR (95% CI)	--	0.73 (0.45, 1.19)	0.54 (0.32, 0.91)
p-value	--	0.1721	0.0121
Investigator-assessed 12-month PFS, % KM estimate, (95% CI)	9 (3, 20)	26 (15, 39)	41 (27, 54)
Overall response rate			
Investigator-assessed, % (95% CI)	54 (39.6, 67.4)	50 (36.1, 63.9)	76 (62.4, 86.5)
Difference, % (95% CI)	--	–4 (-23.1, 15.9)	22 (2.5, 40.7)
p-value	--	0.7730	0.0264
BICR-assessed, % (95% CI)	46 (32.6, 60.4)	39 (25.9, 53.1)	61 (46.9, 74.1)
Difference, % (95% CI)	--	–7 (–26.7, 12.3)	15 (–5.0, 33.7)
p-value	--	0.5008	0.1486
Duration of response			
Investigator-assessed, median, months (95% CI)	5.6 (4.5, 7.4)	9.5 (7.4, -)	10.5 (7.4, 14.9)
n	29	27	41
BICR-assessed, median, months (95% CI)n	7.6 (5.5, -)	11.3 (6.2, -)	7.6 (6.9, -)
n	25	21	33
Overall survival			
HR (95% CI)	--	0.98 (0.51, 1.87)	0.67 (0.34, 1.34)
p-value	--	0.9514	0.2591
12-month survival, KM estimate % (95% CI)	70 (55, 80)	68 (54, 79)	79 (66, 88)

Abbreviations: BICR=blinded independent central review; CI=confidence interval: HR=hazard ratio; KM=Kaplan-Meier; n=number; PFS=progression-free survival

Data Source: BRF113220 Part C Table 12.19, Table 12.23, Table 12.32, Table 12.40, Table 12.63, Table 12.67, Table 12.71, Table 12.142, and Table 12.144

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IV. Bridging Study

The objective of the bridging study was to establish the performance of the THxID –BRAF kit. Because patients in the BRF113220 study were recruited based on results evaluated at 27 local laboratories, retrospective specimens from patients enrolled in BRF113220 were used to evaluate the clinical utility of THxID-BRAF assay as the companion diagnostic device. Evaluation of the THxID -BRAF Kit was based on samples from Parts B, C and D of the BRF 113220 Study.

Clinical Testing Sites for Bridging Study

(b) (4) and Response Genetics, Inc. 1640 Marengo St. 6th Floor, Los Angeles, CA 90033.

Specimen Accountability:

Specimens from subjects with BRAF positive mutations from Part C were included in the evaluation, and specimens from Part B, C, D that were mutant positive, wild-type or out of detectable range by the local laboratory were included in the evaluation. A total of 184 samples were available for retesting by THxID BRAF assay, of which 146 had local BRAF positive subjects, 35 had WT results and 3 had out of detectable range (OODR) results. The wild-type samples were those available from Response Genetics testing. Otherwise, wild-type samples from the remaining labs were not available for re-analysis.

Specimen Characteristics:

Specimens for testing were formalin-fixed, paraffin embedded tissue (slides or block; ~75%) or extracted DNA (~25%). Specimens consisted of lymph nodes, skin and other anatomic sites. The different anatomic sites and were summarized. Specimens were evaluated by pathologist and information relating to necrosis, fatty tissue, hemorrhagic tissue tumor content, tissue area, melanin content, and macrodissection. Specimens with less than 80% tumor content were macrodissected and prepared according to the THxID -BRAF Kit protocol. Specimen characteristics, and the distribution of sample characteristics, were the same as observed in the original studies used to support approval of the bioMérieux THxID BRAF Kit.

Analytical Concordance:

The goal of the analytical bridging study was to demonstrate that the concordance between the THxID -BRAF Kit and the local lab results was sufficiently high to support the conclusions regarding efficacy obtained with the selected population. There were 181 total samples which included samples outside of the Part C study. Only 152 samples were available for analysis after excluding due to discrepancy of tissue types tested by local labs and THxID -BRAF assay. Note the sponsor included all THxID -BRAF V600 positive subjects (131) for the clinical utility analysis regardless of the tissue types. Therefore, it appears more appropriate for the sponsor to provide agreement table for all samples at all local labs (including RGI).

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The agreement between results obtained with local laboratories and THxID -BRAF assay for available samples is summarized below.

		Local Laboratory + 35 WTs from RGI Dataset		
		Positive	**Negative**	**Total**
THxID BRAF Assay	**Positive**	107	0	107
	Negative	1	34	35
	Invalid	9	1	10
	Total	117	35	152*

	Agreements (All)		
	No. of concordance/ No of tests	**Agreement rate (%)**	**95% CI**
PPA	107/117	91.5	[85.0% - 95.3%]
NPA	34/35	97.1	[85.4% - 99.5%]
OPA	141/152	92.8	[87.5% - 95.9%]

PPA=Positive Percent Agreement; NPA=Negative Percent Agreement, OPA=Overall Percent Agreement.

The THxID™-BRAF assay demonstrates a PPA of 91.5%, a NPA of 97.1%, and an OPA of 92.8%. These results demonstrate a strong agreement between the THxID™-BRAF assay and the Local Laboratories' assays.

Because 16 samples were unavailable for analysis, a best case-worst case sensitivity analysis was conducted for impact on agreement conclusions. Invalids were also included in this analysis. When the 16 missing samples are deemed BRAF mutation positive (best case scenario) in the THxID -BRAF assay, the PPA is 99.2%, the NPA is 100.0%, and the OPA is 99.4%. For the worst case scenario whereby the 16 missing samples are BRAF mutation negative (Wild type) in the THxID-BRAF assay, the PPA is 80.5%, the NPA is 97.1%, and the OPA is 83.9%. Note for all assessments, NPA and OPA are estimates as all the wild-types were not available for this analysis.

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Clinical Concordance:

There were 162 subjects in the Part C study BRF113220 and 146 of them had samples available for THxID -BRAF retesting. THxID BRAF mutation positive results were confirmed for 131 subjects out of the 146 subjects. The analysis for THxID BRAF positive results were based on these 131 subjects. The analysis for investigator-assessed progression free survival (PFS) is summarized in the tables below. For local lab positive subjects (ITT population), the hazard ratios for the two treatments (Dabrafenib 150mg BID + Tramatinib 1 mg QD and Dabrafenib 150mg BID + Tramatinib 2 mg QD) versus control are 0.56 and 0.39 respectively, which are slightly larger than 0.45 and 0.33 for subjects with both local lab and THxID positive results. The efficacy of the drug was maintained by local and THxID BRAF positive subjects. Patients with local lab V600 negative results and THxID V600 positive results are those patients which would have been enrolled had the THxID BRAF test been used to screen for enrollment. Impact of those discordant subjects on the efficacy of the treatment for all THxID positive subjects depends on the number of discordant subjects excluded and whether the treatment effectiveness is very different for THxID positive subjects who were enrolled and those who were excluded due to negative local test results. Note, both dependencies are not evaluable, because negative samples from local labs (except RGI) were not available for retest and because (by design) local lab BRAF negative subjects were excluded from the investigation.

Table 28 Summary of Investigator-Assessed Progression Free Survival (THxID BRAF and RGI IUO Mutation Positive Subjects)

	ThxID™ BRAF Assay (N=131)			RGI IUO (N=146)		
	Dabrafenib 150 mg BID (N=48)	Dabrafenib 150 mg BID + Trametinib 1 mg QD (N=41)	Dabrafenib 150 mg BID + Trametinib 2 mg QD (N=42)	Dabrafenib 150 mg BID (N=51)	Dabrafenib 150 mg BID + Trametinib 1 mg QD (N=47)	Dabrafenib 150 mg BID + Trametinib 2 mg QD (N=48)
Subject Classification, n (%)						
n	48	41	42	51	47	48
Progressed or Died (event), n(%)	42 (88%)	29 (71%)	23 (55%)	44 (86%)	34 (72%)	27 (56%)
Censored, Follow-up ended, n(%)	1 (2%)	1 (2%)	1 (2%)	1 (2%)	1 (2%)	2 (4%)
Censored, Follow-up ongoing, n(%)	5 (10%)	11 (27%)	18 (43%)	6 (12%)	12 (26%)	19 (40%)
Hazard Ratio[a]						
Hazard Ratio Estimate (95% CI)		0.45 (0.28,0.72)	0.33 (0.20,0.55)		0.53 (0.34,0.83)	0.38 (0.24,0.61)
Log-Rank P-Value		0.0003	<0.0001		0.0030	<0.0001
Estimates for progression-free survival, months[b]						
1st Quartile	3.8	5.6	7.4	3.8	5.5	5.9
95% CI	(3.6,5.6)	(3.7,8.3)	(5.3,9.2)	(3.6,5.6)	(3.6,7.2)	(5.3,8.7)
Median	5.8	10.2	10.7	5.8	9.2	10.1
95% CI	(4.6,7.4)	(7.2,11.1)	(8.6,16.7)	(5.5,7.4)	(7.1,11.0)	(8.6,16.7)
3rd Quartile	7.6	13.0	16.7	9.1	12.9	16.7
95% CI	(7.4,9.3)	(11.0,NR)	(NR,NR)	(7.4,9.4)	(11.0,NR)	(NR,NR)

Data Source: Appendix 1, Table 7.004, Table 7.005

a. Hazard ratios are estimated using a Pike estimator.

b. Quartiles estimated using the Brookmeyer-Crowley method.

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Table 29 Summary of Investigator-Assessed Progression Free Survival, ITT Population

	Dabrafenib 150 mg BID (N=54)	Dabrafenib 150 mg BID + Trametinib 1 mg QD (N=54)	Dabrafenib 150 mg BID + Trametinib 2 mg QD (N=54)
Subject Classification, n (%)			
Progressed or Died (event)	47 (87)	39 (72)	31 (57)
Censored, Follow-up ended	1 (2)	2 (4)	3 (6)
Censored, Follow-up ongoing	6 (11)	13 (24)	20 (37)
Hazard Ratio[a]			
Estimate (95% CI)	--	0.56 (0.37, 0.87)	0.39 (0.25, 0.62)
Log rank p-value	--	0.0057	<0.0001
Kaplan-Meier Estimates for PFS, months[b]			
1st Quartile (95% CI)	3.8 (3.6, 5.5)	5.5 (3.7, 6.5)	5.8 (5.3, 8.7)
Median (95% CI)	5.8 (4.6, 7.4)	9.2 (6.4, 11.0)	9.4 (8.6, 16.7)
3rd Quartile (95% CI)	9.1 (7.4, 9.4)	12.9 (11.0, -)	16.7 (12.4, 16.7)

Data Source: Appendix 2, Table 12.32

Abbreviations: BID=Two times a day; CI=Confidence interval; PFS=Progression-free survival; QD=Once daily.

Note: P-values are based on 2-sided log rank test. The censoring method included censoring for extended loss to follow-up, new anti-cancer therapy, and excluding symptomatic progression.

a. HRs were estimated using the Pike estimator. A HR <1 indicates a lower risk with this treatment compared with the monotherapy group.

b. Confidence intervals were estimated using the Brookmeyer Crowley method.

The analysis for investigator-assessed best overall response is summarized in the table below. For local positive subjects (ITT), the difference in response rate between control and Dabrafenib 150mg BID + Tramatinib 2 mg QD is 22% (p=0.026). The drug efficacy in response rate was maintained 81%-54%=27% for local lab and THxID positive subjects. Analysis of overall response by all THxID positive subjects has the same dependencies and uncertainties as those noted above for the PFS analysis.

Table 33 Summary of Investigator-Assessed Best Overall Response with Confirmation (THxID BRAF and RGI IUO Mutation Positive Subjects)

	ThxID™ BRAF Assay (N=131)			RGI IUO (N=146)		
	Dabrafenib 150 mg BID (N=48)	Dabrafenib 150 mg BID + Trametinib 1 mg QD (N=41)	Dabrafenib 150 mg BID + Trametinib 2 mg QD (N=42)	Dabrafenib 150 mg BID (N=51)	Dabrafenib 150 mg BID + Trametinib 1 mg QD (N=47)	Dabrafenib 150 mg BID + Trametinib 2 mg QD (N=48)
Best Response, n (%)						
Complete Response (CR)	1 (2)	1 (2)	4 (10)	2 (4)	1 (2)	5 (10)
Partial Response (PR)	25 (52)	22 (54)	30 (71)	26 (51)	23 (49)	31 (65)
Stable Disease (SD)	19 (40)	17 (41)	8 (19)	20 (39)	21 (45)	12 (25)
Non-CR/Non-PD	0	0	0	0	0	0
Progressive Disease (PD)	3 (6)	1 (2)	0	3 (6)	1 (2)	0
Not evaluable (NE)	0	0	0	0	1 (2)	0
Response Rate, n (%)						
CR+PR	26 (54)	23 (56)	34 (81)	28 (55)	24 (51)	36 (75)
95% CI[a]	(39.2, 68.6)	(39.7, 71.5)	(65.9, 91.4)	(40.3, 68.9)	(36.1, 65.9)	(60.4, 86.4)

Data Source: Appendix 1, Table 7.1001 and Table 7.1002

a. Exact 2-sided 95% confidence interval

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Table 34 Summary of Investigator-Assessed Best Overall Response with Confirmation (ITT Population)

	Dabrafenib 150 mg BID (N=54)	Dabrafenib 150 mg BID + Trametinib 1 mg QD (N=54)	Dabrafenib 150 mg BID + Trametinib 2 mg QD (N=54)
Best Response, n (%)			
CR	2 (4)	3 (6)	5 (9)
PR	27 (50)	24 (44)	36 (67)
SD	22 (41)	24 (44)	13 (24)
PD	3 (6)	2 (4)	0
NE	0	1 (2)	0
ORR, n (%)			
CR+PR	29 (54)	27 (50)	41 (76)
95% CI[a]	(39.6, 67.4)	(36.1, 63.9)	(62.4, 86.5)
Difference in ORR			
Difference	--	–4%	22%
95% CI[a]	--	(-23.1, 15.9)	(2.5, 40.7)
P-value[a]	--	0.7730	0.0264

Data Source: Appendix 2, Table 12.19
Abbreviations: BID=Two times a day; CI=Confidence interval; CR=Complete response; NE=Not evaluable; ORR=Overall response rate; PD=Progressive disease; PR=Partial response; QD=Once daily; SD=Stable disease.
Note: Subject 555 (150/1 combination therapy group [V600E, no prior brain metastases]) was NE due to death occurring before the first post-dose assessment.
a. P-values and 95% CIs were calculated based on the unconditional exact method.

To investigate the impact of the subjects incorrectly excluded from the study due to negative local BRAF results and positive THxID results, the sponsor did a questionnaire for participating local labs. Based on the questionnaire, the percentage of V600 positive results from local laboratories ranges from 22% to 50%. The sponsor assumed that P(THxID=+|LOCAL=-) can range from 1% to 7%. With 36% prevalence (average of 22% and 50%) for V600 positivity and P(THxID=+|LOCAL=-)=1%, the impact will be small because only about 182*1%=2 subjects were incorrectly excluded from the study. With 36% prevalence for V600 positive and P(THxID=+|LOCAL=-)=7%, the impact would potentially be large because about 20 V600 discordant subjects would be excluded from the study.

V. Summary

The therapeutics dabrafenib and tramatenib are currently approved as monotherapies for treating patients with an unresectable or metastatic melanoma with BRAF V600E or V600E/K mutation, respectively. Safety and efficacy claims in the V600E/K subset is assured when the companion diagnostic manufactured by bioMérieux THxID BRAF assay is used to aid in the selection of patients. For phase I/II clinical trial BRAF113220, GSK used local laboratory test results to select and enroll patients into the trial for combination treatment. GSK was required to conduct a bridging study between the local lab test results and the approved companion diagnostic test. The current bridging study is lacking the local lab test negatives for analysis. GSK was unable to obtain test-negative specimens and conducted a bridging study between local lab results and the THxID –BRAF test using the test positive cases and the only available test negatives from one of the local labs (RGI). For available samples, the data demonstrated good analytical concordance between the local lab test results and the THxID –BRAF assay. Subjects enrolled on the BRF113220 study due to positive local test results demonstrated progression free survival and

Reference ID: 3429229

overall response rates similar to those for enrolled subjects who tested positive with the THxID BRAF assay.

VI. Conclusion

While GSK was unable to conduct a rigorous bridging study due to the missing local lab test negatives for the analytical concordance study, there is reason to believe that safety and efficacy of the dabrafenib/tramatenib claims supported by results in subjects selected with local lab test results will be similarly supported when subjects are selected by the bioMérieux THxID –BRAF assay:

1. The results demonstrate very good analytical concordance between local lab test positives (treated set) and the THxID- BRAF assay.
2. The test supports efficacy claims in the monotherapies. There is no reason to believe efficacy would not be supported when drugs are administered together.
3. The majority of local laboratory testing indicated similar analytical sensitivity claims to that of the THxID BRAF test (i.e. 5% mutant DNA).
4. Local labs were surveyed for the prevalence of the V600E and V600K markers in melanoma patients screened in their lab (and thus an indicator of the proportions identified by the test) and estimates were similar to the THxID BRAF test prevalence observed in the monotherapy trials (i.e., approximately 40% ± 15%).
5. Accuracy of the THxID -BRAF test when compared to Sanger sequencing indicates very high accuracy. The therapeutic effect on BRAF marker status has been demonstrated in animal models and in vitro studies supporting the biological significance of the marker and hence need for accuracy.
6. Further: GSK is using the THxID BRAF assay in the phase III combination trial and early indicators are showing the same trend in safety and efficacy observed in the phase I/II trial supporting the use of the approved companion diagnostic for this indication.

GSK and bioMérieux propose to submit follow-up data in support of the companion diagnostic from the phase III trial to CDRH simultaneously when they submit the information to CDER.

Reviewer:

Donna M. Roscoe -S
2013.12.10 14:24:55 -05'00'

Reference ID: 3429229

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/s/

NORMA S GRIFFIN
12/30/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Pediatric and Maternal Health Staff Memo

Date: November 25, 2013

From: Carrie Ceresa, Pharm D, MPH
Regulatory Reviewer, Maternal Health Team
Pediatric and Maternal Health Staff

Through: Jeanine Best, MSN, RN, PNP
Team Leader, Maternal Health Team
Pediatric and Maternal Health Staff

Lynne P. Yao, M.D., OND Associate Director,
Pediatric and Maternal Health Staff

To: The Division of Oncology Products 2 (DOP2)

Drug: TAFINLAR (dabrafenib)/MEKINIST (trametinib)

NDAs: 202-806/204-114

Subject: To review the revised labeling based on the indication using the combination therapy.

On July 31, 2013, the Division of Oncology Products 2 (DOP2) consulted the Pediatric and Maternal Health Staff – Maternal Health team to review the TAFINLAR and MEKINIST product labels that had been submitted with new efficacy supplements to NDAs 202-806 and 204-114. The efficacy supplements were submitted for the combination use of these products.

Both products were originally approved on May 29, 2013. MEKINIST is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test, and TAFINLAR is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test.

Reference ID: 3412294

The following are the proposed additions to the current monotherapy indications for both products:

"MEKINIST in combination with dabrafenib is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test"

"TAFINLAR in combination with trametinib is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test"

PMHS-MHT completed a labeling review during the initial review cycle for both products on April 22, 2013. In that review PMHS-MHT provided labeling comments and recommendations with respect to pregnancy, lactation and females and males of reproductive potential. During this review cycle the sponsor did not propose any labeling changes to those labeling subsections. PMHS-MHT refers to the April 22, 2013, review for pregnancy, lactation and females and males of reproductive potential labeling recommendations.

During this review cycle a question arose regarding the recommended amount of time to use highly effective contraception after treatment. For the TAFINLAR labeling the current recommendation is to use highly effective contraception during treatment and for four weeks after treatment. The MEKINIST labeling advises patients to use highly effective contraception during treatment and for four months after treatment. Neither timeline correlates with the half-life of either drug. It generally takes between 4 to 5 half-lives for a drug to be eliminated from human plasma; therefore, PMHS-MHT recommends that recommended post-treatment contraception use be revised to reflect the calculated 5 half-lives for both products.

PMHS-MHT refers to the final NDA actions for final labeling language.

Reference ID: 3412294

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/s/

CARRIE M CERESA
11/25/2013

JEANINE A BEST
11/25/2013

LYNNE P YAO
11/25/2013

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: November 8, 2013

TO: Norma Griffin, Senior Regulatory Health Project Manager
Maitreyee Hazarika, M.D., Medical Officer
Division of Oncology Products 2

FROM: Lauren Iacono-Connors, Ph.D.
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

THROUGH**:** Janice Pohlman, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Acting Branch Chief
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 202806 S-002
NDA: 204114 S-001

APPLICANT: GlaxoSmithKline, LLC

DRUG: Tafinlar (dabrafenib [GSK2118436]) and
Mekinist (trametinib [GSK1120212]) Combination

NME: No
THERAPEUTIC CLASSIFICATION: Priority

INDICATION(S): For the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations.

CONSULTATION REQUEST DATE: August 7, 2013
INSPECTION SUMMARY GOAL DATE: November 26, 2013
DIVISION ACTION GOAL DATE: December 20, 2013
PDUFA DATE: January 9, 2014

I. BACKGROUND:

GlaxoSmithKline, LLC (GSK), submitted an efficacy supplement to their NDA 202806 for Tafinlar® (dabrafenib) to support approval to market Tafinlar® capsules in combination with trametinib for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. GSK submitted a parallel efficacy supplement to their NDA 204114 for Mekinist™ tablets (trametinib) to support approval to market Mekinist™ in combination with dabrafenib for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test. The RAS/RAF/MEK/ERK pathway is a critical proliferation pathway in many human cancers and this pathway can be constitutively activated by alterations in specific proteins, including BRAF.

Dabrafenib (Tafinlar®) is a selective inhibitor of BRAF kinase activity. BRAF mutations have been identified at a high frequency in specific cancers, including approximately 40-60% of melanomas. The frequency of this activating mutation, and the pathway to which it leads, makes mutated BRAF an attractive target for antineoplastic therapy such as dabrafenib. Dabrafenib (Tafinlar®) was developed by GSK as monotherapy for the treatment of BRAF V600E mutation positive metastatic melanoma. It was approved for use against melanoma by the FDA on May 29, 2013.

Trametinib (Mekinist™) is a selective allosteric noncompetitive inhibitor of MEK1/MEK2 activation and kinase activity. MEK1 and MEK2 are proteins in the central signal transduction pathway and are critical for cell proliferation and survival. Trametinib has been developed specifically to address known oncogenic mutations in upstream mitogen-activated protein kinase (MAPK) pathway proteins BRAF and Ras, which signal through MEK1 and MEK2. Trametinib (Mekinist™) was developed by GSK as monotherapy for the treatment of BRAF V600 (E/K) mutation positive metastatic melanoma. It was approved for use against melanoma by the FDA on May 29, 2013.

Both efficacy supplements are supported by safety and efficacy results of the pivotal Phase 2 study, BRF1132 20 (Part C), entitled, “An Open-Label, Dose-Escalation, Phase IB/II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of the BRAF Inhibitor GSK2118436 in Combination with the MEK Inhibitor GSK1120212 in Subjects with BRAF Mutant Metastatic Melanoma”.

The study initially planned to randomize 20 subjects per study arm (Protocol Amendment 1). The sample size was increased to 50 subjects randomized per study arm (Protocol Amendment 2). The study randomized 162 subjects, with 54 subjects each randomized to the 3 treatment

groups, at 16 sites; 2 sites in Australia and 14 sites in the US. This study was conducted under IND 105,032/102,175.

Two clinical sites were chosen for inspection, Site 072218 (Dr. Kevin Kim, Houston, Texas) and Site 085394 (Dr. Hamid Omid, Los Angeles, California) on the basis of enrollment of large numbers of study subjects, and a high rate of treatment responders.

II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
CI#1: Kevin B. Kim (PI) **Michael Davies (Sub-I or Initial PI)** University of Texas MD Anderson Cancer Center 1515 Holcombe Blvd Houston, TX 77030	Protocol: BRF1132 20, Part C Site Number: 072218 Number of Subjects: 21	October 2-15, 2013	Pending Interim classification: VAI
CI#2: Hamid Omid (PI) 11818 Wilshire Blvd Los Angeles, CA 90025	Protocol: BRF1132 20, Part C Site Number: 085394 Number of Subjects: 22	September 16-30, 2013	Pending Interim classification: NAI

Key to Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

1. **CI#1: – Kevin Kim, M.D.**
   University of Texas
   MD Anderson Cancer Center
   1515 Holcombe Blvd-Room 430
   Houston, TX 77030

a. **What was inspected:** The site screened 21 subjects, 21 subjects were enrolled, and 14 completed the study. The study records of 10 subjects were audited. The record audit was in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included subject medical records, subject histories, laboratory results, drug accountability, medication diaries,

concomitant medications, sponsor correspondence, monitoring, informed consent forms, and financial disclosure compliance. The FDA investigator compared source documentation to eCRFs and data listings submitted to NDA 202806 S-002 and NDA 204114 S-001.

b. General observations/commentary: Generally, the investigator's execution of the protocol was found to be adequate. Per the protocol, the primary efficacy endpoints were progression free survival (PFS), overall response rate (ORR), and duration of response. The source records audited at this site supported response rates reported in the applications. Review of source documentation for eligibility, randomization, treatment regimens, study-specified periodic assessments, study drug administration cycles and drug accountability found a few minor discrepancies, none of which should impact study outcome. Adverse events were adequately reported. The FDA field investigator issued a three item FDA Form 483, Inspectional Observations.

1. **Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to conducting study-related tests.**

   Specifically,

   Subject (b) (6) had study related screening labs/dermatology appointment/cardiac function testing and dermatology exam performed prior to signing the Informed Consent Form.

2. **An investigation was not conducted in accordance with the signed statement of investigator and investigational plan.**

   Specifically,

   a. Subject (b) (6) received a urine pregnancy test upon screening; a serum pregnancy test is required per the protocol.
   b. Subjects (b) (6) did not have tissue samples submitted to RGI; this is an exclusion per the protocol.
   c. Subjects (b) (6) all had reportable SAE's that were not reported to the sponsor within the 24 hour reporting timeframe.
   d. Subject (b) (6), Investigational Product was not stopped when his LVEF fell 10% below his baseline LVEF of 60-65%

3. Investigational drug disposition records are not adequate with respect to use by subjects.

Specifically,

a. According to the pill diary for subject (b) (6), the Investigational Product was started on (b) (6) and was discontinued on (b) (6). The last entry from the subject's pill diary was (b) (6). The study staff was unable to locate the subject's pill diary dated (b) (6) through (b) (6). The subject was removed from the study for disease progression on (b) (6).
b. Subject (b) (6) pill diary was mislabeled with the medical information sticker and placed in the medical record of subject (b) (6).

OSI Reviewer Notes: *With respect to observation 1, this was an isolated inspectional observation, and had no impact on subject (b) (6) safety. In addition, according to the FDA field investigator the informed consent form was signed by the subject on the next calendar day. With respect to observation 2.b., the site failed to collect, store or provide tissue samples for the sponsor's laboratory contractor, Response Genetics, Inc. (RGI), for tumor genotyping for Subjects (b) (6). However, according to the records found at the site these subjects all had tumor samples assessed for the protocol-specified mutations at MD Anderson in order to satisfy the entry criteria of having a BRAF mutation. The protocol inclusion criteria do not specify a laboratory to conduct genotyping (mutation assessment) for the tumor tissue for each subject to satisfy the entry criteria. Therefore, having tumor genotyping done at MD Anderson was consistent with the protocol. This inspectional finding should not impact study efficacy or safety outcomes.*

Overall these inspectional observations, while valid, should not importantly impact data generated by this site. All these inspectional observations will be addressed and corrected by this site moving forward.

c. **Assessment of data integrity:** The data for Dr. Kim's site, associated with Study BRF1132 20, Part C, submitted to the Agency in support of NDA 202806 S-002 and NDA 204114 S-001, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

2. **CI#2: – Hamid Omid, M.D.**
   11818 Wilshire Blvd
   Los Angeles, CA 90025

a. **What was inspected:** The site screened 22 subjects, and 17 subjects were enrolled. Portions of the study records of 11 subjects were audited. The record audit was in accordance with the clinical investigator compliance program, CP 7348.811. The record audit included comparison of source documentation to eCRFs and data listings submitted to NDA 202806 S-002 and NDA 204114 S-001, with particular attention paid to inclusion/exclusion criteria compliance, adverse events, treatment regimens, and reporting of AEs in accordance with the protocol. The FDA investigator also assessed informed consent documents, test article accountability, monitoring reports, and financial disclosure forms.

b. **General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. Per the protocol, the primary efficacy endpoints were progression free survival (PFS), overall response rate (ORR), and duration of response. The source records audited at this site supported response rates reported in the applications. Review of source documentation for eligibility, randomization, treatment regimens, study drug administration cycles and drug accountability found no discrepancies. With a few minor exceptions adverse events were adequately reported. Briefly, during the audit of AEs it was found that source records had documented AE end dates; however these end dates were not always reflected in the data listings submitted to the NDAs or in the eCRFs. In the data listings submitted to the NDAs, some of these AEs were noted as "ongoing" for the end dates. This study site staff was informed that when changes are made to a source record, those changes need to be reflected in the CRF as well. The site promised to immediately update the eCRFs to reflect known end dates for AEs. No Form FDA 483 was issued.

c. **Assessment of data integrity:** The data for Dr. Omid's site, associated with Study BRF1132 20, Part C, submitted to the Agency in support of NDA 202806 S-002 and NDA 204114 S-001, appear reliable based on available information.

Note: The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Based on the review of preliminary inspectional findings for clinical investigators Dr. Kevin Kim (Site 072218) and Dr. Hamid Omid (Site 085394) the Study BRF1132 20, Part C, data appear reliable based on available information.

One clinical site inspected, Dr. Kevin Kim (Site 072218) was issued a Form FDA 483 citing inspectional observations and preliminary classification for this inspection is Voluntary Action Indicated (VAI). The preliminary classification for Dr. Hamid Omid's site (085394) is No Action Indicated (NAI).

The inspection of Dr. Kevin Kim's site (072218) found one subject (b) (6) who had certain study related screening procedures conducted the day prior to actually signing the informed consent form. While all AEs appeared to be reported there were several occasions where SAEs were not reported within the required timeframe of 24 hours per protocol. The primary efficacy endpoints were progression free survival (PFS), overall response rate (ORR), and duration of response. The source records audited at this site supported response rates reported in the applications. However, the site failed to collect, store or provide tissue samples for the sponsor's laboratory contractor, Response Genetics, Inc. (RGI), for tumor genotyping for Subjects (b) (6). According to the records found at the site for these subjects, all of them had tumor samples assessed for the protocol-specified mutations at MD Anderson in order to satisfy the entry criteria of having a BRAF mutation. The protocol inclusion criteria do not specify a laboratory to conduct genotyping (mutation assessment) for the tumor tissue for each subject to satisfy the entry criteria. Therefore, having tumor genotyping done at MD Anderson was consistent with the protocol. While these are valid inspectional observations, which will be addressed and corrected by this site, they should not importantly impact data generated by this site.

Although regulatory violations were noted as described above, they are unlikely to importantly impact primary safety and efficacy analyses. The overall data for Study BRF1132 20, Part C, in support of these applications may be considered reliable based on available information.

Note: The observations noted above are based on the preliminary communications provided by the FDA field investigators and preliminary review of available Form FDA 483, inspectional observations. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

{See appended electronic signature page}

Lauren Iacono-Connors, Ph.D.
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CONCURRENCE:

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Janice Pohlman, M.D., M.P.H.
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAUREN C IACONO-CONNORS
11/08/2013

JANICE K POHLMAN
11/08/2013

KASSA AYALEW
11/08/2013

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202806Orig1s002

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 113557

MEETING MINUTES

GlaxoSmithKline, LLC
Attention: Eric Richards, M.S., M.P.H.
Director, Global Regulatory Affairs
1250 South Collegeville Road
UP4110
Collegeville, PA 19426

Dear Mr. Richards:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Trametinib (GSK1120212) and Dabrafenib (GSK2118436)."

We also refer to the teleconference between representatives of your firm and the FDA on December 6, 2012. The purpose of the meeting was to discuss and reach agreement on the format and content of a complete New Drug Application (NDA) submission [redacted] (b) (4)

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Norma Griffin, Regulatory Health Project Manager at (301) 796-4255.

Sincerely,

{See appended electronic signature page}

Norma Griffin
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B; teleconference
Meeting Category: Pre-NDA

Meeting Date and Time: December 6, 2012; 2:00-3:00 PM (ET)
Meeting Location: White Oak Building 22; Room 1421

Application Number: IND 113557
Product Name: Dabrafenib (GSK2118436) and Trametinib (GSK1120212)
Indication: Dabrafenib used in combination with trametinib is indicated for the treatment [redacted] (b) (4)

Trametinib used in combination with dabrafenib is indicated for the treatment [redacted] (b) (4)

Sponsor/Applicant Name: GlaxoSmithKline

List of FDA Participants

Joseph Gootenberg	Deputy Director, DOP2/OHOP
Suzanne Demko	Acting Clinical Team Leader, DOP2/OHOP
Marc Theoret	Clinical Reviewer, DOP2/OHOP
Meredith Libeg	Regulatory Health Project Manager, DOP2/OHOP
Norma Griffin	Regulatory Health Project Manager, DOP2/OHOP
Whitney Helms	Toxicology Team Leader, DHOT/OHOP
Debasis Ghosh	Acting Product Assessment Lead, ONDQA
Jian Wang	Clinical Pharmacology Reviewer, DCP5/OCP/OTS
Kun He	Statistical Team Leader, DBV5/OB
Weishi (Vivian) Yuan	Statistical Reviewer, DBV5/OB
Anthony Murgo	Associate Director for Regulatory Science, OHOP
Kimberly Taylor	Office of Planning and Informatics

CDRH

Donna Roscoe	Scientific Reviewer, DIHD/OIVD

Reference ID: 3237355

Reference ID: 3444185

List of GSK Participants

Rafael Amado, M.D.	Clinical Development
Kiran Patel, M.D., M.B.A.	Clinical Development
Jeff Legos, Ph.D., M.B.A.	Clinical Development
Vicki Goodman, M.D.	Clinical Development
Mary Guckert, M.S.N.	Clinical Development
Kevin Bellew, Ph.D.	Clinical Development
Laurie Sherman, B.S.	Clinical Development
Daniele Ouellet, Ph.D.	Clinical Pharmacology, Modeling, and Simulation
Ramachandran Suresh, Ph.D.	Biostatistics
Alka Joshi, Ph.D.	Biostatistics
Peng Sun, Ph.D.	Biostatistics
Steve Lane, M.S.	Biostatistics
Anne-Marie Martin, Ph.D.	Oncology Biomarkers
Jennifer Dudinack, Pharm.D.	Regulatory Affairs
Eric Richards, M.S., M.P.H.	Regulatory Affairs
Ellen Cutler	Regulatory Affairs
Kevin Wilk, M.S.	Nonclinical Regulatory Affairs
Kevin French, Ph.D.	Nonclinical Safety Assessment
Angela Hughes-Earl, D.V.M.	Nonclinical Safety Assessment
LeAnne Skordos, Pharm.D.	Project Management
Sandra Perreand	Biomerieux Inc.

BACKGROUND

The purpose of this teleconference (TCON) is a follow up to the pre-NDA meeting of September 12, 2012, to discuss the content and format of a complete NDA application (b) (4) including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. GSK also intends to reach agreement with FDA on the submission of a limited number of minor application components to be submitted no later than 30 days after the submission of the original application.

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Reference ID: 3444185

SPONSOR SUBMITTED QUESTIONS AND FDA RESPONSES

1. Does the Agency agree with the proposed content of the NDA as delineated in sections 2 through 8 of this briefing document?

FDA Response:

a. FDA agrees that the proposed contents as outlined in Section 5 (Clinical Pharmacology Content) Table 6 of the briefing document are acceptable.

Discussion During 12/6/2012 Meeting: GSK acknowledged and agreed with FDA's response. There was no further discussion during the meeting.

b. In addition to the content you propose to submit, as delineated in Section 2 (Administrative Content) Table 1 of your briefing document, your application must conform with all requirements as stated in 21 CFR 314 and 201, (e.g., 21 CFR 314.50 *Content and format of an application*, 21 CFR 314.55 *Pediatric Use Information, 21 CFR 201.57 Specific requirements on content and format of labeling for human prescription drug and biological products described in 201.56(b)(1)*). (b) (4) .

Regarding the information delineated in Section 2 (Administrative Content) Table 2, FDA agrees with your proposal to reference pending NDAs by providing Letters of Authorization (LOAs) to NDA 204114 Trametinib and NDA 202806 dabrafenib. If the two drug products will be co-packaged, provide container closure information. In addition, provide an Environmental Assessment (EA) document to support your NDA.

Discussion During 12/6/2012 Meeting: GSK acknowledged FDA's response, and requested clarification regarding whether GSK should submit the Environmental Assessment (EA) documents from each monotherapy NDA or a new "combined" EA? FDA stated that this item will be researched and a clarification will be issued at a later date.

Post-Meeting Clarification (12/19/2012): FDA clarified that GSK should submit a combined EA document for the new NDA.

c. In addition to the content you propose to submit, as delineated in Section 3 [Office of Scientific Investigations (OSI) Content] Table 3 of your briefing document, you must include information as described in OSI's Pre-NDA Comments and Information Request – see the attached OSI Addendum.

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Discussion During 12/6/2012 Meeting: GSK acknowledged and agreed with FDA's response. There was no further discussion during the meeting.

d. In addition to the content you propose to submit, as delineated in Section 4 (Labeling Content) Table 4 of your briefing document, your labeling must also conform with 21 CFR 201 (e.g., 201.56(b) and 201.57). In addition, please also refer to FDA Guidance for Industry *Providing Regulatory Submissions in Electronic Format — Content of Labeling* and *DRAFT Guidance for Industry Labeling for Human Prescription Drug and Biological Products — Implementing the New Content and Format Requirements*.

Discussion During 12/6/2012 Meeting: GSK acknowledged and agreed with FDA's response. There was no further discussion during the meeting.

e. FDA does not agree that the proposed contents as outlined in Section 6 (Clinical and Statistical Content), Section 9 (Description of ISS and ISE Content), and Section 10 (Safety Data for Dabrafenib HPMC Capsule in Combination with Trametinib) are complete. FDA has the following comments concerning the proposed clinical and statistical content:

- FDA again strongly recommends that the format for data submission be in CDISC to avoid data quality issues which are hindering efficient review of the trametinib (NDA 204114) and dabrafenib (NDA 202806) applications.

  Discussion During 12/6/2012 Meeting: FDA continues to have significant issues related to the quality of the data for the trametinib (NDA 204114) and dabrafenib (NDA 202806) monotherapy applications. FDA strongly reiterates that the data submission for the combination therapy application be formatted in CDISC.

- Although the proposed ISE and ISS general construct described in Section 9 appears consistent with FDA advice communicated to GSK during the Type B pre-NDA meeting held on September 12, 2012, FDA requests that GSK present ISS pooled data from only those parts of trial BRF113220 that used the same formulation of dabrafenib. Table 12 which proposes to present adverse event incidences based on a pooled analysis of Part B, Part C, and Part D of Trial BRF113220 should not include safety data from Part D of the trial because this is the only Part of the trial which exclusively administered the HPMC capsule formulation.

  Discussion During 12/6/2012 Meeting: GSK agreed to provide analyses of adverse events based on both pooled analyses and individual analyses of parts A through D of the trial. In addition, the datasets will include pooled datatsets, including flags identifying patients from the individual parts of the trial, and individual datatsets for parts A through D.

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- In addition to the proposed GSK-modified standardized medical queries (SMQs), please provide verbatim terms and terms for all levels of the MedDRA hierarchy in the datasets. In addition, provide analyses for narrow- and broad-based MedDRA SMQs.

  Discussion During 12/6/2012 Meeting: FDA clarified that the analyses of the safety profile for the combination drug product should include both GSK's proposed modified standardized medical queries, and additional narrow- and broad-based MedDRA SMQs.

- Please confirm that Module 2.5, Clinical Overview, will conform with the ICH harmonized tripartite guidelines, the common technical document for the registration of pharmaceuticals for human use, efficacy – M4E(R1), clinical overview and clinical summary of module 2, module 5 : clinical study reports which can be accessed at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4__R1__Efficacy/M4E__R1_.pdf

  Discussion During 12/6/2012 Meeting: There was no discussion.

- Please provide a detailed description of the safety data that will be contained in the blinded tables/listings of the MEK115306 study and submitted with the initial NDA as well as with the 90 day or 120 day safety update in order for FDA to determine to determine if the proposed safety data package, as delineated in Section 10, will be sufficient to evaluate the clinical impact on tolerability of the dabrafenib HPMC capsule in combination with trametinib.

  Discussion During 12/6/2012 Meeting: GSK will provide additional response to this.

- In addition to the blinded tables/listings and independent data monitoring committee (IDMC) recommendations form, please confirm that the IDMC (or the contract research organization working with the IDMC) will submit all meeting minutes from the IDMC for the November 2012 and February 2013 IDMC review of the data.

  Discussion During 12/6/2012 Meeting: GSK will provide additional response to this.

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Information Received from GSK via 12/6/2012 Email (post-TCON) and was formally submitted to the IND on 12/12/2012 (Sequence 0055): The following was provided by GSK in response to 1.e (5th and 6th bullet) above:

The follow can be provided to FDA via the CRO:

Unless otherwise stated, summaries of demography and efficacy data will be performed on the intent-to-treat (IIT) population and summaries of safety data will be based on the safety population, as defined in the protocol.

The IDMC will review the following data from all three studies separately (i.e. no integrated analysis combining all three studies will be performed).

1. Summary of demographic information (including ECOG performance status at baseline).
2. Summary of baseline disease characteristics.
3. Summary of the disposition of subjects.
4. Overall incidence of adverse events (AEs) by maximum grade.
5. Summary and listing of non-fatal and fatal serious adverse events.
6. Summary of AEs leading to study treatment discontinuation.
7. Summary of the following laboratory data shifts from baseline using the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 (NCI CTCAE v4.0)
   - Alanine transaminase (ALT)
   - Aspartate aminotransferase (AST)
   - Total Bilirubin
   - Complete blood count and platelets
   - Serum creatinine
8. Summary of ECHO data, QT prolongation and hypertension.
9. Summary of other AEs of special interest including: non-melanoma skin lesions (squamous cell carcinoma, and actinic keratoses / keratoacanthomas), cardiac related events, visual disorder, pyrexia, skin related toxicities and hepatic events.
10. Safety reports or narratives on subjects with concomitant elevations in ALT>3X upper limit of normal (ULN) and total bilirubin 2X ULN.; subjects with all grades of decreased LVEF events; subjects with RVO and CSR; and subjects with Pyrexia as SAE.
11. Summary of dose modifications.
12. Summary of study treatment status.

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13. Summary and list of deaths.

Additional safety information will be provided by the Sponsor to the IDMC as needed to assist safety evaluations, such as the updated Clinical Investigator Brochures and safety alerts that are applicable for dabrafenib, trametinib monotherapies and the dabrafenib plus trametinib combination.

Data are obtained from the electronic case report form (eCRF) database and cleaned per the data query process. The summaries and data listings will be provided to the IDMC by the SDAC via an External alliance Portal (EAP) within an agreed time frame, but not more than 10 days before, before the scheduled IDMC meeting. Only the SDAC and the IDMC member will have access to the EAP.
Data will be presented by the SDAC to the IDMC with treatment assignment identified.

Lastly, GSK can arrange for the IDMC chair to send the IDMC meeting minutes directly to the FDA, since per the IDMC charter the meeting minutes are to be retained by the IDMC charter until the study is unblinded.

f. FDA does not agree that the proposed contents as outlined in Section 7 (Nonclinical Content) Table 10 are complete and will allow substantive review since data with the combination alone are not adequate to support the proposed NDA. In addition, provide the site (or hyperlink to the site) for all relevant data for each drug which is intended to support the proposed application, including cross-reference to the applicable NDA (NDA 202806 and NDA 204114) where the data are located.

Discussion During 12/6/2012 Meeting: FDA clarified that they are requesting that the cross-reference documents (i.e., cross-reference to NDA 202806 and cross-reference to NDA 204114) be included in the [redacted] (b) (4) submission. GSK agreed to provide cross-reference documents.

g. FDA does not agree that the proposed contents as outlined in Section 8 (Companion Diagnostic Content) Table 11 are complete. GSK should incorporate a bridging study between the local testing lab and the bioMerieux approved test kit by having the local labs send forward the test negatives - preferably from the trial screening, otherwise, any banked melanoma BRAF V600 negatives the lab may have.

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Discussion During 12/6/2012 Meeting: FDA re-iterated their request for a bridging study between the local testing lab and the bioMerieux approved test kit by having the local labs send forward the test negatives - preferably from the trial screening, otherwise, any banked melanoma BRAF V600 negatives the lab may have. GSK indicated that they will continue discussions with CDRH regarding feasible approaches to the bridging analyses.

2. **Does the Agency agree that the description of the ISE/ISS construct (Section 9) is in accordance with the advice given by the Agency on September 12, 2012 and does the Agency have any additional advice to offer?**

   FDA Response: Please see FDA response to Question 1.

3. **Does the Agency agree that the proposed display of ISS data as described in Section 9 will aide in review and that pooling of safety data across NDA 204114, NDA 202806, [redacted] (b) (4) into a single database is not necessary?**

   FDA Response: Please see FDA response to Question 1.

4. **Does the Agency agree that the proposed safety data package, as delineated in Section 10, will be sufficient to evaluate the clinical impact on tolerability of the dabrafenib HPMC capsule in combination with trametinib?**

   FDA Response: Please see FDA response to Question 1.

5. **As noted in section 10.2.2, does the Agency agree with the proposed plan for GSK to send the data information (list below) from MEK115306?**

   1) **Blinded tables/listings**
   2) **Recommendations form IDMC**

   FDA Response: Please see FDA response to Question 1.

Reference ID: 3237355

Reference ID: 3444185

GSK BRIEFING DOCUMENT ADDENDUM (received via email 11/21/2012)

GSK have appreciated the opportunities to meet with the statistical review team at FDA with regard to the trametinib and dabrafenib monotherapy NDAs; NDA 204114 and NDA 202806 respectively. These face-to-face meetings have been vitally important for GSK in understanding the needs of the Agency review team, so that GSK can provide clearer documentation and explanation of the statistical package for these applications.

GSK intends to take the information we have learned from these interactions and apply them to the proposed [redacted] (b) (4). Nonetheless, it is possible that additional questions may arise that are specific to the statistical package for the [redacted] (b) (4). As such, GSK proposes the following interactions:

6. The GSK and FDA statistical teams meet face-to-face during the first week of January (i.e. prior to submission) to review the proposed Statistical package, including the proposal for inclusion of datasets, executable SAS code and navigation of the Define File.
Note: This can be done either by GSK bringing sample data/documents on laptops, or by filing samples to the IND (IND 113557) that may be navigated during the meeting.
The GSK and FDA statistical teams schedule a tentative face-to-face meeting around the beginning to middle of March to discuss any issues that may have arisen post-submission of the combination file.

FDA Response: No. A complete and reviewable submission does not require any additional meetings between GSK and FDA. GSK should ensure that the submission follows the relevant and recommended data guidelines and that it does not need any additional data cleaning in order for FDA to review. [redacted] (b) (4) If GSK is not confident that their current data system can meet the requirements, then the submission should be filed in CDISC format.

7. GSK proposes that a single statistical point of contact at GSK be provided to the Agency, so that if during the review, relatively straight-forward questions regarding the statistical package (e.g. navigation-type questions) can be resolved over email directly from the FDA statistical reviewer to the GSK statistics contact. **Does the Agency agree with this approach? If so, does the Agency have a preference regarding the provision of sample data/documents for the proposed January meeting; i.e. on laptop of via the IND?**

FDA Response: Please see FDA response for Question 6.

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DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

  Discussion During 12/6/2012 Meeting *(Summary and Agreements)*: See discussion in 1.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

  Discussion During 12/6/2012 Meeting *(Summary and Agreements)*: FDA stated to GSK that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and GSK stated that they do not believe there is need for a REMS.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission.

  FDA and GSK agreed that the following minor application component and this component only may be submitted within 30 calendar days after the submission of the original application:

  - GSK indicated that they will continue discussions with CDRH regarding feasible approaches to the bridging analyses. GSK will send a questionnaire to the local laboratories that tested patient samples to gather information about the testing methods used at those sites to supplement the bridging analyses. FDA agreed to accept this information as a late submission, i.e., within 30 calendar days after submission of the original application.

  Prominently identify each submission containing your late component with the following wording in bold capital letters at the top of the first page of the submission:

  NDA/BLA NUMBER: LATE COMPONENT – COMPANION DIAGNOSTIC

PREA PEDIATRIC STUDY PLAN

The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. You should review this law and assess if your application will be affected by these changes. If you have any questions, please email the Pediatric Team at Pedsdrugs@fda.hhs.gov.

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Reference ID: 3444185

PRESCRIBING INFORMATION

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.
Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

MANUFACTURING FACILITIES

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

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Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

ADDENDUM

- OSI Pre-NDA Comments and Information Request

Reference ID: 3237355

Reference ID: 3444185

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 3 clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)

2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 3 clinical trials:
   a. Number of subjects screened for each site by site
   b. Number of subjects randomized for each site by site
   c. Number of subjects treated who prematurely discontinued for each site by site

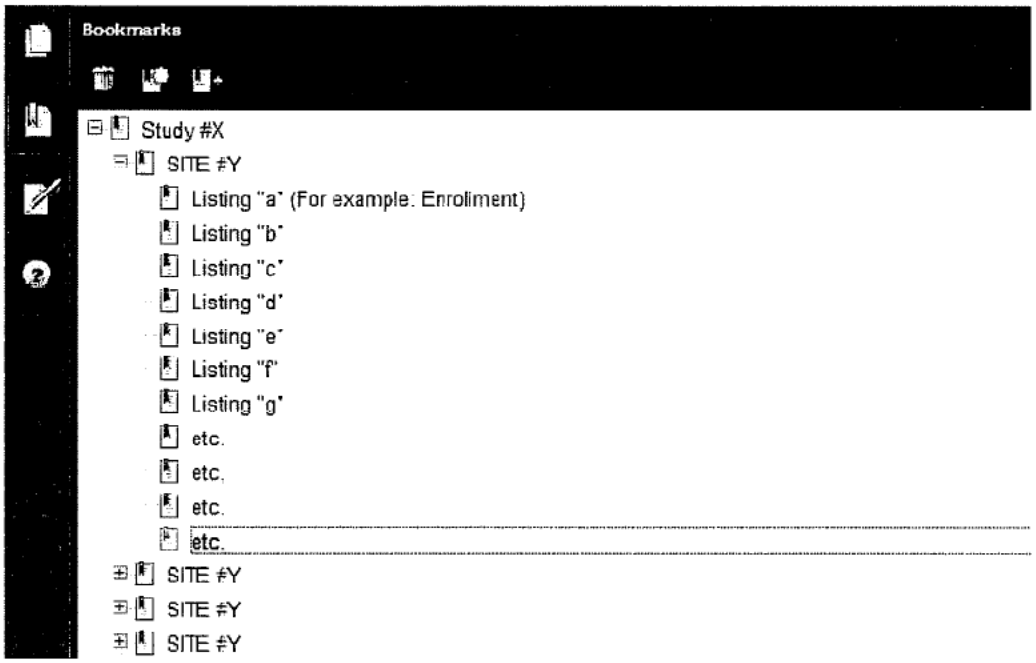
3. Please include the following information in a tabular format in the NDA for each of the completed Phase 3 clinical trials:
   a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
   b. Name, address and contact information of all CROs used in the conduct of the clinical trials
   c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
   d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)

4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).
5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data ("line") listings. For each site provide line listings for:
   a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
   b. Subject listing for treatment assignment (randomization)
   c. Subject listing of drop-outs and subjects that discontinued with date and reason
   d. Evaluable subjects/ non-evaluable subjects and reason not evaluable
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of laboratory tests performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset: [Omitted by CDER]

Attachment 1 [Omitted by CDER]

Attachment 2

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items

I, and II below should be linked into this BIMO STF, using file tags indicated below.

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf

B. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

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

/s/

NORMA S GRIFFIN
12/28/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 113557

MEETING MINUTES

GlaxoSmithKline, LLC
Attention: Eric Richards, M.S., M.P.H.
Director, Global Regulatory Affairs
1250 South Collegeville Road; UP4110
Collegeville, Pennsylvania 19426

Dear Mr. Richards:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "Trametinib (GSK1120212) and Dabrafenib (GSK2118436)."

We also refer to the teleconference between representatives of your firm and the FDA on September 12, 2012. The purpose of the Type B pre-NDA meeting was to discuss and share the headline, mature data from study BRF113220, involving the combination of trametinib and dabrafenib, and to gain agreement [redacted] (b) (4) for the use of these two agents used in combination.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4255.

Sincerely,

{See appended electronic signature page}

Norma Griffin
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B Teleconference Meeting
Meeting Category:	Pre-NDA
Meeting Date and Time:	Wednesday, September 12, 2012; 11:00 to 12:00 PM (ET)
Meeting Location:	White Oak Building 22/Room 2327
Application Number:	113557
Product Name:	Trametinib (GSK1120212) and Dabrafenib (GSK2118436)
Indication:	[redacted] (b) (4)
Sponsor/Applicant Name:	GlaxoSmithKline, LLC
Meeting Chair:	Suzanne Demko
Meeting Recorder:	Meredith Libeg

FDA ATTENDEES

Richard Pazdur, M.D.	Office Director, OHOP
Patricia Keegan, M.D.	Director, DOP2/OHOP
Joseph Gootenberg, M.D.	Duty Director, DOP2/OHOP
Suzanne Demko, P.A.-C.	Acting Clinical Team Leader, DOP2/OHOP
Marc Theoret, M.D.	Clinical Reviewer, DOP2/OHOP
Meredith Libeg	Regulatory Health Project Manager, DOP2/OHOP
Alexander Putman, Ph.D.	Toxicology Reviewer, DHOT/OHOP
Kareen Riviere	Biopharmaceutics Reviewer, ONDQA
Weishi (Vivian) Yuan	Statistical Reviewer, DBV5/OB
Lauren Iacono-Connor	DGCPC, OSI
James Schlick	OSE/OMEPRM/DMEPA
John Jenkins, M.D.	Director, OND
Meghna Alimchandani	NIH visiting fellow

CDRH

Donna Roscoe	Scientific Reviewer, DIHD/OIVD
Maria Chan	Division Director, DIHD

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Reference ID: 3444185

SPONSOR ATTENDEES

Rafael Amado, M.D.	Clinical Development
Paolo Paoletti	Clinical Development
Kiran Patel, M.D., M.B.A.	Clinical Development
Vicki Goodman, M.D.	Clinical Development
Michael Streit, M.D.	Clinical Development
Jeff Legos, Ph.D., M.P.H.	Clinical Development
Daniele Ouellet, Ph.D.	Clinical Development
Ramachandran Suresh, Ph.D.	Biostatistics
Ohad Amit, Ph.D.	Biostatistics
Peng Sun, Ph.D.	Biostatistics
Anne-Marie Martin, Ph.D.	Oncology Biomarkers
Jennifer Dudinak, Pharm.D.	Regulatory Affairs
Eric Richards, M.S., M.P.H.	Regulatory Affairs
Ellen Cutler	Regulatory Affairs

1.0 MEETING OBJECTIVES

To discuss and share the high-level, mature data from study BRF113220, and to gain agreement [redacted] (b) (4) for the use of trametinib (GSK1120212) and dabrafenib (GSK2118436) in combination for the proposed indications:

- Dabrafenib used in combination with trametinib is indicated for the treatment [redacted] (b) (4)
- Trametinib used in combination with dabrafenib is indicated for the treatment [redacted] (b) (4)

2.0 BACKGROUND

Dabrafenib (GSK2118436) is a selective inhibitor of BRAF kinase activity and trametinib (GSK1120212) is a selective inhibitor of MEK1/MEK2 activation and kinase activity. GSK is developing dabrafenib monotherapy (IND 105032), trametinib monotherapy IND 102175), and combination dabrafenib plus trametinib therapy (IND 113557) for the treatment [redacted] (b) (4) GSK filed New Drug Applications (NDA) for dabrafenib monotherapy in July 2012 and for trametinib monotherapy in August 2012. Premarket approval (PMA) applications for a companion in-vitro diagnostic test, bioMerieux THxID BRAF test, to select subjects with BRAF V600E/K mutations were submitted in coordination with the drug marketing applications.

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On January 27, 2012, FDA held a Type B, Pre-IND meeting with GSK to discuss the development program for the combination of trametinib plus dabrafenib in patients with [redacted] (b) (4) for the combination of trametinib plus dabrafenib based on mature results of Part C of trial BRF113220. The trial is a randomized (1:1:1) three-arm trial of approximately 150 patients with BRAF and MEK inhibitor naïve, BRAFV600 mutation-positive unresectable melanoma designed to detect an absolute 17% decrease in squamous cell carcinoma (SCC) in patients who receive the combination dose of GSK1120212 and GSK2118436 (pC=3%) compared to patients who receive 150 mg BID GSK2118436 administrated alone (pM=20%). GSK presented the following results of the first interim efficacy analysis which included response rate and PFS data at the January 27, 2012, pre-IND meeting:

	Dose level dabrafenib BID/ trametinib QD		
	150 / 0 Mono (N=47)	150/ 1 Combination (n=50)	150/ 2 Combination (n=49)
Best RR			
CR	0	1 (2%)	3 (6%)
PR	23 (49%)	21 (42%)	34 (69%)
SD	20 (43%)	24 (48%)	12 (24%)
PD	4 (9%)	2 (4%)	0
NE	0	2 (4%)	0
Response Rate (95% CI)	23 (49%) (34.1%, 63.9%)	22 (44%) (30.0%, 58.7%)	37 (76%) (61.1%, 86.7%)
PFS			
Events	25	18	12
Median, months (95% CI)	5.6 (3.9, 5.8)	7.2 (5.6, 7.3)	NR
HR (versus dabrafenib alone) (95% CI)		0.70 (0.39,1.28)	0.33 (0.17,0.63)

Key agreements and comments at the January 27, 2012, pre-IND meeting included the following:

- FDA and GSK agreed that interpretation of mature results from Part C of trial BRF113220 would pose multiple difficulties due to the open-label design of the trial and the lack of pre-specified statistical criteria around the efficacy endpoints. FDA stated that GSK must identify and adequately address potential sources of bias in the design, conduct, analysis and interpretation of the results of BRF113220 at the time of [redacted] (b) (4) submission to provide evidence of a treatment effect as well as an estimate of the size of a treatment effect.
- GSK stated that it removed the second interim efficacy analysis.

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- FDA advised that, in addition to providing safety and efficacy data with the two formulations, GSK provide information on drug interactions between dabrafenib (GSK2118436) and trametinib (GSK1120212) for the intended commercial formulation for dabrafenib. Of note, GSK reported that patients in Part C of BRF113220 were transitioned during the trial from the gelatin capsule to the HPMC formulation, the to-be-marketed form of dabrafenib. Upon identification of the 1.8 fold increase in dabrafenib exposure (AUC) with the dabrafenib HPMC capsule formulation compared to the dabrafenib gelatin capsule, patients in Part C were transitioned back to the gelatin capsule to maintain the integrity of the study.
- GSK stated that BRAFV600 mutation status was determined by local testing, not the Response Genetics or the bioMerieux IUO assay. GSK planned to obtain all available patient samples to perform a retrospective bridging study using the bioMerieux THxID BRAF IUO Assay.
- FDA stated that an application based on the combination trial should contain information indicating that combination therapy is better than sequential therapy.
- FDA stated that there were deficiencies in the trial design and conduct that undermine confidence in the results and requested a firm understanding that if confirmatory trials are negative, GSK should withdraw the indication.

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Development Program

The development program for the combination of dabrafenib and trametinib for the treatment of BRAF mutation-positive unresectable or metastatic melanoma includes an ongoing Phase 1/2 study (BRF113220) and two ongoing randomized Phase 3 studies (MEK115306 and MEK116513) as follows:

Study/Status	Design	N	Patient Population	Primary Endpoint(s)
BRF113220 (Ongoing)	Part A: Drug-Drug Interaction	8	Subjects with BRAF V600E/K/D mutation-positive melanoma or other tumor type	PK
	Part B: Dose Escalation	135	Subjects with BRAF V600E/K/D mutation-positive melanoma or other tumor type	Safety
	Part C: Randomized Phase 2	162	Subjects with BRAF V600E/K/D mutation-positive melanoma	ORR, DOR PFS, Safety
	Part D: Randomized Dabrafenib HPMC	110	Subjects with BRAF V600E/K mutation-positive melanoma	PK, Safety
MEK115306 (Ongoing)	Phase 3, two-arm, randomized, double-blinded	340	Subjects with unresectable (Stage IIIC) metastatic (Stage IV) BRAF V600E/K mutation-positive melanoma	PFS
MEK116513 (Ongoing)	Phase 3, two-arm, open-label, randomized	694	Subjects with unresectable (Stage IIIC) metastatic (Stage IV) BRAF V600E/K mutation-positive melanoma	OS

Fast Track designation was granted to the trametinib / dabrafenib combination on June 29, 2012, for the treatment of patients with BRAF V600E or BRAF V600K mutation-positive, unresectable or metastatic melanoma to demonstrate improved overall response rate, progression-free survival, and overall survival. In addition, GSK submitted an Orphan Drug application for use of the combination to the Orphan Drug Office, which was received on July 23, 2012.

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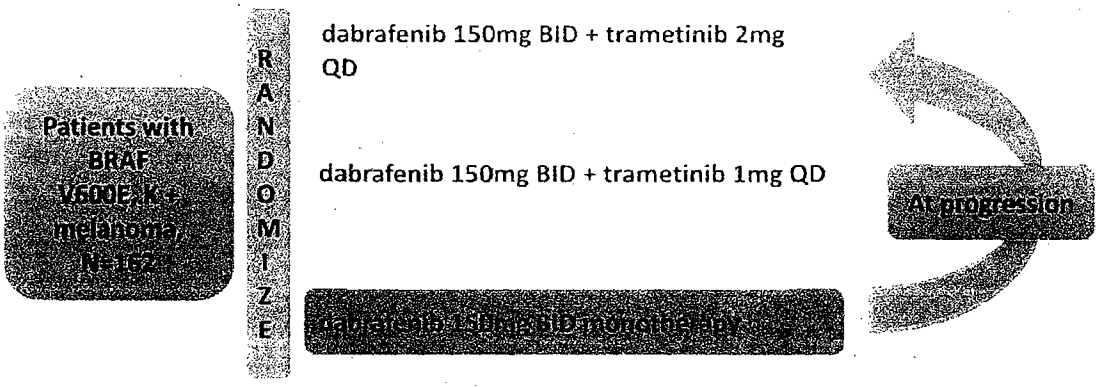
BRF113220

BRF113220, titled "An Open-Label, Dose-Escalation. Phase I/II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of the BRAF Inhibitor GSK2118436 in Combination with the MEK Inhibitor GSK1120212 in Subjects with BRAF Mutant Metastatic Melanoma," is an open-label, multicenter trial to investigate the safety, pharmacokinetics, pharmacodynamics, and clinical activity of dabrafenib and trametinib in combination which consists of four parts:

- Part A: to evaluate the effect of repeat doses of trametinib on the pharmacokinetics of single dose dabrafenib
- Part B: to determine the safety, tolerability, and range of tolerated dose combinations using a dose-escalation procedure
- Part C: to evaluate the safety and efficacy of dabrafenib at 150 mg twice daily in combination with two different doses of trametinib (1 mg once daily and 2 mg once daily)
- Part D: to evaluate the pharmacokinetics and safety of dabrafenib administered as HPMC capsules alone and in combination with trametinib

Part C as amended is an open-label, randomized, three-arm trial of dabrafenib (gelatin) administered at 150 mg BID alone or in combination with two different doses of trametinib (1 mg QD and 2 mg QD) as shown in the figure below.



•Open-label; Investigator assessed; cross-over post-progression in dabrafenib mono arm to 150/2
• Gelatin based encapsulation of dabrafenib
Key Inclusion Criteria
• BRAF mutation V600E or K
• ECOG 0 or 1
• Up to 1 chemo and/or IL-2 for advanced/metastatic melanoma
• No prior exposure to BRAF or MEK inhibitors
• Stable brain met (if present)

Source: Pre-NDA briefing document, page 14

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Key inclusion criteria include (1) BRAF-mutation positive melanoma (i.e., V600E, V600K, or V600D), (2) measurable disease by RECIST, and (3) ECOG performance status of 0 or 1. Key exclusion criteria include (1) prior exposure to BRAF or MEK inhibitors, (2) more than one prior chemotherapy regimen and/or IL-2, (3) active brain metastases, and (4) history of retinal vein occlusion or central serous retinopathy.

The protocol specifies the following primary objectives of PART C of the trial:

- to determine the clinical activity of dabrafenib and trametinib by assessing the response rate (RR), duration of response (DOR), and progression-free survival (PFS)
- to determine the safety, tolerability, and range of tolerated doses of dabrafenib and trametinib dosed in combination.

Secondary objectives are to characterize the population PK parameters and to assess clinical activity as determined by overall survival.

GSK presents high-level results from Part C based on a data cut-off date of May 31, 2012. Part C of the trial randomized (1:1:1) 162 patients, 54 onto each arm. The dabrafenib plus trametinib 2 mg combination arm compared to the dabrafenib monotherapy arm enrolled more men (34 vs. 29) and patients with V600E mutations (47 vs. 45) but fewer patients with a history of brain metastases (2 vs. 4) or an elevated LDH (22 vs. 27). The demographics and patient characteristics are shown in the following table:

Characteristics	**150 mg Mono (N=54)**	**150mg/1mg Combination (n=54)**	**150mg/2mg Combination (n=54)**
Mean age, yrs	51.8	49.9	55.9
Gender, Male	29 (54%)	30 (56%)	34 (63%)
ECOG 0	34 (63%)	38 (70%)	35 (65%)
Prior h/o brain mets	4 (7%)	7 (13%)	2 (4%)
BRAF Mutation V600E V600K	 45 (83%) 9 (17%)	 45 (83%) 9 (17%)	 47 (87%) 7 (13%)
Stage IV M1c	37 (69%)	33 (61%)	38 (70%)
LDH - >ULN	27 (50%)	25 (46%)	22 (41%)

Source: Pre-NDA briefing document, page 16

The median duration of follow-up was 14 months and all subjects had at least 10 months of follow-up. Eighty percent (n=43) of subjects randomized to dabrafenib monotherapy crossed over to the dabrafenib plus trametinib 2 mg QD arm upon disease progression. GSK reports that the primary analysis of investigator-assessed PFS demonstrated a median PFS of 9.4 months on the dabrafenib 150 mg plus trametinib 2 mg combination arm compared to a median PFS of 5.8 months on the dabrafenib monotherapy arm, a 61% reduction in the risk of progression or death in the dabrafenib 150 mg plus trametinib 2 mg combination arm compared to the

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dabrafenib monotherapy arm [HR 0.39 (95% CI: 0.25, 0.62), p<0.0001]. GSK states that the PFS results on the dabrafenib plus trametinib 1 mg QD arm compared to the dabrafenib monotherapy arm suggest a dose response with a median PFS of 9.2 months for the dabrafenib plus trametinib 1 mg QD arm and a 46% reduction in the risk of progression or death [HR 0.56 (95% CI: 0.37, 0.87), p=0.0057]. The following table shows the PFS results as assessed by the investigator and by Blinded Independent Review Committee (BICR):

	150 mg Mono (N=54)	**150mg/1mg Combination (n=54)**	**150mg/2mg Combination (n=54)**
Investigator Assessed			
Subject Classification, n (%)			
Progressed or died (event)	47 (87%)	39 (72%)	31 (57%)
Censored, follow-up ended	1 (2%)	2 (4%)	3 (6%)
Censored, follow-up ongoing	6 (11%)	13 (24%)	20 (37%)
Adjusted hazard ratio [a]			
Estimate		0.56	0.39
(95% CI)		(0.37, 0.87)	(0.25,0.62)
Stratified log-rank p-value [a]		0.0057	<0.0001
Kaplan Meier Estimate for PFS, (months) [b]			
1st quartile (95% CI)	3.8 (3.6,5.5)	5.5 (3.7,6.5)	5.8 (5.3,8.7)
Median (95% CI)	5.8 (4.6,7.4)	9.2 (6.4,11.0)	9.4 (8.6,16.7)
3rd quartile (95% CI)	9.1 (7.4,9.4)	12.9 (11.0,NR.)	16.7 (12.4,16.7)
Blinded Independent Review Committee (BICR)			
Subject Classification, n (%)			
Progressed or died (event)	32 (59%)	36 (67%)	29 (54%)
Censored, follow-up ended	17 (31%)	6 (11%)	5 (9%)
Censored, follow-up ongoing	5 (9%)	12 (22%)	20 (37%)
Adjusted hazard ratio [a]			
Estimate		0.73	0.55
(95% CI)		(0.45,1.19)	(0.33,0.93)
Stratified log-rank p-value [a]		0.1721	0.0154
Kaplan Meier Estimate for PFS (months) [b]			
1st quartile (95% CI)	3.7 (3.2,5.6)	3.8 (3.6,5.6)	6.3 (4.6, 7.6)
Median (95% CI)	7.3 (5.5,9.4)	8.3 (5.6,11.3)	9.2 (7.4, NR)
3rd quartile (95% CI)	9.7 (7.5,NR)	14.8 (11.1,NR)	NR (12.4, NR)

Source: Pre-NDA Briefing Document, pages 16 and 19
Abbreviations: CI = confidence interval; PFS = progression free survival; NR, not reported
[a]. Hazard ratios are estimated using the Pike estimator. A hazard ratio <1 indicates a lower risk with this treatment compared with the monotherapy arm.
[b]. Quartiles estimated using the Brookmeyer-Crowley method.

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The pre-NDA briefing document (Section 3.2.2.3) includes a summary of the results of several sensitivity analyses to evaluate potential sources of bias and to evaluate the robustness of the treatment effect as per the investigator-assessment. As shown in the table above, GSK performed a sensitivity analysis of PFS based upon a BICR. GSK states that the smaller reduction in the risk of progression or death observed in the BICR analyses [HR 0.55 (95% CI: 0.33, 0.93)] compared to that in the investigator analyses [HR 0.39 (95% CI: 0.25, 0.62)] was due in part to an imbalance in informative censoring between the dabrafenib monotherapy arm and the dabrafenib 150 mg plus trametinib 2 mg combination arm. In the BICR analysis, 17 subjects in dabrafenib mono-therapy arm were censored at the time of investigator assessed PD compared to 2 subjects in the dabrafenib 150 mg plus trametinib 2 mg combination arm. According to GSK, one factor contributing to the difference in censoring by BIRC is the difference in the number of subjects who had disease assessments available for IRC review at time points after investigator-assessed progression: 9 Subjects in the dabrafenib 150mg plus trametinib 2mg arm compared to 2 subjects on the dabrafenib monotherapy arm had scans available to the IRC at time points beyond investigator assessed PD. Per protocol, subjects were allowed to continue on randomized treatment beyond investigator assessed PD; the scans obtained at subsequent time points were then available for BICR review. GSK states that the additional follow-up beyond investigator assessed PD available to the BIRC in dabrafenib 150mg plus trametinib 2mg combination arm relative to the mono-therapy arm led to an imbalance in amount of informative censoring between the two arms.

Additional efficacy endpoints include response rate (RR) and overall survival (OS).
The confirmed RR as assessed by the investigator and by BICR, respectively, for the 3 treatment arms were 76% and 61% for dabrafenib plus trametinib 2 mg, 50% and 39% for dabrafenib plus trametinib 1 mg, and 54% and 46% for dabrafenib monotherapy. The best confirmed responses by treatment arm as assessed by the investigator and by BICR are shown in the following table:

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Best Confirmed Response	150 mg Mono (N=54) n (%)		150mg/1mg Combination (n=54) n (%)		150mg/2mg Combination (n=54) n (%)	
	Invest	BICR	Invest	BICR	Invest	BICR
CR	2 (4)	4 (7)	3 (6)	4 (7)	5 (9)	7 (13)
PR	27 (50)	21 (39)	24 (44)	17 (31)	36 (67)	26 (48)
SD	22 (41)	20 (37)	24 (44)	26 (48)	13 (24)	13 (24)
Non-CR/ Non-PR	NR	3 (6)	NR	3 (6)	NR	4 (7)
PD	3 (6)	6 (11)	2 (4)	2 (4)	0	3 (6)
NE	0	0	1 (2)	2 (4)	0	1 (2)
Overall Response Rate (95% CI)	29 (54%) (39.6, 67.4)	25 (46%) (32.6, 60.4)	27 (50%) (36.1, 63.9)	21 (39%) (25.9, 53.1)	41 (76%) (62.4, 86.5)	33 (61%) (46.9, 74.1)
p-value[a]			0.7730	0.5008	0.0264	0.1486
Duration of Response in Months (95% CI)	5.6 (4.5, 7.4)		9.5 (7.4, NA)		10.5 (7.4, 14.9)	

Source: Pre-NDA briefing document, pages 25-26
NR, not reported
[a] [compared to dabrafenib monotherapy], statistical test not specified in the briefing document

The overall survival results of Part C of BRF113220 are immature. GSK reports an OS hazard ratio of 0.67 (95% CI 0.34, 1.34, p=0.25) for dabrafenib plus trametinib 2 mg compared to dabrafenib mono-therapy. Of note, GSK reports that 43 of 54 subjects (80%) crossed over from the dabrafenib mono-therapy arm to the full dose combination (150mg/2mg) arm.

MEK115306

MEK115306 is a Phase 3, randomized (1:1), double-blind trial comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to dabrafenib and placebo in patients with unresectable (Stage IIIc) or metastatic (Stage IV) BRAF V600E/K mutation-positive melanoma in 340 patients. MEK115306 is under a Special Protocol Assessment agreement per the May 17, 2012 agreement letter. The primary objective of this two-arm study is to establish the superiority of dabrafenib and trametinib combination therapy over dabrafenib and trametinib-placebo (BRAFi mono-therapy) with respect to progression-free survival (PFS) for subjects with unresectable/metastatic BRAF V600E/K mutation-positive melanoma

MEK116513

MEK116513, is a two-arm, open-label, randomized (1:1), Phase 3 study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to the BRAF inhibitor vemurafenib in subjects with unresectable (Stage IIIc) or metastatic (Stage IV) BRAF V600E/K mutation-positive melanoma. The primary objective of this two-arm study is to establish the superiority of dabrafenib and trametinib combination therapy over vemurafenib with respect to overall survival (OS) for subjects with advanced/metastatic BRAF V600E/K mutation-positive cutaneous melanoma.

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Companion Diagnostic Development

Subjects for BRF113220 were screened using local testing. To address this, GSK is testing all available subject samples (collected in Part C of the study) retrospectively with the bioMérieux IUO assay. GSK now possesses 91% of the samples from this part of the study and is working with their diagnostic partner bioMerieux (bMx) to perform a retrospective bridging study to establish the BRAF mutation status of the samples using the bMx THxID BRAF IUO Assay under the current IDE (G120011). Agreement between the original BRAF mutation result and the result obtained using the bMx THxID BRAF IUO will be established, and statistical analyses will be performed to establish the relationship of the bMx THxID BRAF mutation result and clinical endpoints (ORR and PFS). All statistical analyses have been outlined in a Statistical Analysis Plan. A PMA supporting the dabrafenib and trametinib mono-therapy NDA submissions was filed to OIVD/CDRH on July 27 2012. [redacted] (b) (4)

3.0 SPONSOR SUBMITTED QUESTIONS AND FDA RESPONSE:

Clinical

1. **Does the Agency agree that the data from BRF113220 provides compelling evidence that the combination of trametinib and dabrafenib addresses an unmet medical need, and therefore** [redacted] (b) (4)

   FDA Response: [redacted] (b) (4)

   [redacted] (b) (4) (b) (4)

   If GSK would like FDA to make a preliminary assessment of the adequacy of the proposed contents of the application to permit filing as a complete application, GSK should provide, as soon as possible, a detailed description of the proposed data package for evaluation of risks from treatment in the proposed NDA as an amendment to the IND.

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This description should include (but not be limited to) the following:

- Total safety population (N)
- Number that received dabrafenib (gelatin capsule formulation) 150 mg BID plus trametinib 2 mg QD and the duration of exposure, e.g., ≤ 6 months, >6 months to 12 months, and > 12 months
- Number of patients that received dabrafenib (HPMC formulation) 150 mg BID plus trametinib 2 mg QD and the duration of exposure
- Description of any other patient subgroups that will be included in the safety population

Discussion During Meeting on 9/12/2012: FDA clarified their response, noting that (b) (4) [redacted] FDA does believe an application should be submitted under a request for accelerated approval based on the following rationale:

- Compelling scientific rationale for the interactions between dabrafenib plus trametinib, [redacted] (b) (4)
- A nominal increase in overall response rate for the combination of dabrafenib plus trametinib over dabrafenib monotherapy
- [redacted] (b) (4)

FDA stated that the application should also include a discussion, based on clinical trial data, as to why dabrafenib/trametinib treatment administered sequentially is ineffective.

FDA further stated that the BRF113220 trial is likely to be evaluated as three single-arm trials rather than rely on comparison between arms to establish efficacy. GSK confirmed that efficacy will be verified in ongoing trials MEK115306 and MEK116513 and confirmed previous statements that the accelerated approval for the combination therapy will be withdrawn voluntarily if the confirmatory trials do not verify clinical benefit.

2. **GSK believes the data from BRF113220, as well as data from dabrafenib mono-therapy studies, supports the conclusion that the change in capsule likely has little clinical relevance and does not negatively impact the generalizability of the results from Part B and Part C of BRF113220. Therefore, GSK proposes that, pending full review of Part D of BRF113220 (which used the HPMC capsule), the data from Part C of BRF113220 that used the gelatin capsule can be utilized as pivotal data to support filing the combination of dabrafenib and trametinib. Does the Agency agree?**

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FDA Response: No. A formal bioequivalent study should be conducted to establish the bioequivalence between the to-be-marketed HPMC formulation and the gelatin formulation used in the registration trial (Part C of BRF113220). If the gelatin capsule and HPMC capsule are not bioequivalent, and HMPC capsule has higher exposure than gelatin capsules observed in the monotherapy studies, GSK will need to address the safety concern with regard to the HPMC capsule formulation.

Discussion During Meeting on 9/12/2012: FDA stated that the appropriate staff was not available; therefore, FDA will setup a separate teleconference to discuss this issue. FDA stated that the need and timing for submission of the requested bioequivalence study should be addressed during this teleconference. GSK stated that available data shows that the two dabrafenib formulations (gelatin and HPMC capsule) are not bioequivalent with higher exposure in patients receiving HPMC capsules. GSK will provide relevant data prior to the teleconference with FDA's clinical pharmacology staff.

FDA and GSK agreed this greater exposure would not alter conclusions regarding product efficacy, but raise concerns about the tolerability of the proposed recommended dose of dabrafenib when administered in combination with trametinib. GSK agreed to include available safety data from part D of study BRF113220, in which 25% of the 54 patients will have been exposed for up to 6 months, in the NDA at time of submission. GSK agreed to provide additional safety information in support of the proposed recommended dose for the HPMC capsule in the 120-day safety update consisting of:

- Updated safety data from the 54 patients enrolled in part D of study BRF113220 to include safety data for at least 6 months of exposure in all 54 patients.
- The interim, high level, blinded safety results from both treatment arms of the MEK115306 study, as generated by the independent safety monitoring committee during the next planned meeting.

3. Does the Agency agree with content and timing of the proposed Safety Update outlined in Section 7?

FDA Response: The briefing document contains an insufficient level of detail to allow FDA to provide agreement with the timing and content of the proposed Safety Update.

Discussion During Meeting on 9/12/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

Regulatory

4. Does the Agency agree with the NDA contents as outlined in Section 6?

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FDA Response: No, FDA does not agree with the proposal to exclude a Summary of Clinical Efficacy (Module 2.7.3), Summary of Clinical Safety (Module 2.7.4), and an Integrated Summary of Effectiveness from the NDA submission.

Please confirm that the proposed NDA will contain:

a. A summary of clinical efficacy, summary of clinical safety, and integrated summaries of safety and effectiveness (ISS/ISE), as required by 21 CFR 314.50. These documents should conform with the following guidance documents:

- FDA Guidance for Industry, Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document which can be accessed at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf
- FDA Guidance for Industry, Integrated Summary of Effectiveness which can be accessed at (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf)
- ICH harmonised tripartite guideline, The common technical document for the registration of pharmaceuticals for human use, Efficacy – M4E(R1), Clinical overview and clinical summary of module 2 module 5 : clinical study reports which can be accessed at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/CTD/M4__R1__Efficacy/M4E__R1_.pdf

b. Completed study reports in Module 5.3 as this is not clearly identified in Table 16

c. Detailed information, including a narrative (data listings are not an acceptable substitute for a narrative), for all patients who died while on study or who terminated study drug or participation in the study prematurely including those categorized as other, lost to follow up, physician decision, or subject decision.

d. Complete case report forms (CRFs) for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events.

The proposed contents will not include a Module 3; this is not acceptable. Please confirm that the proposed NDA will contain the necessary letters of authorization to the specific information necessary to support this section. Failure to include this information may result in a determination that the application is not complete for filing. There is insufficient information to determine the proposed contents of Module 4. Therefore FDA cannot determine whether this module will be complete at the time of filing.

FDA notes that BRAF testing and patient selection was conducted by local laboratories, and that a bridging study to the bioMerieux THxID BRAF test will be conducted. In general, a bridging study includes testing specimens from patients with both positive and negative results by the local test. This bridging data should be submitted under the

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NDA regardless of whether the data is also submitted to a PMA. Indicate whether GSK will have test negatives as well as test positives, and if not, how GSK will account for this missing data when claiming safety and efficacy in a target population selected by the bioMerieux BRAF test.

Discussion During Meeting on 9/12/2012:

a. GSK confirmed that the NDA will contain an ISS and ISE which provides a thoughtful discussion of the evidence establishing efficacy and safety. The ISS and ISE will also contain links to cross referenced material in other applications as appropriate.

b. GSK agreed to provide a detailed description of the contents of the NDA. This will include a listing of the complete study reports to be provided in module 5.3 and links to those study reports referenced in other NDA applications. Specifically, FDA noted that the clinical study report for MEK113583 should also be included in the proposed NDA; GSK agreed.

c. GSK agreed to provide complete data sets containing primary data, derived data, and all SAS programs used to generate derived data and analyses. GSK confirmed and agreed that all comments regarding expected application content provided for NDAs 202806 and 204114 will also be applied to the content of the proposed application.

GSK agreed to provide narratives for deaths on study in all treatment arms for all studies contributing information to the safety database.

d. GSK agreed to provide CRFs for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events either directly or though crossing reference to other applications.

GSK agreed to provide data in module 3 either directly or though crossing reference to other applications.

GSK confirmed that the clinical report and all bridging data supporting the BRAF test kit will be submitted to the NDA. GSK stated that the bridging studies contain no information on central evaluation of "test-negative" subjects identified through local screening. FDA stated that additional discussion is required on the adequacy of the bridging data. FDA and GSK agreed to hold a subsequent teleconference on this topic as soon as feasible and prior to the submission (b) (4)

<u>Additional Clinical / OSI Comments:</u>

5. Please refer to the DOP2 "End of Phase 2 General Advice for Planned Marketing Applications (Attachment 1)-whether or not GSK plans to submit data in CDISC format. If GSK does not plan to submit, or adhere to the recommended format of any component listed in the "NDA/BLA content and format" section of the document, please discuss this with the Division in advance of an NDA filing to ensure that the application will be complete at the time of submission.

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Discussion During Meeting on 9/12/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

6. Regarding study BRF113220 (Phase I/II; specifically, Part C), please provide a listing of all clinical sites, by country and then attribution of each site by Site Number, CI name and address/facility. Include in this table the total number of subjects enrolled at each site, and randomization by Arm. In addition, include the number of protocol violations (major and minor, including the definition) that occurred at each Site. Based upon this active site listing, DOP2 and OSI may request additional information be included in the application to support clinical site selection for conduct of clinical inspections, and support FDA field investigators' preparation for the clinical site inspections.

   Discussion During Meeting on 9/12/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

7. Please note that the pre-IND briefing document submitted to IND 113557 intended to support the January 27, 2012, pre-IND meeting reported the number of randomized patients in each arm of Part C of trial BRF113220—as summarized in the FDA Advice/Information Request Comment #1 sent to GSK on September 5, 2012—in the following part of Section 4.3.1.3 of the pre-IND briefing document:

   In Part C, a total of 162 subjects with BRAF mutation-positive (V600 E or K) metastatic melanoma who were BRAFi naïve were randomized to three arms.

   - Mono-therapy dose (n=53): dabrafenib 150 mg BID
   - Combination dose level 1 (n=54): dabrafenib 150 mg BID; trametinib 2 mg QD
   - Combination dose level 2 (n=55): dabrafenib 150 mg BID; trametinib 1 mg QD

   FDA acknowledges GSK's response provided on September 6, 2012, which confirmed that the number of subjects randomized to each arm (n=54) of Part C of the trial BRF113220 was correct as reported in the pre-NDA briefing document.

   Discussion During Meeting on 9/12/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

Additional Statistical Comments:

8. Please confirm that the proposed NDA will contain separate raw datasets and derived datasets with different dataset names for raw datasets and derived datasets.
   Provide clarification and description of the structure of all datasets submitted, i.e. provide a pdf document that summarizes the contents of each dataset, including but not limited to, the sort key(s), number of observations per patient. Failure to do so may result in a determination that the application is not complete to file.

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Discussion During Meeting on 9/12/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

9. Please confirm that the proposed NDA will contain all datasets using one unique patient identifier.

   Discussion During Meeting on 9/12/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

10. Please confirm that the proposed NDA will contain a dataset for efficacy analyses at subject level, i.e., each patient has one record; and a dataset with complete demographic, baseline characteristics and screening information at subject level.

    Discussion During Meeting on 9/12/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

11. Please confirm that the proposed NDA will contain the SAS programs used to create the derived datasets for the efficacy endpoints and the SAS programs used for efficacy data analysis. If the SAS programs use any SAS macro, please provide all necessary macro programs. Failure to include this information may result in a determination that the application is not complete for filing.

    Discussion During Meeting on 9/12/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

12. Please confirm that the proposed NDA will contain SAS programs for derived datasets and the analyses which are associated with the results presented in the proposed package insert. Failure to include this information may result in a determination that the application is not complete for filing.

    Discussion During Meeting on 9/12/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

13. Please confirm that the proposed NDA will contain a mock-up define file to show the variables which will be included in the derived datasets for the primary and key secondary efficacy analyses including, but not limited to, the variables for reasons of censoring, dates of IRC determined PFS (or investigator assessed PFS) event or censoring and variables for subgroup analyses, etc. Variables used for sensitivity Analysis of the SAP should be included as well. In addition, provide the hyperlinks of the variables and datasets that have been used in deriving the analysis data, and the hyperlinks of the raw data variables in the annotated CRF. Provide adequate comment for variable label, data format decode of categorical and numerical variable(s), and algorithm(s) to derive new variable from raw data to derived data. Consolidate the define file for all datasets into one pdf file. Failure to include this information may result in a determination that the application is not complete for filing.

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Discussion During Meeting on 9/12/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

Additional Clinical Pharmacology Comments:

14. Please address the following clinical pharmacology related questions in the original NDA submission:

a. What is the basis for selecting the dose(s) and dosing regimen used in the registration trial(s)?

b. What are the exposure-response relationships (dose-response, exposure-response) for efficacy?

c. What are the exposure-response relationships (dose-response, exposure-response) for safety?

d. How is the QT prolongation potential of the combination therapy assessed? What are the conclusion and proposed labeling description?

e. What are the characteristics of absorption, distribution, metabolism and excretion of dabrafenib and trametinib?

f. What are the effects of food on the bioavailability of dabrafenib and trametinib and dosing recommendation with regard to meals or meal types?

g. What influence do the intrinsic factors (as listed below but not limited to) have on dabrafenib and trametinib exposure and/or its pharmacodynamic response? What is their clinical impact? What dose and dosing regimen adjustments are recommended?

   i. gender
   ii. race
   iii. weight
   iv. disease
   v. genetic polymorphism
   vi. hepatic impairment
   vii. renal impairment

h. What influence do the extrinsic factors (as listed below but not limited to) have on dabrafenib and trametinib exposure and/or its pharmacodynamic response? What is their clinical impact? What dose and dosing regimen adjustments are recommended?

   i. concomitant medications
   ii. CYP and/or transporter based drug-drug interaction
   iii. diet
   iv. smoking

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Discussion During Meeting on 9/12/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

15. Please apply the following advice in preparing clinical pharmacology sections of the NDA submission:

a. Submit bioanalytical method(s) and validation reports for clinical pharmacology and biopharmaceutics studies.

b. Provide complete datasets for clinical pharmacology and biopharmaceutics studies. The datasets should not be limited to PK/PD. For example, domains related to safety (e.g., AE's), demographics, non-PK laboratory values, concomitant drug use should be included. All of these are important in identifying patterns of potential clinical pharmacology related causes of clinical safety outcomes and facilitating exploratory exposure-response analyses and population PK analyses.

c. Provide all concentration-time and derived PK parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

d. Present the PK parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate in the study reports.

e. Provide a table listing of patients with renal or hepatic impairment who have received DRUG, organized by trial number. Include available renal and hepatic function parameters such as SCr, CLCr calculated by the Cockcroft Gault equation and/or eGFR calculated by MDRD, AST/ALT, Total Bilirubin, etc for each patient in the listing. Also, provide a summary of the following information for each patient: PK and PD data, safety, and clinical efficacy.

f. Submit the following datasets to support the population PK analysis:

- SAS transport files (*.xpt) for all datasets used for model development and validation
- Description of each data item provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets
- Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submit these files as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt)
- Model development decision tree and/or table which gives an overview of modeling steps

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For the population analysis reports, submit

- Standard model diagnostic plots
- Individual plots for a representative number of subjects including observed concentrations, the individual prediction line and the population prediction line
- Model parameter names and units in tables. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1).
- Summary of the report describing the clinical application of modeling results.

Refer to the following pharmacometric data and models submission guidelines at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm for more information

g. Explore exposure-response (measures of effectiveness, biomarkers and toxicity) relationships for DRUG and its major active metabolite(s) in the targeted patient population and include the results of this exploratory analysis in the NDA submission. Refer to Guidance for Industry found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf and http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf for more information.

h. Submit the following items for QTc study/assessment

- Copy of the QT/QTc study protocol
- Copy of the Investigator's Brochure
- Annotated CRF
- Define file which describes the contents of the electronic data sets
- Electronic data sets as SAS transport files (in CDISC SDTM format – if possible) and all the SAS codes for the analyses
- ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
- Completed Highlights of Clinical Pharmacology Table

Discussion During Meeting on 9/12/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

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Additional Comments (from Division of Medication Error Prevention and Analysis):

16. In an email correspondence to OSE on August 10, 2012, GSK noted that they are considering [redacted] (b) (4)

Discussion During Meeting on 9/12/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

Additional Comments Regarding the Content of a Complete Application

17. As stated in FDA's July 31, 2012, communication granting this meeting, if, at the time of submission, [redacted] (b) (4) Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. GSK and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission. Discussions and agreements on the content of a complete application will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes.

In addition, FDA reminds GSK that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities. [redacted] (b) (4)

Discussion During Meeting on 9/12/2012:

The content of a complete application was discussed, but no agreement was reached. FDA stated that there was insufficient detail in the pre-meeting package to reach agreement on the proposed contents. GSK agreed to provide a detailed description of the proposed contents and discussion on the content will continue in a subsequent teleconference. GSK should provide written confirmation that the NDA will include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

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For additional discussion regarding content of a complete application, see discussion during the meeting for GSK's Question 4.

A preliminary discussion on the need for a REMS was held. FDA and GSK agreed that, based on available information, a REMS does not appear to be required in order to ensure safe use of this drug combination.

Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. GSK stated they intend to submit a complete application and therefore, there are no agreements for late submission of application components.

Additional Comments Regarding PREA Pediatrics Study Plan

18. The Food and Drug Administration Safety and Innovation Act of 2012 changes the timeline for submission of a PREA Pediatric Study Plan and includes a timeline for the implementation of these changes. GSK should review this law and assess if the proposed application will be affected by these changes. If GSK has any questions, please email the Pediatric Team at Pedsdrugs@fda.hhs.gov.

Discussion During Meeting on 9/12/2012: GSK notified the reviewing division that they have applied for orphan drug designation and expect to provide a request for waiver to conduct studies under PREA.

4.0 ACTION ITEMS

Action Item	Description	Owner	Due Date	Status
4.a	FDA will setup a separate teleconference to discuss the need for a formal bioequivalent study (Question 2). GSK will provide relevant data prior to the teleconference.	Sponsor and FDA	As soon as feasible	See Addendum for meeting summary of 9/26/2012
4.b	FDA and GSK will setup a separate teleconference to discuss the content of a complete application as needed. GSK will provide a detailed description of the proposed contents prior to the teleconference.	Sponsor and FDA	As soon as feasible and prior to the application submission	To be scheduled
4.c	FDA (CDRH) and GSK will setup a separate teleconference to discuss the adequacy of the bridging data.	Sponsor and FDA	As soon as feasible and prior to the application submission	To be scheduled

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5.0 ATTACHMENTS AND HANDOUTS

- DOP2's End-of-Phase 2 General Advice for Planned Marketing Applications
- Additional DOP2 CDISC Guidance
- Addendum – Meeting Summary of September 26, 2012 (Follow up for Question 2 and Action Item 4.a.

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DOP2's End-of-Phase 2
General Advice for Planned Marketing Applications

NDA and BLA applications must comply with all applicable statutes and regulations (e.g. 21 CFR 314, 21 CFR Part 201, and 21 CFR Parts 600 and 601). In addition, FDA has published many guidance documents (available at: www.fda.gov/RegulatoryInformation/Guidances/default.htm) that contain important information necessary for preparing a complete, quality application.

Based on our experience with marketing applications, the following tables focus on specific areas of an application and are intended to help you plan and prepare for submitting a quality application. These comments do not include all issues you need to consider in preparing an application, but highlight areas where we have seen problems and/or issues that can delay our timely review of applications. These are general comments; if you believe some are inapplicable to your planned application we encourage you to provide justification and discuss it with us.

If you will be submitting your application in CDISC format, a separate **Study Data Standards Common Issues Document** can be found at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm
The purpose of the document is to highlight important aspects of CDISC and STDM datasets that should be addressed by the Sponsor/Applicant regarding submission of CDISC data in support of an application for registration. In addition to the information and guidance provided at the above FDA link and CDISC links contained therein, the Division Oncology Products 2 (DOP2) has attached a separate document that details additional Oncology Specific domains and variables that we request be used for all oncology submissions. These domains and variable specifications have been developed by CDISC and will be included in the implementation guidance in the near future. DOP2 is using these domains

GENERAL
Special Protocol Assessment (SPA) Requests
1) It is strongly recommended that you discuss protocols for SPA request at an EOP2 meeting. The SPA protocol should be limited to one indication. Discussions of other indications may warrant another meeting. In addition, the Agency may agree that a specific finding (e.g., a particular p-value on the primary efficacy endpoint) of a study will satisfy a specific objective (e.g., demonstration of efficacy) or support an approval decision. However, final determinations are made after a complete review of a marketing application and are based on the entire data in the application.
SPA Requests for a Single Trial Intended to Support Marketing Approval:
2) If the protocol for your SPA request is intended to be used as the sole registration trial to support marketing approval, this single trial should be optimally designed and the development program optimally planned. Therefore, you should address the following in your SPA request, and you may also briefly describe these items in your EOP2 meeting briefing document: • Justification of why a single trial and not multiple trials are appropriate or not possible for drug development and marketing approval for an NME or substantially different indication (e.g., a study is designed to show a clinically meaningful effect on mortality, irreversible morbidity, or prevention of disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible. See 'Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products'). • A description of your drug development plan, including each indication that is being or has been studied and a timetable for submission of the planned studies. You should also include

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information on where the drug/biologic is marketed outside of the U.S. or indicate if an application for the drug/biologic has been submitted to foreign regulators.
Additional Content for SPA Request Submission:
3) Please submit/address the items below in your SPA request. • The protocol must be complete, including a FINAL detailed statistical analysis plan for the evaluation of primary and secondary clinical trial endpoints that potential claims will be sought. The cover letter should identify the need for an expert statistical review if the planned trial includes (1) adaptive design, (2) enrichment design, (3) non-inferiority hypotheses, or (4) novel, new or composite endpoints. • If study is blinded, discuss toxicities of agents (or regimens) that may unmask blinding. • If radiologic, you should discuss whether an external radiological review will be performed of primary endpoint • If your trial uses an *in vitro* diagnostic test to identify the treatment population, you should meet with CDRH to discuss the plans for co-development of the diagnostic test prior to the SPA request. Also, you should provide your plans for a commercially available test at the time of proposed approval. The testing procedure used in your clinical trial should be identical (or "bridged") to your proposal for a commercial kit. • If registration trial is to be primarily completed outside of the U.S., the following issues need to be addressed: ➢ How assessment of safety and efficacy of U.S. minorities will be examined (e.g., will another study be conducted?) ➢ Applicability of comparator treatment or of disease characteristics to U.S. population • Any single arm submission should be accompanied by an adequate explanation of the reasons a randomized trial cannot ethically be performed.
Accelerated or Regular Approval:
4) You should include a statement of whether you are seeking approval under 21 CFR 314 Subpart H/21 CFR 601 Subpart E (accelerated approval) or regular approval in your meeting briefing document, SPA request and NDA/BLA submission. If seeking accelerated approval, there should be a description of all protocols for confirmatory trials (including a timetable for expected trial initiation(s), completion of the planned trial(s), submission of final clinical study report(s)), which under § 314.510 and 601.41 would usually be underway at the time of accelerated approval in your SPA request and NDA/BLA submission. • If surrogate endpoint is being used for accelerated approval, you should justify (i.e., from the literature) why the proposed effect on this surrogate is reasonably likely to predict clinical benefit.

NDA/BLA content and format
CLINICAL
1) Original versions of all protocols, statistical analysis plans, Data Safety Monitoring Board (DSMB) and adjudication committee charters, and all amendments.
2) Minutes of all DSMB and efficacy endpoint review/adjudication committee meetings.
3) Investigator instructions that may have been produced in addition to the protocol and investigator

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brochure
4) All randomization lists and, if used, IVRS datasets (in SAS transport format)
5) All datasets used to track adjudications (in SAS transport format)
6) A Reviewers Guide to the data submission that includes, but is not limited to the following: a) description of files and documentation b) description of selected analysis datasets c) key variables of interest, including efficacy and safety variables d) SAS codes for sub-setting and combining datasets e) coding dictionary used f) methods of handling missing data g) list of variable contained in every dataset h) listing of raw data definitions i) analysis data definitions j) annotated CRF (the annotated CRF should contain links connecting to the document that defines the variable name and lists the data sets that contain the specific item) k) documentation of programs
7) Clinical study report(s) for all trials (should follow the ICH E3 Structure and Content of Clinical Study Reports guidance (www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129456.pdf).
8) Pediatric Studies: All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is exempt (i.e. orphan designation), waived or deferred. We request that you submit a pediatric plan that describes development of your product to provide important information on the safe and effective use of in the pediatric population where it may be used. If the product will not be used in pediatric populations your application must include a specific waiver request with the NDA submission, including supporting data. A request for deferral, must include a pediatric plan, certification of the grounds for deferring the assessments, and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time.
9) Quantitative Safety Analysis Plan (QSAP): The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. When unanticipated safety issues are identified the QSAP may be amended. At a minimum the Safety Analysis Plan should address the following components: a) Study design considerations (See: FDA Guidance to Industry: Premarketing Risk Assessment, (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf). b) Safety endpoints for Adverse Events of Special Interest (AERI) c) Definition of Treatment Emergent Adverse Event (TEAE) d) Expert adjudication process (Expert Clinical Committee Charter or Independent Radiology

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Review Charter)) e) Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP) f) Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.
10) Integrated summaries of safety and effectiveness (ISS/ISE) as required by 21 CFR 314.50 and in conformance with the following guidance documents: a) Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf) b) Cancer Drug and Biological Products-Clinical Data in Marketing Applications (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071323.pdf)
11) Perform SMQs on the ISS adverse event data that may further inform the safety profile for your investigational agent, and include the results in the ISS report
12) A statement that the manufacturing facilities are ready for inspection upon FDA receipt of the application
13) A chronology of prior substantive communications with FDA and copies of official meeting/telecom minutes.
14) References: There should be active links from lists of references to the referenced article.
Studies, Data And Analyses
15) Provide a table listing all of the manufacturing facilities (e.g. drug product, drug substance, packaging, control/testing), including name of facility, full address including street, city, state, country, FEI number for facility (if previously registered with FDA), full name and title, telephone, fax number and email for on-site contact person, the manufacturing responsibility and function for each facility, and DMF number (if applicable).
16) Provide a table with the following columns for each of the completed Phase 3 clinical trials: a) Site number b) Principle investigator c) Location: City State, Country d) Number of subjects screened e) Number of subjects randomized f) Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites for inspection) g) Number of protocol violations (Major, minor, including definition)
17) Provide an assessment of safety as per the Guidance for Industry: Premarketing Risk Assessment (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf).
18) Provide detailed information, including a narrative (data listings are not an acceptable substitute for a narrative), for all patients who died while on study or who terminated study drug or participation in the study prematurely including those categorized as other, lost to follow up, physician decision, or

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subject decision. Narrative summaries should contain the following components:

a) subject age and gender
b) signs and symptoms related to the adverse event being discussed
c) an assessment of the relationship of exposure duration to the development of the adverse event
d) pertinent medical history
e) concomitant medications with start dates relative to the adverse event
f) pertinent physical exam findings
g) pertinent test results (for example: lab data, ECG data, biopsy data)
h) discussion of the diagnosis as supported by available clinical data
i) a list of the differential diagnoses, for events without a definitive diagnosis
j) treatment provided
k) re-challenge and de-challenge results (if performed)
l) outcomes and follow-up information
m) an informed discussion of the case, allowing a better understanding of what the subject experienced.

19) Provide complete case report forms (CRFs) for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events. You should be prepared to supply any additional CRFs with a rapid turnaround upon request.

20) Provide reports for any autopsies conducted on study.

21) For patients listed as discontinued to due "investigator decision," "sponsor request," "withdrew consent," or "other," the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated. In addition, the verbatim description from the CRF should be included as a variable in the adverse event data set.

22) Regulations require that the safety and effectiveness data be presented for subgroups including "by gender, age, and racial subgroups". Therefore, as you are gathering your data and compiling your application, we request that you include this data and pertinent analysis

23) The clinical information contained in the NDA/BLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP) 6010.3 (www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm080121.pdf). To facilitate the review, we request you provide analyses and discussion, where applicable, that will address the items in the template, including:

a) Other Relevant Background Information – important regulatory actions in other countries or important information contained in foreign labeling.
b) Exposure-Response Relationships – important exposure-response assessments.
c) Less common adverse events (between 0.1% and 1%).
d) Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
e) Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
f) Marked outliers and dropouts for laboratory abnormalities.

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g) Analysis of vital signs focused on measures of central tendencies.
h) Analysis of vital signs focused on outliers or shifts from normal to abnormal.
i) Marked outliers for vital signs and dropouts for vital sign abnormalities.
j) A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in a SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.
k) Overview of ECG testing in the development program, including a brief review of the nonclinical results.
l) Standard analyses and explorations of ECG data.
m) Overdose experience.
n) Analysis and summary of the reasons and patterns of discontinuation of the study drug. Identify for each patient the toxicities that result in study discontinuation or dose reduction.
o) Explorations for:
   i) Possible factors associated with a higher likelihood of early study termination; include demographic variables, study site, region, and treatment assignment.
   ii) Dosedependency for adverse findings, which should be supported by summary tables of the incidence of adverse events based on the cumulative dose and the average dose administered.
   iii) Time dependency for adverse finding, which should be supported by analyses summarizing the length of time subjects experience adverse events and whether recovery occurs during treatment.
   iv) Drug-demographic interactions
   v) Drug-disease interactions
p) Drug-drug interactions
   i) Dosing considerations for important drug-drug interactions.
   ii) Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

24) Marketing applications must include the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Provide all appropriate data as well as a clinical study report for any study performed to evaluate QT/QTc prolongation.

Financial Disclosure Information

25) Marketing applications must include certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies, including those at foreign sites, covered by the regulation. This requires that investigators provide information to the sponsor during the course of the study and after completion. See Guidance for Industry - Financial Disclosure by Clinical Investigators (www.fda.gov/RegulatoryInformation/Guidances/ucm126832.htm).

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Physician's Labeling Rule
Highlights
1) Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]
2) The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
3) The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]
4) The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]
5) The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to 21 CFR 201.57(a) (4) and to www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom).
6) For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d) (9) and Implementation Guidance]. Recent major changes apply to only 5 sections (Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions).
7) The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights: (a) "(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."
8) Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.
9) Refer to 21 CFR 201.57 (a) (11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
10) A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a) (11)].
11) Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights
12) The Patient Counseling Information statement must appear in Highlights and must read "See 17 for PATIENT COUNSELING INFORMATION." [See 21 CFR 201.57(a)(14)]
13) A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a) (15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.
14) A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

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Table of Contents
15) The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]
16) The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
17) Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous for a subsection heading.
18) Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
19) When a subsection is omitted, the numbering does not change [see 21 CFR 201.56(d) (1)]. For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows: 8.1 Pregnancy 8.3 Nursing Mothers *(not 8.2)* 8.4 Pediatric Use *(not 8.3)* 8.5 Geriatric Use *(not 8.4)*
20) When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading "Full Prescribing Information: Contents" must be followed by an asterisk and the following statement must appear at the end of the Contents: "*Sections or subsections omitted from the Full Prescribing Information are not listed."
Full Prescribing Information (FPI)
22) Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
23) Other than the required bolding [See 21 CFR 201.57(d) (1), (d) (5), and (d) (10)], use bold print sparingly. Use another method for emphasis such as italics or underline.
24) Do not refer to adverse reactions as "adverse events." Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format" (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf).
25) The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [see Use in Specific Populations (8.4)] not See Pediatric Use (8.4). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf]
26) Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
27) Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21

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CFR 201.57 (c)(18)]
28) The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.
29) There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.
30) The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.
31) If the "Rx only" statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.
32) Refer to www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format.
33) Refer to the Institute of Safe Medication Practices' website (http://www.ismp.org/Tools/abbreviationslist.pdf) for a list of error-prone abbreviations, symbols, and dose designations.

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Additional DOP2 CDISC Guidance

The following two tables identify variables and domains that the division uses in conducting standardized analyses on data for marketing or licensing applications. Following the tables is a description of the Tumor Identification (TU), Tumor Results (TR), Response (RS), domains and variables therein. These are provided because DOP2 uses these domains and variables in analysis tools developed by FDA. These domains and variables will be added to the CDISC implementation guide in the near future, however, we request that you implement the use of this STDM format with all your upcoming submissions.

Please use the draft CDISC *Oncology Disease-Specific Therapeutic Area Supplement to the SDTM Implementation Guide* (http://www.cdisc.org/sdtm) for submitting tumor identification, results, and response data to DOP2 as soon as they become available.

Please follow the guidance as provided in the CDER Data Standards Issues Document that can be found at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

Table 1: Variables that DOP2 requires for analyses of OS, PFS, RR, Disposition, and Adverse Reactions

Domain	Variable Name	Variable Label	Required Variable Values	Currently Available	CDISC Core	CDISC Data Type	CDISC Code List
ADSL	STRATA<N>	Based on definition of strata variable	0,1	No		Num	0,1
AE	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
AE	AEBODSYS	Body System or Organ Class	--	Yes	Exp	Char	
AE	AEDECOD	Dictionary-Derived Term	--	Yes	Req	Char	
AE	AETOXGR	Standard Toxicity Grade	--	Yes	Perm	Char	
AE	AESTDTC	Start Date/Time of Adverse Event	--	Yes	Exp	Char	ISO 8601
CM	CMCAT	Category for Medication	ANTI-CANCER	Yes	Perm	Char	--
CM	CMDECOD	Standardized Disposition Term	--	Yes	Perm	Char	NCOMPLT (Completion/Reason for Non-Completion)

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CM	CMENDTC	End Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
CM	CMSTDTC	Start Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
CM	CMSTDY	Study Day of Start of Medication	--	Yes	Perm	Num	--
CM	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
DM	AGE	Age	--	Yes	Req	Num	--
DM	AGEU	Age Units	--	Yes	Exp	Char	AGEU
DM	ARM	Description of Planned Arm	--	Yes	Req	Char	--
DM	ACTARM		--	New			--
DM	ARMCD	Planned Arm Code	--	Yes	Req	Char	--
DM	COUNTRY	Country	--	Yes	Req	Char	ISO 3166 3- char. code
DM	DTHDTC	Date of Death	--	New		Char	ISO 8601
DM	DTHFL	Subject Death Flag	Y	New		Char	--
DM	ETHNIC	Ethnicity	--	Yes	Perm	Char	--
DM	RACE	Race	--	Yes	Exp	Char	--
DM	RFPENDTC	Date/Time of End of Participation	--	New		Char	ISO 8601
DM	SEX	Sex	--	Yes	Req	Char	M, F, U
DM	SITEID	Study Site Identifier	--	Yes	Req	Char	--
DM	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
DS	DSCAT	Category for Disposition Event	PROTOCOL MILESTONE	Yes	Perm	Char	DSCAT
DS	DSDECOD	Standardized Disposition Term	DEATH, RANDOMIZED, LOST TO FOLLOW-UP, ALIVE, ADVERSE EVENT, PROGRESSIVE DISEASE	Yes	Req	Char	NCOMPLT (Completion/Reason for Non-Completion)
DS	DSDTC	Date/Time of Collection	--	Yes	Perm	Char	ISO 8601

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DS	DSSCAT	Subcategory for Disposition Event	STUDY DISCONTINUATION, TREATMENT DISCONTINUATION, STUDY TERMINATION	Yes	Perm	Char	--
DS	DSSTDTC	Start Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
DS	DSSTDY	Study Day of Start of Disposition Event	--	Yes	Perm	Num	--
DS	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
EX	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
EX	EXSTDTC	Start Date/Time of Treatment	--	Yes	Exp	Char	ISO 8601
EX	EXENDTC	End Date/Time of Treatment	--	Yes	Perm	Char	ISO 8601
LB	LBBLFL	Baseline Flag	Y	Yes	Exp	Char	NY
LB	LBNRIND	Reference Range Indicator	HIGH, LOW	Yes	Exp	Char	--
LB	LBTEST	Lab Test or Examination Name	--	Yes	Req	Char	--
LB	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
MH	MHDECOD	Dictionary-Derived Term	--	Yes	Perm	Char	--
MH	MHENDTC	End Date/Time of Medical History Event	--	Yes	Perm	Char	ISO 8601
MH	MHSTDTC	Start Date/Time of Medical History Event	--	Yes	Perm	Char	ISO 8601
MH	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
RS	RSACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
RS	RSDTC	Date/Time of Response Assessment	--	Yes	Exp	Char	ISO 8601

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RS	RSEVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
RS	RSSTAT	Response Assessment Status	NOT DONE	Yes	Perm	Char	ND
RS	RSSTRESC	Response Assessment Result in Std Format	CR or COMPLETE RESPONSE, PR or PARTIAL RESPONSE, SD or STABLE DISEASE, PD or PROGRESSIVE DISEASE, NE or NOT EVALUABLE	Yes	Exp	Char	--
RS	RSTESTCD	Response Assessment Short Name	OVRLRESP. looks for TGRESP, NTGRESP & BESTRESP	Yes	Req	Char	--
RS	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
RS	VISIT	Visit name	Must contain "UNSCH" for unscheduled	Yes	Perm	Char	
SV	SVSTDTC	Start Date/Time of Visit	--	Yes	Exp	Char	ISO 8601
SV	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
TA	ANCHDTC	Anchor date of assessment schedule	Variable in ADSL - no name determined	NEW		Char	
TA	MAXPRD	Maximum length of assessment schedule		NEW		Char	ISO 8601 Duration
TA	MINPRD	Minimum length of assessment schedule		NEW		Char	ISO 8601 Duration
TA	STOFFSET	Start time from anchor date		NEW		Char	ISO 8601 Duration
TA	TGTPRD	Length of assessment schedule		NEW		Char	ISO 8601 Duration
TR	TRACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
TR	TRDTC	Date/Time of Tumor Measurement	--	Yes	Exp	Char	ISO 8601
TR	TREVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL

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TR	TRLINKID	Link ID	--	Yes	Exp	Char	--
TR	TRLNKGRP		--	NEW		Char	--
TR	TRSTAT	Tumor Assessment Status	NOT DONE	Yes	Perm	Char	ND
TR	TRSTRESC	Character Result/Finding in Std. Format	If TRTESTCD equals "TUMSTATE" Looks for PRESENT, ABSENT, UNEQUIVOCAL PROGRESSION	Yes	Exp	Char	--
TR	TRSTRESN	Numeric Result/Finding in Std. Format	--	Yes	Exp	Num	--
TR	TRTESTCD	Tumor Assessment Short Name	LDIAM, TUMSTATE. Looks for SUMLDIAM	Yes	Exp	Char	--
TR	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
TS	DCUTDTC	Data cut off date	--	New		Char	ISO 8601
TS	TSPARMCD	Trial Summary Parameter Short Name	PSSDDUR, PSCDUR	New	Req	Char	--
TS	TSVAL	Parameter Value	ISO Duration	New	Req	Char	--
TU	TUACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
TU	TUDTC	Date/Time of Tumor Identification	--	Yes	Exp	Char	ISO 8601
TU	TUEVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
TU	TULINKID	Link ID	--	Yes	Exp	Char	--

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TU	TULOC	Location of Tumor	--	Yes	Exp	Char	LOC
TU	TUMETHOD	Method of Identification	--	Yes	Exp	Char	
TU	TUSTRESC	Tumor Identification Result Std. Format	NEW	Yes	Exp	Char	
TU	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--

Please ensure that the following domains and variables are included in your CDISC data submissions. Although the CDISC Implementation guide lists many variables as permissible, in order for DOP2 to conduct efficient and timely reviews of the clinical trial data, most permissible variables should be considered as required variables. Please consult with the division on any permissible variables that you intend not to include in your data files so we can determine the impact this will have on the review process and the acceptability of the omission.

Table 2: Additional variables in SDTM and ADaM that are necessary for efficient review

DOMAIN	VARAIBLE	DATA TYPE
ADaM		
ADSL	STUDYID	C
ADSL	USUBJID	C
ADSL	TRT01A	C
ADSL	TRT01P	C
ADSL	ARM	C
ADSL	AGE	N
ADSL	AGEGR1	C
ADSL	SEX	C
ADSL	RACE	C
ADSL	TRTEDT	N
ADSL	TRTEDTM	N
ADSL	TRTSDT	N
ADSL	TRTSDTM	N
ADSL	DEATHDSC	C
SDTM		
AE	STUDYID	C
AE	USUBJID	C
AE	AEDECOD	C
AE	AEBODSYS	C
AE	AEREL	C
AE	AESEV	C
AE	AETOXGR	C

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AE	AESTDTC	C
AE	AEENDTC	C
AE	AESTDY	N
AE	AEENDY	N
AE	AEDUR	C
CM	STUDYID	C
CM	USUBJID	C
CM	CMDECOD	C
CM	CMSTDTC	C
CM	CMENDTC	C
CM	CMENDY	N
CM	CMSTDY	N
CM	CMDUR	C
DM	STUDYID	C
DM	USUBJID	C
DM	AGE	N
DM	SEX	C
DM	RACE	C
DM	ARM	C
DM	RFENDTC	C
DM	RFSTDTC	C
DS	STUDYID	C
DS	USUBJID	C
DS	DSDECOD	C
DS	DSCAT	C
DS	DSSTDTC	C
DS	DSSTDY	N
EX	STUDYID	C
EX	USUBJID	C
EX	EXTRT	C
EX	EXDOSE	N
EX	EXSTDTC	C
EX	EXENDTC	C
EX	EXSTDY	N
EX	EXENDY	N
EX	EXDUR	C
LB	STUDYID	C
LB	USUBJID	C
LB	LBTEST	C
LB	LBSTRESN	N
LB	LBSTNRHI	N
LB	LBSTNRLO	N
LB	LBDTC	C
LB	LBDY	N
MH	STUDYID	C
MH	USUBJID	C
MH	MHDECOD	C
MH	MHBODSYS	C

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VS	STUDYID	C
VS	USUBJID	C
VS	VSTEST	C
VS	VSSTRESN	N
VS	VSDTC	C
VS	VSDY	N

CDISC Oncology Domains

Introduction

Assessment of the change in tumor burden is an important feature of the clinical evaluation of cancer therapeutics: both tumor shrinkage (objective response) and disease progression are useful endpoints in cancer clinical trials[1]. RECIST (Response Evaluation Criteria in Solid Tumors)[2] has been widely adopted in solid tumor clinical trials where the primary endpoints are objective response or progression and is accepted by regulatory authorities as an appropriate guideline for these assessments. The SDTM domains presented here were developed with RECIST Criteria in mind. However, the domains are intended to represent data collected in clinical trials where tumors are identified and then repeatedly measured/assessed at subsequent timepoints and used in an evaluation of response(s). As such these domains would be equally applicable for criteria other than RECIST e.g. Chesson classification[3] in the assessment lymphomas, or, MacDonald Response[4] in the assessment of malignant gliomas.

The tumor assessment package consists of three SDTM domains based on the SDTM Findings Observation Class. The three domains are related but each domain has a distinct purpose:

TU (Tumor Identification): The TU domain represents data that uniquely identifies tumors. The tumors are identified by an investigator and/or independent assessor and in RECIST terms this equates to the identification of Target, Non-Target or New tumors. A record in the TU domain contains the following information: a unique tumor ID value; anatomical location of the tumor; method used to identify the tumor; role of the individual identifying the tumor; and timing information.

TR (Tumor Results): The TR domain represents quantitative measurements and/or qualitative assessments of the tumors identified in the TU domain. These measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. A record in the TR domain contains the following information: a unique tumor ID value; test and result; method used; role of the individual assessing the tumor; and timing information.

Clinically accepted evaluation criteria expect that a tumor identified by the tumor ID is the same tumor at each subsequent assessment. The TR domain does not include anatomical location information on each measurement record because this would be a duplication of information already represented in TU. This duplication of data was a deciding factor in multi-domain approach to representing this data.

RS (Response): The RS domain represents the response evaluation determined from the data in TR. Data from other sources (in other SDTM domains) might also be used in an assessment of response for example, MacDonald Response Criteria includes a neurological aspect.

New variables:
--LINKID – The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). Therefore a new ID variable --LINKID is being proposed in order to support the linking requirements. The --LINKID variable is specifically designed to support a relrec dataset to dataset relationship. Values of LINKID could concatenate values of other variables when more than one variable are needed to do join data rows.

--ACPTFL – The Acceptance Flag identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.

--EVALID – The Evaluator Specified variable is used in conjunction with TREVAL to provide an additional level of detail. When multiple assessors play the role identified in TREVAL, values of TREVALID will attribute a row of data to a

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particular assessor. For example TREVAL="INDEPENDENT ASSESSOR" and TREVALID="RADIOLOGIST 1". The --EVALID variable is not subject to Controlled Terminology. When --EVALID is populated --EVAL must also be populated.

References:

(1) E.A. Eisenhauera,*, P. Therasseb, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) *EUROPEAN JOURNAL OF CANCER 45 (2009) 228–247*
(2) RECIST Criteria - http://www.eortc.be/recist/
(3) Bruce D. Cheson, Beate Pfistner, et al. Revised Response Criteria for Malignant Lymphoma *Journal of Clinical Oncology. Vol 25 Number 5 Feb 10 2007*
(4) DR Macdonald, TL Cascino, et al. Response criteria for phase II studies of supratentorial malignant glioma *Journal of Clinical Oncology, Vol 8, 1277-1280*

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1. Oncology Domains:

1.1. TUMOR IDENTIFICATION - TU

tu.xpt, Tumor Identification - Findings, Version 3..*x.x* ..... One record per identified tumor per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	TU	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App.C2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
TUSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
TUGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TUREFID	Reference ID	Char		Identifier	Internal or external identifier. Example:	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TUSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TULINKID	Link ID	Char		Identifier	Identifier used to link identified tumors to the assessment results over the course of the study.	Exp	
TUTESTCD	Tumor Identification Short Name	Char	*	Topic	Short name of the TEST in TUTEST. TUTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: TUMIDENT, NEWTUMOR. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
TUTEST	Tumor Identification Test Name	Char	*	Synonym Qualifier	Verbatim name of the test for the tumor/lesion identification. The value in TUTEST cannot be longer than 40 characters. Examples: Tumor Identification, New Tumor Identified. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
TUCAT	Category for Tumor Identification	Char		Grouping Qualifier	Used to categorize tumors.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
TUSCAT	Sub-Category for Tumor Identification	Char		Grouping Qualifier	A further classification of the TUTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

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Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TUORRES	Tumor Identification Result	Char	*	Result Qualifier	Result of the Tumor identification. Examples: When TUTESTCD=TUMIDENT (Tumor Identification), values of TUORRES might be: TARGET or NON-TARGET. When TUTESTCD=NEWTUMOR the value of TUORRES might be: Y When TUTESTCD=BENIGNAB the value of TUORRES might be: BENIGN RENAL LESIONS	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TUSTRESC	Tumor Identification Result Std. Format	Char	*	Record Qualifier	Contains the result value for all findings copied from TUORRES.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TUNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the Tumor Identification.	Perm	SDTM 2.2.3
TULOC	Location of the Tumor	CHAR	(LOC)	Record Qualifier	Used to specify the anatomical location of the identified tumor. Example: Gastrointestinal Tract. Note: When anatomical location is broken down and collected as distinct pieces of data that when combined provide the overall location information (e.g. organ / laterality /location / sub-location) then the additional information should added as supplemental qualifiers. See Assumption 3	Exp	SDTMIG 2.2.3
TUMETHOD	Method of Identification		*	Record Qualifier	Method used to identify the tumor. Examples: X-ray, MRI, CT-Scan.	Exp	SDTMIG 2.2.3
TUEVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST This column can be left *Null* when the Investigator provides the complete set of data in the domain. However the column should contain no *Null* values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.4

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Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TUEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with TUEVAL to provide an additional level of detail. When multiple assessors play the role identified in TUEVAL, values of TUEVALID will attribute a row of data to a particular assessor. TUEVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2.. The TUEVALID variable would not be subject to CDISC Controlled Terminology. See Assumption 5.	Perm	
TUACPTFL	Accepted Record Flag	Char	*	Record Qualifier	In cases where more than one independent assessor (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide independent assessments at the same timepoint this flag identifies the record that is considered to be the accepted assessment.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISITDY	Planned Study Day of Visit	Num		Timing		Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TUDTC	Date/Time of Tumor Identification	Char	ISO 8601	Timing		Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TUDY	Study Day of Tumor Identification	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

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1.1.1. ASSUMPTIONS FOR THE TUMOR IDENTIFICATION DOMAIN MODEL

TU Definition: The TU domain represents data that uniquely identifies tumors. The tumors are identified by an investigator and/or independent assessor and in RECIST terms this equates to the identification of Target, Non-Target or New tumors. A record in the TU domain contains the following information: a unique tumor ID value; anatomical location of the tumor; method used to identify the tumor; role of the individual identifying the tumor; and timing information.

1. The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). The --LINKID variable is used for values that support a relrec dataset to dataset relationship and to provide a unique code for each identified tumor.

2. The values of TUTESTCD and TUTEST will be relatively simple and will either represent that the Tumor is identified and categorized at screening or that the Tumor is identified as New (has appeared since the Screening assessment).

   Proposed TUTESTCD / TUTEST values for this domain:

TUTESTCD	TUTEST
TUMIDENT	Tumor Identification
NEWTUMOR	New Tumor Identified
BENIGNAB	Benign Abnormality
TUSPLIT	Tumor Split or Divided
TUMERGE	Tumor Merged or Coalesced

   During the course of a trial when a new Tumor (or lesion) is identified information about that new tumor may be collected to different levels of detail. The following three scenarios represent the most commonly seen data collection methods employed when a new Tumor (or lesion) is identified. The scenarios set out below are not intended to be exhaustive. The sponsor must decide the appropriate collection method based on their analysis needs or internal processes and it is possible that a sponsor's chosen method is not reflected in the scenarios presented below.

   a. The occurrence of a New Tumor is the sole piece of information that a sponsor collects because this is a sign of disease progression and no further details are required. In such cases a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y".

   b. The occurrence of a New Tumor and the anatomical location of that newly identified Tumor are the only collected pieces of information. In this case it is expected that a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y", and the TULOC variable would be populated with the anatomical location information (the additional location variables may be populated depending on the level of detail collected).

   c. A sponsor might record the occurrence of a New Tumor to the same level of detail as Target and Non-Target Tumors. In this case the occurrence of the new tumor and the anatomical location information, and also measure the New Tumor. In this case it is expected that a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y", and the identifier, TULINKID, would all be populated. The measurement/assessment of the New Tumor would be recorded in the TR domain.

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3. TUCAT and TUSCAT have been included as they are standard domain variables however these columns would generally not be needed and so the variables are not included in the accompanying examples.

4. Anatomical Location information might be collected in a number of ways the simplest way is as a long text string and in these cases the text string is captured in the TULOC variable. However, anatomical location might also be collected through a number of distinct and separate variables (that might possibly be subject to controlled terminology) and in such cases the additional information would be recorded in the following Supplemental Qualifiers:

QNAM	QLABEL	Definition
TUSUBLOC	Sub-location of the Tumor	Anatomical location information with more specificity than a gross location
TULOCDET	Detailed Location Information	Detailed anatomical location information that would include details such as: direction (Superior, Posterior); relative direction (Proximal, Distal); axes (Dorsoventral, Mediolateral); planes (Sagittal, Coronal); and any other divisions or sub-anatomy information.
TUORGAN	Organ Affected	Actual Body Organ location of the tumor. This is more specific than Body Organ Class
TULAT	Tumor Location Laterality	Lateral location used to distinguish Right & Left sides. For example if a Tumor was located in the "Right Lung" then the TULOC and QNAM.TULAT values would be TULOC=LUNG; QNAM.TULAT=RIGHT.

5. The Acceptance Flag variable (TUACPTFL) identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.

6. The Evaluator Specified variable (TUEVALID) is used in conjunction with TUEVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the TUEVAL variable. For example TUEVAL="INDEPENDENT ASSESSOR" and TUEVALID="RADIOLOGIST 1". The TUEVALID variable is not subject to Controlled Terminology. TUEVAL must also be populated when TUEVALID is populated.

7. The following proposed supplemental Qualifiers would be used to represent information regarding previous irradiation of a tumor when that information is known:

QNAM	QLABEL	Definition
PREVIR	Previously Irradiated	Indication of previous irradiation to a tumor.
PREVIRP	Irradiated then Subsequent Progression	Indication of documented progression subsequent to irradiation.

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TUMOR RESULTS - TR

tr.xpt, Tumor Results - Findings, Version 3..*x.x* ..... One record per tumor measurement/assessment per tumor per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	TR	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App, 2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
TRSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
TRGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TRREFID	Reference ID	Char		Identifier	Internal or external identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TRSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4
TRLINKID	Link ID	Char		Identifier	Identifier used to link the assessment result records to the tumor identification record.	Exp	
TRTESTCD	Tumor Assessment Short Name	Char	*	Topic	Short name of the TEST in TRTEST. TRTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: LDIAM, DIAM. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
TRTEST	Tumor Assessment Test Name	Char	*	Synonym Qualifier	Verbatim name of the test or examination used to obtain the measurement or finding. The value in TRTEST cannot be longer than 40 characters. Examples: LONGEST DIAMETER, LONGEST PERPENDICULAR, AXIAL THICKNESS, VOLUME, AREA. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
TRCAT	Category for Tumor Assessment	Char	*	Grouping Qualifier	Used to categorize assessments. Examples: Measurement Categorical	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
TRSCAT	Sub-Category for Tumor Assessment	Char		Grouping Qualifier	A further classification of the TRTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

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Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TRORRES	Result or Finding in Original Units	Char		Result Qualifier	Result of the Tumor measurement/assessment as originally received or collected.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRORRESU	Original Units	Char	(UNIT)	Variable Qualifier	Original units in which the data were collected. The unit for TRORRES. Example: mm	Exp	SDTMIG 2.2.3 SDTMIG 4.1.3.2
TRSTRESC	Character Result/Finding in Std Format	Char		Record Qualifier	Contains the result value for all findings, copied or derived from TRORRES in a standard format or standard units. TRSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in TRSTRESN	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRSTRESN	Numeric Result/Finding in Standard Units	Num		Result Qualifier	Used for continuous or numeric results or findings in standard format; copied in numeric format from TRSTRESC. TRSTRESN should store all numeric test results or findings.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRSTRESU	Standard Units	Char	(UNIT)	Variable Qualifier	Standardized unit used for TRSTRESN.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.3.2 SDTMIG 4.1.5.1
TRSTAT	Tumor Assessment Status	Char	(ND)	Result Qualifier	Used to indicate a measurement was not done, or a tumor measurement was not taken. Should be Null if a result exists in TRORRES.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
TRREASND	Reason Tumor Measurement Not Performed	Char		Record Qualifier	Describes why a measurement or test was not performed. Examples: BROKEN EQUIPMENT or SUBJECT REFUSED. Used in conjunction with TRSTAT when value is NOT DONE.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
TRNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the Tumor measurement or assessment.	Perm	SDTM 2.2.3
TRMETHOD	Method used to identify the Tumor		*	Record Qualifier	Method used to measure the tumor. Examples: X-ray, MRI, CT-Scan.	Exp	SDTMIG 2.2.3

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Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TREVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST This column can be left *Null* when the Investigator provides the complete set of data in the domain. However the column should contain no *Null* values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.4
TREVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with TREVAL to provide an additional level of detail. When multiple assessors play the role identified in TREVAL, values of TREVALID will attribute a row of data to a particular assessor. TREVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The TREVALID variable would not be subject to CDISC Controlled Terminology. Note TREVAL must also be populated when TREVALID is populated. See Assumption 4	Perm	
TRACPTFL	Accepted Record Flag	Char	*	Record Qualifier	In cases where more than one independent assessor (e.g. where TREVALID has values of "RADIOLOGIST 1" & "RADIOLOGIST 2") provide independent assessments at the same timepoint this flag identifies the record that is considered to be the accepted assessment.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISITDY	Planned Study Day of Visit	Num		Timing		Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4

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Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TRDTC	Date/Time of Tumor Measurement	Char	ISO 8601	Timing		Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TRDY	Study Day of Tumor Measurement	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.2. ASSUMPTIONS FOR THE TUMOR RESULTS DOMAIN MODEL

TR Definition: The TR domain represents quantitative measurements and/or qualitative assessments of the tumors identified in the TU domain. These measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. A record in the TR domain contains the following information: a unique tumor ID value; test and result; method used; role of the individual assessing the tumor; and timing information.

1. The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). The --LINKID variable is used for values that support a relrec dataset to dataset relationship and to provide a unique code for each identified tumor. TRLINKID is a required variable as the records in the TR domain must relate back to an identification record in TU.

2. TRTESTCD / TRTEST values for this domain (this is for illustration purposes these values will be published as Controlled Terminology):

TRTESTCD	TRTEST
AREA	Area
AXTHICK	Axial Thickness
DIAM	Diameter
LDIAM	Longest Diameter
LMAXSP	Major Axis Axial Plane, Long Diameter Target
LPERP	Longest Perpendicular
METVOLNO	Average Metabolic SUV
MJAX3SP	Major Axis 3D (All Planes)

MNAX3SP	Minor Axis 3D
MNAXSP	Minor Axis
MXSUVSSP	Maximum SUV (1 cm Spot)
MXSUVVSP	Maximum SUV (Single Voxel)
PCCHBL	Percent Change From Baseline
PCCHNAD	Percent Change From Nadir
PREVIR	Lesion Previously Irradiated
PREVIRP	Lesion Progressing Since Irradiated
PRODUCT	Product
RADDESP	Radio Density
SAXIS	Short Axis
SUMAREA	Sum of Area
SUMAXTHK	Sum of Axial Thickness
SUMLDIAM	Sum of Longest Diameter
SUMLPERP	Sum of Longest Perpendicular
SUMPDIAM	Sum of the product of the diameters
SUMPROD	Sum of Product
SUMVOL	Sum of Volume
VOLPETSP	Total Tumor Volume
VOLUME	Volume
XPRO3SP	Cross Product 3D
XPRODSP	Cross Product

Note: The sponsor should not derive results for any test indicated in the list above (e.g. "Percent Change From Nadir") if the result was not collected. Tests would be included in the domain only if those data points have been collected on a CRF or have been supplied by an external assessor as part of an electronic data transfer. It is not intended that the sponsor would create derived records to supply those values.

3. The Acceptance Flag variable (TRACPTFL) identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.

4. The Evaluator Specified variable (TREVALID) is used in conjunction with TREVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the TREVAL variable. For example TREVAL="INDEPENDENT ASSESSOR" and TREVALID="RADIOLOGIST 1". The TREVALID variable is not subject to Controlled Terminology. TREVAL must also be populated when TREVALID is populated.

Reference ID: 3444185

RESPONSE – RS

rs.xpt, Response - Findings, Version 3..*x.x* ..... One record per response assessment per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	RS	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App.C2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
RSSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
RSGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
RSREFID	Reference ID	Char		Identifier	Internal or external identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
RSSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4
RSLINKID	Link ID	Char		Identifier	Used to link the response assessment to the appropriate measurement records (in TR) used to determine the response result.	Perm	
RSTESTCD	Response Assessment Short Name	Char	*	Topic	Short name of the TEST in RSTEST. RSTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: TRGRESP, BESTRESP, SYMPTPD	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
RSTEST	Response Assessment Name	Char	*	Synonym Qualifier	Verbatim name of the response assessment. The value in RSTEST cannot be longer than 40 characters. Examples: Target Response, Best Overall Response, Symptomatic deterioration	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
RSCAT	Category for Response Assessment	Char		Grouping Qualifier	Used to categorize tumors.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Reference 3199869

Reference ID: 3444185

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
RSSCAT	Sub-Category for Response Assessment	Char		Grouping Qualifier	A further classification of the RSTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
RSORRES	Response Assessment Original Result	Char		Result Qualifier	Result of the Response assessment as originally received, collected, or calculated.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
RSSTRESC	Response Assessment Result in Std Format	Char		Record Qualifier	Contains the result value for the response assessment, copied or derived from RSORRES in a standard format or standard units. RSSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in RSSTRESN	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
RSSTAT	Response Assessment Status	Char	(ND)	Result Qualifier	Used to indicate the response assessment was not performed. Should be Null if a result exists in RSORRES.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
RSREASND	Reason Response Assessment Not Performed	Char		Record Qualifier	Describes why a response assessment was not performed. Examples: Subject does not have target lesions. Used in conjunction with TRSTAT when value is NOT DONE.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
RSNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the response assessment.	Perm	SDTM 2.2.3
RSEVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST This column can be left *Null* when the Investigator provides the complete set of data in the domain. However the column should contain no *Null* values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.4

Reference ID: 3199869

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
RSEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with RSEVAL to provide an additional level of detail. When multiple assessors play the role identified in RSEVAL, values of RSEVALID will attribute a row of data to a particular assessor. RSEVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The RSEVALID variable would not be subject to CDISC Controlled Terminology. See Assumption 5	Perm	
RSACPTFL	Accepted Record Flag	Char		Record Qualifier	In cases where more than one independent assessor (e.g. independent Oncologist) provides an evaluation of response this flag identifies the record that is considered to be the accepted evaluation.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
RSDTC	Date/Time of Response Assessment	Char	ISO 8601	Timing	Date may be derived if based on multiple dates of scans Exception: derived data in RS needed for reviewer	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
RSDY	Study Day of Response Assessment	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. May be from rand date not first dose date 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.3. ASSUMPTIONS FOR THE TUMOR RESPONSE DOMAIN MODEL

RS Definition: The RS domain represents the response evaluation determined from the data in TR. Data from other sources (in other SDTM domains) might also be used in an assessment of response for example, MacDonald Response Criteria includes a neurological aspect.

1. The RSLINKID variable is used for values that support a relrec dataset to dataset relationship. RSLINKID would be required when a response evaluation relates back to an individual tumor.

2. RSTESTCD / RSTEST values for this domain(this is for illustration purposes these values will be published as Controlled Terminology):

RSTESTCD	RSTEST	Definition
TRGRESP	Target Response	
NTRGRESP	Non-target Response	
OVRLRESP	Overall Response	
BESTRESP	Best Response	
LESNRESP	Lesion Response	
SYMPTPD	Symptomatic Deterioration	

3. When an evaluation of Symptomatic Deterioration is recorded (which is symptomatic of progressive Disease) and additional description of the clinical symptoms is collected then that information would be recorded in the following Supplemental Qualifier:

QNAM	QLABEL	Definition
CLSYMP	Clinical Symptoms of PD	Textual description of clinical symptoms that led to the evaluation of Symptomatic deterioration

4. ***TS – TSPARM/TSVAL needed to represent the Response Criteria used in the clinical trial.***

5. The Evaluator Specified variable (RSEVALID) is used in conjunction with RSEVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the RSEVAL variable. For example RSEVAL="INDEPENDENT ASSESSOR" and RSEVALID="RADIOLOGIST 1". The RSEVALID variable is not subject to Controlled Terminology. RSEVAL must also be populated when RSEVALID is populated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: September 26, 2012

From: Norma S. Griffin, Regulatory Health Project Manager – CDER/OHOP/DOP2

Subject: IND 113557 (GSK) - Memo to File - Meeting Summary of 9.26.2012 Sponsor Teleconference –Follow Up to Question 2 of 9/12/2012 Type B pre-NDA Meeting with Clinical Pharmacology

FDA Participants
Patricia Keegan - Director
Suzanne Demko – Acting Clinical Team Leader
Hong Zhao – Clinical Pharmacology Team Leader
Jian Wang – Clinical Pharmacology Reviewer
Meredith Libeg – Regulatory Health Project Manager
Norma Griffin - Regulatory Health Project Manager

GSK Participants

Jeff Legos	Development Leader (dabrafenib)
Eric Richards, M.S.,M.PH.	Regulatory
Jennifer Dudinak Pharm D.	Regulatory
Amita Chaudhari, M.S.	Regulatory
Kiran Patel, M.D., M.B.A.	Clinical
Michael Streit, M.D., M.B.A.	Clinical
Rafael Amado, M.D.	Clinical
Daniele Ouellet, PhD.	Clinical Pharmacology
Alka Joshi, PhD.	Statistics
Giselle Limentani	CMC

Background: A teleconference (TCON) was held with GlaxoSmithKline (GSK) on September 26, 2012 (3:00 pm ET). The purpose of this TCON was a follow up to Question 2 of the September 12, 2012 pre-NDA meeting to discuss the need for a formal bioequivalent study – see Question 2 and the first Action Item (4.a) of the 9/12/2012 pre-NDA Meeting Minutes. Clinical Pharmacology was the team lead for this meeting.

On Monday, September 24, 2012, GSK submitted a meeting briefing document with supporting information to be used for discussion in the September 26, 2012 teleconference.

The topic of discussion for this TCON is Question 2 from the pre-NDA meeting of 9/12/2012. The following information on Question 2 is taken from the September 12, 2012 meeting minutes:

> **Question 2 - GSK believes the data from BRF113220, as well as data from dabrafenib mono-therapy studies, supports the conclusion that the change in capsule likely has little clinical relevance and does not negatively impact the generalizability of the results from Part B and Part C of BRF113220. Therefore, GSK proposes that, pending full review of Part D of BRF113220 (which used the HPMC capsule), the data from Part C of BRF113220 that used the gelatin capsule can be utilized as pivotal data to support filing the combination of dabrafenib and trametinib. Does the Agency agree?**
>
> **FDA Response:** No. A formal bioequivalent study should be conducted to establish the bioequivalence between the to-be-marketed HPMC formulation and the gelatin formulation used in the registration trial (Part C of BRF113220). If the gelatin capsule and HPMC capsule are not bioequivalent, and HMPC capsule has higher exposure than gelatin capsules observed in the monotherapy studies, GSK will need to address the safety concern with regard to the HPMC capsule formulation.
>
> **Discussion During Meeting on 9/12/2012:** FDA stated that the appropriate staff was not available; therefore, FDA will setup a separate teleconference to discuss this issue. FDA stated that the need and timing for submission of the requested bioequivalence study should be addressed during this teleconference. GSK stated that available data shows that the two dabrafenib formulations (gelatin and HPMC capsule) are not bioequivalent with higher exposure in patients receiving HPMC capsules. GSK will provide relevant data prior to the teleconference with FDA's clinical pharmacology staff.

Discussion During Teleconference on 9/26/2012: FDA and GSK agreed this greater exposure would not alter conclusions regarding product efficacy, but raise concerns about the tolerability of the proposed recommended dose of dabrafenib when administered in combination with trametinib. GSK agreed to include available safety data from part D of study BRF113220, in which 25% of the 54 patients will have been exposed for up to 6 months, in the NDA at time of submission. GSK agreed to provide additional safety information in support of the proposed recommended dose for the HPMC capsule in the 120-day safety update consisting of:

- Updated safety data from the 54 patients enrolled in part D of study BRF113220 to include safety data for at least 6 months of exposure in all 54 patients.
- The interim, high level, blinded safety results from both treatment arms of the MEK115306 study, as generated by the independent safety monitoring committee during the next planned meeting.

GSK acknowledged that the to-be-marketed HPMC capsules are not bioequivalent to gelatin capsules, with higher exposure observed in a bioequivalence study. As discussed during the 9/12/2012 meeting, the clinical impact of the higher exposure with HPMC capsules on safety parameters needs to be addressed.

GSK agreed with FDA in that the data collected in the combination trials is not adequate to demonstrate bioequivalence between the to-be-marketed product and the clinical trial product. Therefore, FDA reiterated that GSK should provide additional safety data for the to-be-marketed product given the higher exposure observed with this product..

GSK acknowledged and agreed with FDA's statements/request.
The teleconference concluded at approximately 3:15 pm ET.

Reference

- IND 113557 GSK Briefing Document (SDN 042) (GSK Serial Number 0039)

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

/s/

NORMA S GRIFFIN
10/05/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 113557

MEETING MINUTES

GlaxoSmithKline, LLC
Attention: Ellen Cutler
Global Regulatory Affairs
1250 South Collegeville Road
UP4110
Collegeville, PA 19426

Dear Ms. Cutler:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "trametinib (GSK1120212) and dabrafenib (GSK2118436)."

We also refer to the teleconference between representatives of your firm and the FDA on May 15, 2012. The purpose of the meeting was to discuss your proposed combination development of trametinib (GSK1120212) and dabrafenib (GSK2118436) for adjuvant treatment of (b) (4)

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-7255.

Sincerely,

{See appended electronic signature page}

Norma Griffin
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	May 15, 2012
TIME:	2:00-3:00 PM (ET)
APPLICATION:	IND 113557
SPONSOR:	GlaxoSmithKline LLC (GSK)
DRUG NAME:	Dabrafenib (GSK2118436) and Trametinib (GSK1120212)
TYPE OF MEETING:	Teleconference; Type B EOP2/Pre-Phase 3
MEETING CHAIR:	Joseph Gootenberg
MEETING RECORDER:	Norma Griffin

LIST OF FDA ATTENDEES

CDER

Patricia Keegan, M.D.	Director, DOP2/OHOP
Joseph Gootenberg, M.D.	Deputy Director, DOP2/OHOP
Marc Theoret, M.D.	Clinical Reviewer, DOP2/OHOP
Norma Griffin	Regulatory Health Project Manager, DOP2/OHOP
Kun He, Ph.D.	Statistical Team Leader, DBV5/OB
Anthony Murgo, M.D.	Associate Director for Regulatory Science, OHOP
Gregory Reaman, M.D.	Associate Director for Oncology Sciences, OHOP
Toyotaka Iguchi	Visiting Fellow

CDRH

Donna Roscoe, Ph.D.	Scientific Reviewer, DIHD/OIVD

LIST OF SPONSOR ATTENDEES

Vicki Goodman, M.D.	Clinical Development
Mark Cornfeld, M.D., M.P.H.	Clinical Development
Mary Guckert	Clinical Development
Jeff Legos, Ph.D., M.P.H.	Clinical Development
Kiran Patel, M.D., M.B.A.	Clinical Development
Steve Lane, Ph.D.	Biostatistics
Alka Joshi	Biostatistics
Jennifer Dudinak, Pharm.D.	Regulatory Affairs
Eric Richards, M.S., M.P.H.	Regulatory Affairs
Ellen Cutler	Regulatory Affairs

1.0 MEETING OBJECTIVES

To discuss proposed combination development of dabrafenib (GSK2118436) and trametinib (GSK1120212) for adjuvant treatment of [redacted] (b) (4)

2.0 BACKGROUND

Dabrafenib (GSK2118436) is a selective inhibitor of BRAF kinase activity and trametinib (GSK1120212) is a selective inhibitor of MEK1/MEK2 activation and kinase activity. GSK currently has both agents under development (INDs 105032 and 102175) as mono-therapy and in combination (IND 113557) for the treatment of [redacted] (b) (4) GSK plans to file New Drug Applications (NDA) for dabrafenib monotherapy in July 2012 and for trametinib as monotherapy or as combination therapy with dabrafenib in the fourth quarter of 2012. An *in-vitro* companion diagnostic test for a premarket approval (PMA) application to select subjects with BRAF mutations will be submitted in coordination with the drug marketing applications.

At a pre-IND/End-of-Phase 2 (Pre-IND 113557) meeting on January 27, 2012, GSK discussed a proposed development program for the combination of dabrafenib and trametinib for the treatment of BRAF mutation-positive unresectable or metastatic melanoma which included an ongoing randomized Phase II study (BRF113220) and two proposed randomized Phase III studies (MEK115306 and MEK116513). FDA advised GSK to schedule a separate meeting to discuss development of the trametinib and dabrafenib combination for the adjuvant treatment of melanoma.

The development program of the trametinib and dabrafenib combination for the treatment of patients with BRAF mutation-positive melanoma includes the following clinical studies:

Reference ID: 3131713

Reference ID: 3444185

Study/Status	Design	N[a]	Patient Population	Primary Endpoint(s)
BRF113220 (Ongoing)	Part A: Drug-Drug Interaction	8	Subjects with BRAF V600E/K/D mutation-positive melanoma or other tumor type	PK
	Part B: Dose Escalation	133	Subjects with BRAF V600E/K/D mutation-positive melanoma or other tumor type	Safety
	Part C: Randomized Phase 2	162	Subjects with BRAF V600E/K/D mutation-positive melanoma	ORR, DOR PFS, Safety
	Part D: Randomized Dabrafenib HPMC	82[a]	Subjects with BRAF V600E/K mutation-positive melanoma	PK, Safety
MEK115306 (Planned)	Phase 3, two-arm, randomized, double-blinded	340	Subjects with unresectable or metastatic (Stage IIIC or IV) BRAF V600E/K mutation-positive melanoma	PFS
MEK116513 (Planned)	Phase 3, two-arm, open-label, randomized	640	Subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive melanoma	OS
BRF115532 (Proposed)	Phase 3, two-arm, double-blinded, randomized	852	Subjects with Stage III, surgically resected BRAF V600E/K mutation-positive melanoma	RFS

Source: Type B/EOP2 Meeting Briefing Document submitted to IND 113,557 on April 12, 2012
PK, pharmacokinetics; ORR, objective response rate; DOR, duration of response; PFS, progression-free survival; OS, overall survival
[a] enrollment ongoing

Reference ID: 3131713

Reference ID: 3444185

BRF113220

This is an ongoing study titled "An Open-Label, Dose-Escalation, Phase I/II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of the BRAF Inhibitor GSK2118436 in Combination with the MEK Inhibitor GSK1120212 in Subjects with BRAF Mutant Metastatic Melanoma." The study consists of four parts:

- Part A: to investigate the effect of repeat doses of trametinib on the pharmacokinetics of single dose dabrafenib
- Part B: to identify the range of tolerated dose combinations using a dose-escalation procedure
- Part C: to evaluate dose combinations of dabrafenib and trametinib based on results from the dose escalation cohorts
- Part D: to evaluate the pharmacokinetics and safety of dabrafenib administered as HPMC capsules alone and in combination with trametinib

Part C as amended is an open-label, randomized (1:1:1), three-arm trial in 162 patients with BRAF-mutation-positive advanced unresectable or metastatic melanoma (i.e., V600E, V600K, or V600D) comparing dabrafenib (gelatin) administered at 150 mg BID alone or in combination with two different doses of trametinib (1 mg QD and 2 mg QD). The primary objectives of Part C of the trial are: (1) to determine the clinical activity of dabrafenib and trametinib by assessing the response rate (RR), duration of response (DOR), and progression-free survival (PFS) and (2) to determine the safety, tolerability, and range of tolerated doses of dabrafenib and trametinib dosed in combination. Secondary objectives are to characterize the population PK parameters and to assess clinical activity as determined by overall survival (OS).

The following Table shows the RR for those patients enrolled in Part C who have undergone at least two consecutive tumor assessments as well as the interim PFS results by treatment arm:

	Dabrafenib 150 mg BID / Trametinib QD		
	150 mg/0 (N=47)	**150/ 1 (N=50)**	**150/ 2 (N=49)**
Best Confirmed RR			
Response Rate, n (%) (95% CI)	23 (49%) (34.1%, 63.9%)	22 (44%) (30.0%, 58.7%)	37 (76%) (61.1%, 86.7%)
CR, n (%)	0	1 (2%)	3 (6%)
PR, n (%)	23 (49%)	21 (42%)	34 (69%)
PFS			
Events, n	25	18	12
Median, months (95% CI)	5.6 (3.9, 5.8)	7.2 (5.6, 7.3)	NR
HR (versus dabrafenib alone) (95% CI)	-	0.70 (0.39,1.28)	0.33 (0.17,0.63)

NR, not reached

Reference ID: 3131713

Reference ID: 3444185

MEK115306

On February 16, 2012, GSK submitted (under pre-IND 113557) study MEK115306 titled, "A Phase III, randomized, double-blinded study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to dabrafenib and placebo as first-line therapy in subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma" for Special Protocol Assessment (SPA) by FDA. Based on FDA advice provided in a teleconference held with GSK on April 2, 2012, and provided in an Advice/Information Request email communication issued to GSK on April 6, 2012, GSK submitted a revised reporting and analysis plan on April 4, 2012, and revised protocol MEK115306 on April 24, 2012, respectively. FDA expects to issue correspondence regarding the SPA for Protocol MEK115306 in the very near future.

MEK115306 is a two-arm, double-blinded, randomized (1:1), Phase III study comparing dabrafenib and trametinib combination therapy to dabrafenib administered with a trametinib placebo (dabrafenib monotherapy) in 340 patients with histologically confirmed cutaneous melanoma that is either unresectable or metastatic (Stages IIIC or IV), and BRAF V600E/K mutation-positive as determined by testing at a central laboratory. Patients randomized to the experimental arm will receive dabrafenib 150 mg orally twice daily continuously and trametinib 2 mg orally once daily continuously. Patients randomized to the control arm will receive dabrafenib 150 mg orally twice daily continuously and trametinib placebo orally once daily continuously. Patients in both arms will continue treatment until disease progression, death, unacceptable toxicity, or withdrawal of consent. Crossover is not permitted.

The primary endpoint of the trial is PFS as assessed by the investigator. Secondary objectives are OS (key secondary endpoint), overall response rate (ORR), and DOR. The study will have 90% power to detect a 70% improvement in OS (HR = 0.5889) in patients treated with combination therapy (assumed median PFS = 9 months) compared with patients treated with dabrafenib monotherapy (assumed median PFS = 5.3 months). The protocol specifies that no interim analyses will be performed for efficacy or futility. The final analysis for PFS will be performed when a total of 155 events have occurred. One interim analysis for OS is planned at the time of the final PFS analysis; the final OS analysis is planned after observation of approximately 70% of the total enrolled population has died or been lost to follow-up (n=220 deaths assuming a 5% lost to follow-up rate).

MEK116513

In the original IND submission on March 29, 2012, GSK requested a waiver of the 30-day review period and submitted a new protocol, MEK116513, titled "A phase III, randomized, open-label study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to the BRAF inhibitor vemurafenib in subjects with unresectable (Stage IIIC) or metastatic (stage IV) BRAF V600E/K mutation-positive cutaneous melanoma." On April 17, 2012, FDA granted the waiver of the 30-day review period for IND 113,557.

Reference ID: 3131713

Reference ID: 3444185

Trial MEK116513, is a two-arm, open-label, randomized (1:1), Phase III study comparing the combination of the dabrafenib and trametinib to single agent vemurafenib as first-line treatment in 694 patients with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma. Patients randomized to the experimental arm will receive dabrafenib 150 mg orally twice daily and trametinib 2 mg orally once daily. Patients randomized to the control arm will receive vemurafenib 960 mg orally twice daily. Patients in both arms will continue treatment until disease progression, death, unacceptable toxicity, or withdrawal of consent. Crossover will not be permitted.

The primary endpoint is OS, and secondary endpoints include PFS, ORR, and DOR. The study will have 90% power to detect a 50% improvement in OS (HR = 0.675) in patients treated with combination therapy (assumed median OS = 20 months) compared with patients treated with vemurafenib (assumed median OS = 13.5 months). The final analysis for OS will be performed when a total of 288 deaths have occurred. One interim analysis for futility and efficacy is planned after observation of approximately 70% of the total number of deaths required for the final analysis.

BRF115532

The purpose of this new meeting is to discuss a Phase 3 randomized double-blinded study to evaluate the dabrafenib (GSK2118436) plus trametinib (GSK1120212) combination as an adjuvant treatment of Stage III (b) (4)

GSK proposes to conduct a multinational, two-arm, randomized (1:1), double-blinded, Phase 3 study of dabrafenib in combination with trametinib versus placebo in 852 patients with Stage III, BRAF V600E/K mutation-positive melanoma that has been completely resected. The primary objective of the study is to demonstrate the clinical efficacy in terms of prolongation of relapse-free survival (RFS) of dabrafenib and trametinib as a combination therapy compared to placebo. Secondary objectives are to compare OS of dabrafenib/trametinib combination therapy to placebo, to compare distant metastasis-free survival (DMFS), freedom from relapse (FFR), and to evaluate the safety of this regimen in the overall study population.

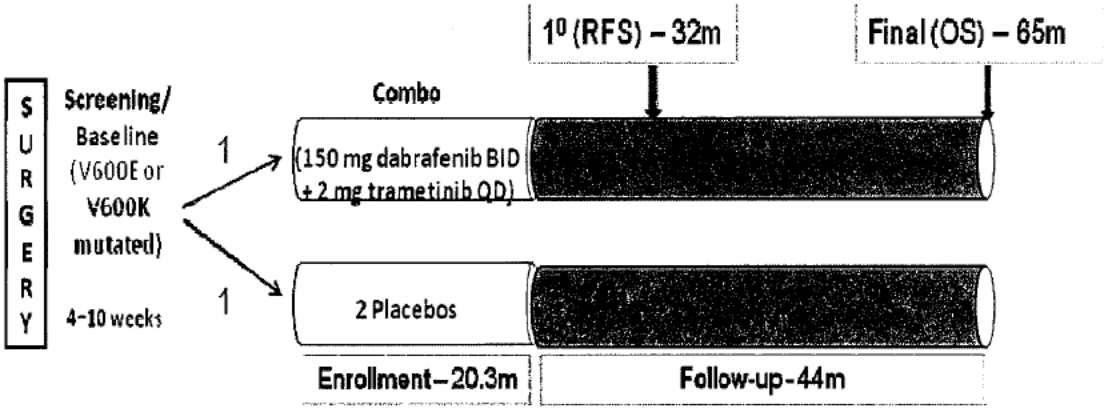
Key eligibility criteria include the following:

- histologically confirmed cutaneous melanoma that is determined to be BRAF V600E/K mutation-positive by central laboratory using an Investigational Use Only (IUO) assay under bioMerieux Investigational Device Exemption (IDE) G12001
- Stage IIIA (if >1 mm in diameter), IIIB, or IIIC disease
- complete surgical resection performed no longer than 10 weeks prior to randomization
- absence of in-transit metastases
- no evidence of distant metastatic disease on screening evaluation
- no prior systemic anti-cancer treatment or radiotherapy administered for melanoma.

Reference ID: 3131713

Reference ID: 3444185

Randomization will be stratified by type of mutation ($BRAF^{V600E}$ or $BRAF^{V600K}$) and disease stage (IIIA, IIIB, or IIIC). Patients randomized to the experimental arm will receive dabrafenib 150 mg twice daily plus trametinib 2 mg once daily continuously for 12 months. Patients randomized to the control arm will receive matched placebo. The proposed study schematic is shown in the following Figure:



Patients will be followed by clinical examination every month while on treatment and every 3 months thereafter. Imaging evaluations will be performed every 3 months for the first 2 years and every 6 months thereafter until progression or withdrawal from study.

The proposed primary endpoint is RFS and is defined as the time from randomization to disease recurrence or death from any cause. The proposed definition of RFS does not include the occurrence of any second primary malignancies, including melanoma, as RFS events. The proposed sample size will allow detection of a hazard ratio of 0.7143 (median RFS time of 15 and 21 months in the placebo arm and the combination therapy arm, respectively) with >90% power and a two-sided alpha of 5% based on a 20 month enrollment and 12 month follow-up period. The final analysis of RFS will be performed when a total of 467 events (relapses or deaths) have occurred. With 467 RFS events, it will be possible to detect a statistically significant improvement as low as 19.3% (HR = 0.833) which equates to a median RFS of 15 and 17.9 months in the placebo arm and the combination therapy arm, respectively.

All randomized subjects will be included in the analyses to test the hypotheses of interest regardless of length of follow-up or whether or not study treatment was administered (i.e., subjects will not be replaced). At the time of the primary analysis of RFS, all secondary endpoints will also be summarized. OS is a key secondary endpoint of the trial. Assuming an OS hazard ratio of 0.77 which corresponds to an 18 month improvement in median OS, 372 events will be required for 70% power. GSK estimates that 171 OS events will have occurred by the time of the primary analysis of RFS. Patients will be followed until 70 percent of the expected deaths have occurred, at which time an OS analysis will be performed. All statistical tests, unless otherwise specified, will be stratified for treatment and stratification factors.

Preliminary responses were communicated to GSK on Friday, May 11, 2012

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3.0 DISCUSSION

SPONSOR SUBMITTED QUESTIONS AND FDA RESPONSE:

Clinical

1. **Does the Agency agree there are sufficient safety data and evidence of clinical activity as well as a valid scientific rationale to support proceeding with a phase 3 study in the proposed high-risk (Stage IIIA≥1mm, IIIB, IIIC) adjuvant melanoma population?**

   FDA Response: FDA agrees with GSK's proposal to evaluate the trametinib plus dabrafenib combination as adjuvant therapy in a high-risk melanoma population based on the information provided.

   GSK Email Response of 5/14/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

2. **Does the Agency agree with the following design aspects of the proposed study?**

   a. **Placebo comparator as there is no generally accepted standard of care.**

      FDA Response: The proposed placebo-controlled design is acceptable. Please note that the relative effect of the trametinib plus dabrafenib combination compared to standard interferon or an alternative, potentially active comparator will not be addressed by this trial.
      GSK Email Response of 5/14/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

   b. **Dose rationale supporting dabrafenib 150 mg orally twice daily and trametinib 2 mg orally daily.**

      FDA Response: Yes. The dose rationale supporting dabrafenib 150 mg orally twice daily and trametinib 2 mg orally daily appears acceptable.

      GSK Email Response of 5/14/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

   c. **The proposed 12-month duration of treatment.**

      FDA Response: The rationale for the proposed duration of treatment based on the period for highest risk for relapse appears appropriate. However, there is insufficient information at the present time to determine whether the treatment strategy is reasonably safe. FDA agrees that a DMC should monitor this study in real time for safety. In addition, please note that the optimal duration of treatment with the trametinib plus dabrafenib combination will not be addressed by the proposed trial.

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GSK Email Response of 5/14/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

d. The primary endpoint of relapse-free survival (RFS) and the definition and assessment of RFS.

FDA Response: A primary endpoint of RFS is acceptable. However, any documented recurrence of melanoma, including cutaneous lesions believed to be a second primary rather than a cutaneous metastasis, must be considered an RFS-defining event.

GSK Email Response of 5/14/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

e. The statistical analysis plan to support clinical benefit of the proposed RFS endpoint.

FDA Response: The statistical analysis plan does not contain adequate detail to address this question. Based on FDA's review, the study does not contain adequate power to detect a clinically meaningful effect on overall survival. In addition:

1) Please provide the estimated OS median time for the placebo arm.
2) Please provide the percentage of subjects to be enrolled in the US.

GSK Email Response of 5/14/2012: GSK would like to discuss Question 2e.

Discussion During Meeting of 5/15/2012: GSK stated that they will conduct an evaluation of survival at the time of final RFS analysis and provide descriptive information in the NDA supplement with a plan to a conduct definitive analysis of overall survival at 597 deaths which should provide 78% power to detect an increase in median OS from 48 months in the control arm to 60 months in the experimental arm. This will be clearly stated in the protocol and statistical analysis plan to be submitted to the IND. FDA stated that this is acceptable.

GSK clarified that an estimated 15% of patients will be enrolled in the U.S. FDA acknowledged the response.

Does the Agency have any further comments regarding the study design?

FDA Response: FDA has the following additional comments regarding the study design:

- Please be advised that the secondary endpoint, distant metastasis-free survival (DMFS) is not a recognized regulatory endpoint to serve as a supportive evidence of a robust treatment effect.
- Consider adding ophthalmologic examinations to list of safety measurements as listed in the secondary endpoint.

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- Include sparse pharmacokinetic sample collection in the proposed trial BRF115532 to explore exposure-response (measures of effectiveness, biomarkers and toxicity) relationships for the combination use of dabrafenib and trametinib in the targeted patient population. For more information, refer to Guidance for Industry found at

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf and

  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf.

GSK Email Response of 5/14/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

3. **Does the Agency agree that the contribution of each individual agent to the combination would be provided by the planned phase 3 study of the combination vs. dabrafenib in the metastatic setting (MEK115306) with support from the phase 2 combination study (BRF113220) and the nonclinical and comprehensive monotherapy development programs?**

FDA Response: In the absence of the results from each study, FDA is unable to determine the adequacy of trials MEK115306 and BRF113220 to demonstrate the contribution of trametinib to the combination of trametinib plus dabrafenib treatment. Please note that neither trial is sufficiently designed to demonstrate the contribution of dabrafenib to the combination. Therefore in a future NDA submission, GSK should discuss the role of the clinical studies in the metastatic/unresectable setting and the nonclinical program to demonstrate the contribution of each component to the effect of combination therapy.

Please also refer to the FDA response to Question # 2 as well as the discussion of this question during the Pre-IND meeting for IND 113,557 held on January 27, 2012.

GSK Email Response of 5/14/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

4. **Does the Agency agree with the overall registration plan to support a supplemental marketing application for dabrafenib and trametinib used in combination for the adjuvant treatment of Stage III patients with (b) (4) ?**

FDA Response: The overall registration plan to support supplemental marketing applications for dabrafenib and trametinib used in combination for the adjuvant treatment of Stage III melanoma patients is acceptable. Please also see FDA response to Question 3.

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GSK Email Response of 5/14/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

Regulatory

5. **Does the Agency support proceeding with a Special Protocol Assessment (SPA) for the proposed registration-directed study with the condition that results from BRF115306 demonstrate the relative contribution of trametinib to the combination in the metastatic setting?**

FDA Response: Yes. To permit an adequate evaluation of the protocol, please also include all case report forms pertaining to safety in addition to the other content generally included in the submission of an SPA request. Please refer to the FDA "Guidance for Industry: Special Protocol Assessment" which can accessed at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080571.pdf.

GSK Email Response of 5/14/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

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/s/

NORMA S GRIFFIN
05/16/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 113557

MEETING MINUTES

GlaxoSmithKline LLC
Attention: Ellen Cutler
Global Regulatory Affairs
1250 South Collegeville Road
UP4110
Collegeville, PA 19426

Dear Ms. Cutler:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for "GSK1120212 and GSK2118436."

We also refer to the meeting between representatives of your firm and the FDA on January 27, 2012. The purpose of the meeting was to discuss proposed combination development of the above investigational agents for treatment (b) (4)

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Erik Laughner, Senior Regulatory Health Project Manager at (301) 796-1393.

Sincerely,

{See appended electronic signature page}

Norma Griffin
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	January 27, 2012
TIME:	2:30-3:30 PM ET
APPLICATION:	Pre-IND 113557
SPONSOR:	GlaxoSmithKline LLC (GSK)
DRUG NAME:	Dabrafenib (GSK2118436) and Trametinib (GSK1120212)
TYPE OF MEETING:	Face-to-Face; Type B; Pre-Phase 3
MEETING CHAIR:	Joseph Gootenberg
MEETING RECORDER:	Norma Griffin

LIST OF FDA ATTENDEES:

CDER

Richard Pazdur, M.D.	Director, OHOP
Anthony Murgo, M.D.	Associate Director for Regulatory Science, OHOP
Patricia Keegan, M.D.	Director, DOP2/OHOP
Marc Theoret, M.D.	Clinical Reviewer, DOP2/OHOP
Joseph Gootenberg, M.D.	Deputy Director DOP2/OHOP
Norma Griffin	Regulatory Health Project Manager, DOP2/OHOP
Andrew McDougal, Ph.D.	Acting Team Leader, DHOT/OHOP
Margaret Brower, Ph.D.	Toxicology Reviewer, DHOT/OHOP
Jian Wang	Clinical Pharmacology, DCP5/OCP/OTS
Lillian Zhang, Ph.D.	Clinical Pharmacology Reviewer, DCP5/OCP/OTS
Weishi (Vivian) Yuan, Ph.D.	Statistical Reviewer, DBV5/OB
Kun He, Ph.D.	Statistical Team Leader, DBV5/OB

CDRH

Donna Roscoe, Ph.D.	Scientific Reviewer, DIHD/OIVD

LIST OF SPONSOR ATTENDEES:

Rafael Amado, M.D.	Clinical Development
Kiran Patel, M.D., M.B.A.	Clinical Development
Vicki Goodman, M.D.	Clinical Development
Mark Cornfield, M.D.	Clinical Development
Michael Streit, M.D., M.B.A.	Clinical Development
Jeff Legos, Ph.D.	Clinical Development
Doug DeMarini, Ph.D.	Clinical Development
Daniele Ouellet, Ph.D.	CPMS
Steve Lane, M.S.	Biostatistics
Anne-Marie Martin, Ph.D.	Oncology Biomarkers
Jennifer Dudinak, Pharm D.	Regulatory Affairs
Eric Richards, M.S., M.P.H.	Regulatory Affairs
Ellen Cutler	Regulatory Affairs
Angela Hughes-Earle, Ph.D.	Preclinical safety assessment (by phone)
Kevin French, Ph.D.	Preclinical safety assessment (by phone)
Ben Stockham	Regulatory Affairs (by phone)
Caroline Pothet, Pharm D.	Regulatory Affairs (by phone)

1.0 MEETING OBJECTIVES:

To discuss the proposed development of the combination of two investigational products, dabrafenib (GSK2118436) and trametinib (GSK1120212), for the proposed indication "for the treatment of BRAF V600 E/K mutation positive unresectable or metastatic melanoma."

2.0 BACKGROUND:

On October 11, 2011, GSK requested a Pre-IND/Pre-Phase 3 meeting with FDA to discuss proposed combination development of the above investigational agents for treatment (b) (4)

Dabrafenib (GSK2118436) is a selective inhibitor of B-RAF kinase activity and trametinib (GSK1120212) is a selective inhibitor of MEK1/MEK2 activation and kinase activity. GSK currently has both agents under development (INDs 105032 and 102175) as monotherapy and in combination for the treatment (b) (4) GSK has partnered with bioMerieux in the co-development of an *in vitro* companion diagnostic test for an eventual PMA application for selection of patients with BRAF mutations for enrollment in trials of dabrafenib as monotherapy or in combination with other agents.

GSK has proposed a development program for the combination of dabrafenib and trametinib for the treatment of BRAF mutation-positive, unresectable or metastatic melanoma which includes an ongoing randomized activity-estimating trial (BRF113220) and two proposed randomized trials (MEK115306 and MEK116513). FDA held a Type B meeting with GSK on February 24,

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2011, to discuss the design of the proposed trial MEK115306. GSK proposed a three-arm study (single agent dabafenib, single agent trametanib, and the combination of both drugs) with a co-primary endpoint of progression-free survival (PFS) and overall survival (OS). FDA stated that the three-arm study design appeared acceptable provided that dabrafenib demonstrated high single agent activity in other studies. FDA further stated that a response rate in the activity-estimating trial (BRF113370) of single agent dabrafenib should show a response rate of at least 50% to demonstrate "high single agent activity" but a conclusion of demonstration of sufficient activity will be a review issue. FDA did not agree with the proposed co-primary endpoints of PFS and OS and stated that OS should be the sole primary endpoint and that the magnitude of the effect must be clinically robust in order to support approval of the combination of the two drugs. GSK agreed to OS as the sole primary endpoint.

BRF113220

This is an ongoing study entitled "An Open-Label, Dose-Escalation, Phase I/II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Clinical Activity of the BRAF Inhibitor GSK2118436 in Combination with the MEK Inhibitor GSK1120212 in Subjects with BRAF Mutant Metastatic Melanoma." The initial protocol was submitted in January of 2010 (protocol submitted to both IND 105302 and IND 102175). There have been subsequent amendments which have resulted in the study now consisting of four parts:

- Part A: to investigate the effect of repeat doses of trametinib on the pharmacokinetics of single dose dabrafenib
- Part B: to identify the range of tolerated dose combinations using a dose-escalation procedure
- Part C: to evaluate dose combinations of dabrafenib and trametinib based on results from the dose escalation cohorts
- Part D: to evaluate the pharmacokinetics and safety of dabrafenib administered as HPMC capsules alone and in combination with trametinib

Part C as amended is an open-label, randomized, three-arm trial of dabrafenib (gelatin) administered at 150 mg BID alone or in combination with two different doses of trametinib (1 mg QD and 2 mg QD). Key inclusion criteria include (1) BRAF-mutation positive melanoma (i.e., V600E, V600K, or V600D), (2) measurable disease by RECIST, and (3) ECOG performance status of 0 or 1. Key exclusion criteria include (1) prior exposure to BRAF or MEK inhibitors, (2) more than one prior chemotherapy regimen and/or IL-2, (3) active brain metastases, and (4) history of retinal vein occlusion or central serous retinopathy.

The protocol specifies the following primary objectives of PART C of the trial:

- to determine the clinical activity of dabrafenib and trametinib by assessing the response rate (RR), duration of response (DOR), and progression-free survival (PFS)
- to determine the safety, tolerability, and range of tolerated doses of dabrafenib and trametinib dosed in combination.

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Secondary objectives are to characterize the population PK parameters and to assess clinical activity as determined by overall survival.

A total of 162 patients with BRAF mutation-positive (V600E or K) metastatic melanoma who were BRAF inhibitor (BRAFi) naive were randomized across three arms:

- Mono-therapy dose (n=53): dabrafenib 150 mg BID
- Combination dose level 1 (n=54): dabrafenib 150 mg BID; trametinib 1 mg QD
- Combination dose level 2 (n=55): dabrafenib 150 mg BID; trametinib 2 mg QD

Part C of Protocol BRF113220 specified formal hypothesis testing to determine if the incidence rate of squamous cell carcinoma (SCC) is less than with combination therapy (dabrafenib + trametinib) than with dabrafenib monotherapy. The protocol specified a sample size of 50 patients per arm to provide an 82% statistical power to detect an absolute 17% decrease in the incidence of SCC in patients, assuming 20% incidence in the dabrafenib monotherapy arm and 3% pooled incidence in the combination arms. The protocol specified two interim analyses of melanoma tumor response data (amended from response rates) to occur after approximately 75 patients across all three treatment arms had completed at least three post-dose disease assessments (including week 24 assessment) and to occur after all 150 patients had completed at least three post-dose disease assessments (including week 24 assessment). The final analysis for Part C was to be conducted when, for all three treatment arms combined, at least 70% patients had either progressed or died. Response assessment for all patients was performed by the investigator. All scans are collected for the purpose of independent assessment. Patients in the dabrafenib monotherapy arm were allowed to crossover after confirmation of progression per RECIST 1.1 by investigator assessment.

The Internal Data Review Committee performed the first pre-specified interim efficacy analysis on November 8, 2011. The following Table summarizes results reported in the briefing document meeting package and shows the response rates for those patients who have undergone at least 2 consecutive tumor assessments as well as the interim results for PFS by treatment arms in Part C of the study.

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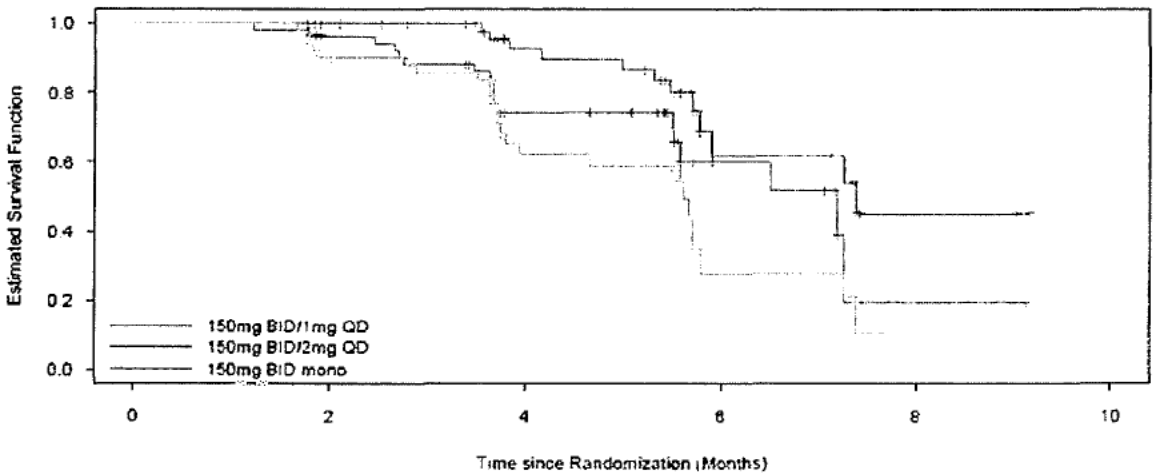
Table 1: Confirmed RR and PFS, Part C, Study BRF113220

	Dose level dabrafenib BID/ trametinib QD		
	150 / 0 Mono (N=47)	150/ 1 Combination (n=50)	150/ 2 Combination (n=49)
Best RR			
CR	0	1 (2%)	3 (6%)
PR	23 (49%)	21 (42%)	34 (69%)
SD	20 (43%)	24 (48%)	12 (24%)
PD	4 (9%)	2 (4%)	0
NE	0	2 (4%)	0
Response Rate (95% CI)	23 (49%) (34.1%, 63.9%)	22 (44%) (30.0%, 58.7%)	37 (76%) (61.1%, 86.7%)
PFS			
Events	25	18	12
Median, months (95% CI)	5.6 (3.9, 5.8)	7.2 (5.6, 7.3)	NR
HR (versus dabrafenib alone) (95% CI)		0.70 (0.39,1.28)	0.33 (0.17,0.63)

The Figure below reproduced from the briefing document shows the Kaplan-Meier curve for PFS. At the time of the PFS analysis, approximately 50% of the patients had only week 8 and/or week 16 follow-up.



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GSK believes that should the mature data from Part C of BRF113220 prove compelling then early registration for the combination in the treatment of BRAF mutation-positive metastatic melanoma may be possible. Based on information provided in the meeting briefing document, GSK believes there is currently a statistically significant improvement in PFS with dabrafenib in combination with 2 mg QD GSK112012 over dabrafenib monotherapy. However, the median progression-free survival for dabrafenib 150 mg BID in combination with trametinib at 2 mg QD arm is yet to be reached. GSK's Internal Data Review Committee has recommended that the study continue as planned without any modification. The final analysis requiring 70% of PFS events is projected to occur in June 2012 with final data expected in the 3rd quarter of 2012. The projected median follow-up time at the time of final analysis will be approximately 15 months. The projected follow-up time will be approximately18.6 months since first patient was enrolled and approximately12 months since the last patient was enrolled in Part C.

MEK115306

This is a planned randomized (1:1), double-blinded trial comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib, to dabrafenib and placebo as first-line treatment in 340 patients with unresectable (Stage IIIc) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma. Patients in the combination therapy arm will receive dabrafenib 150 mg orally twice daily and trametinib 2 mg orally once daily; patients in the dabrafenib monotherapy arm will receive dabrafenib 150 mg orally twice daily and placebo orally once daily. Patients receiving dabrafenib monotherapy will not be permitted to crossover to the combination therapy arm at the time of progression.

The primary endpoint is PFS as determined by investigator assessment. Analyses of PFS based on central review will be performed as a sensitivity analysis. The study will have 90% power to detect a 69.8% improvement in PFS (HR = 0.5889) in patients treated with combination therapy (assumed median PFS = 9 months) compared with patients treated with the dabrafenib monotherapy arm (assumed median PFS = 5.3 months). Secondary endpoints include OS, objective response rate (ORR), and DOR.

The final analysis for PFS will be performed when a total of 155 events have occurred. With 155 events, it will be possible to detect an improvement as low as 37.7% (HR = 0.726 which equates to median PFS times of 7.3 and 5.3 months in the dabrafenib/trametinib combination and dabrafenib monotherapy arms, respectively). The study requires 192 OS events for 80% power to detect an OS HR of 0.667. GSK estimates that the required number of OS events will occur approximately 26 months from the start of the study.

MEK116513

A planned, randomized (1:1), open-label study comparing the combination of the dabrafenib and trametinib to single agent vemurafenib as first-line treatment in 640 patients with unresectable (Stage IIIc) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma. Patients randomized to the experimental arm will receive dabrafenib 150 mg orally twice daily and trametinib 2 mg orally once daily. Patients randomized to the control arm will receive vemurafenib 960 mg orally twice daily. Crossover will not be permitted.

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The primary endpoint is OS, and secondary endpoints include PFS, ORR and DOR. The study will have 90% power to detect a 50% improvement in OS (HR = 0.6667) in patients treated with combination therapy (assumed median OS = 18 months) compared with patients treated with vemurafenib (assumed median OS = 12 months).

The final analysis for OS will be performed when a total of 271 deaths have occurred. An interim analysis of data based on OS will occur once the minimal enrollment target is met and approximately 70% of the total number of deaths have been observed. The O'Brien Flemming boundary method will be utilized for alpha adjustement.

This comparative study is being conducted to support global reimbursement of the combination outside of the US and will provide OS data comparing the combination to the current standard of care for patients BRAF mutation-positive metastatic melanoma; i.e., vemurafenib. If the magnitude of benefit on PFS is not sufficiently robust from BRF113220 and MEK115306, then MEK116513 may provide additional evidence of clinical benefit.

Draft FDA responses were communicated to GSK on January 25, 2012.

3.0 DISCUSSION

SPONSOR SUBMITTED PREAMBLE TO QUESTIONS AND QUESTIONS, AND FDA RESPONSE:

GSK'S CLINICAL QUESTIONS

1. Feasibility of an early file for use of the combination based on mature results for the Phase I/II study BRF113220

BRF113220 is an open-label, dose escalation study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of dabrafenib and trametinib in combination.

This study has four parts, A-D. The four-part design employs a systematic approach to evaluation of the combination of dabrafenib and trametinib. Part C is an ongoing randomized phase II expansion cohort to assess safety and efficacy at different doses based on results from the dose escalation cohorts. A total of 162 subjects were randomized across three arms:

- Combination dose level 1: dabrafenib 150 mg BID; trametinib 2 mg QD
- Combination dose level 2: dabrafenib 150 mg BID; trametinib 1 mg QD
- Mono-therapy dose: dabrafenib 150 mg BID

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Interim efficacy data showed a clinical compelling interim efficacy signal of dabrafenib 150 mg BID in combination with trametinib at 2 mg QD arm relative to dabrafenib mono-therapy. Specifically, the study demonstrates improvements in confirmed Overall Response Rates; including higher Complete Response rates and lower Progressive Disease events with the combination compared to dabrafenib mono-therapy. There is a statistically significant improvement in PFS with dabrafenib in combination with 2 mg QD GSK112012 over dabrafenib mono-therapy. The median progression-free survival for dabrafenib 150 mg BID in combination with trametinib at 2 mg QD arm is yet to be reached. The Internal Data Review Committee recommended continuing the study as planned without any modification.

Should the mature data from this study continue to prove compelling, GSK intends to file based on the results of BRF113220 for the use of the combination for the treatment of BRAF mutation-positive unresectable or metastatic melanoma. Importantly, GSK is committed to completing enrolment of both Phase III studies, MEK115306 (section 4.4.2) and MEK116513 (section 4.4.3), regardless of any potential early file based on mature results from BRF113220. MEK115306 is projected to complete enrolment by Q1-2013 and MEK116513 is projected to completed enrolment by 2H-2013.

Notwithstanding the promising early results from BRF113220, GSK acknowledges that a mature dataset in terms of PFS would be needed to fully ascertain the viability of filing on the data from BRF113220. GSK also acknowledges that Part C of this study, although a randomized Phase II comparison, will pose some difficulty in evaluation due to the study's open-label nature, lack of pre-specified statistical criteria around the efficacy endpoints. Additional trial design and execution factors that would need to be addressed prior to considering submission are as follows:

- GSK has maintained all scans and therefore a blinded independent central review (i.e. IRC review) of the scans can occur.

- Patients for BRF113220 were screened using local testing, not the RGI or the bioMérieux IUO assay. To address this issue, GSK intends to test all patient samples retrospectively with the bioMérieux IUO assay. GSK now possesses ~75% of the samples from this study (60% tissue and 15% DNA) and is in the process of obtaining the majority of samples.

- BRF113220 was conducted using the gelatin capsule of dabrafenib, not the intended to-be-marketed HPMC capsule. As noted during the 5MAY11 teleconference with FDA and summarized in Appendix 1 Section 1.3.3, the HPMC encapsulation resulted in higher exposure compared to the gelatin capsule (LS mean ratios (90% CIs) for AUC(0-∞) of 1.80 (1.32, 2.46)). Results from Part D of Study BRF113220 using HPMC capsules will be used to guide the dose selection for the proposed Phase III studies.

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GSK plans to conduct final PFS analysis of BRF113220 when 70% events have occurred with ~15 months of median follow-up time. It is projected that this number of events will be achieved by approximately June of 2012. Importantly, MEK115306 (PFS study) will be enrolling with a projected enrollment completion in Q1 2013 and MEK116513 (OS study) will also be enrolling with a projected enrolment completion in 2H 2013. Should the mature data from BRF113220 continue to provide compelling evidence of an improvement in durable response and PFS of the combination dabrafenib+trametinib over dabrafenib mono-therapy, GSK believes BRF113220 could warrant an early file for the use of dabrafenib+trametinib used in combination for the treatment of unresectable or metastatic melanoma. Does the Agency agree?

FDA RESPONSE: Although the high-level results from Part C of study BRF113220 are not mature they are interesting. FDA would encourage GSK to arrange an additional meeting with this Office when the data becomes more mature.

FDA agrees with GSK's acknowledgement that interpretation of mature results from Part C of BRF113220 would pose multiple difficulties due to the study's open-label nature and lack of pre-specified statistical criteria around the efficacy endpoints.

Potential sources of bias in the design, conduct, analysis, and interpretation of the results of BRF113220 would need to be identified and adequately addressed at the time of an NDA submission to provide evidence of a treatment effect as well as an estimate of the size of a treatment effect for the dabrafenib/trametinib combination.

Potential sources of bias may include:

- unknown type I error and type II error considerations for any efficacy variable because the pre-specified primary and only hypothesis specified for Part C of the protocol concerned a safety endpoint, the protocol did not include a pre-specified hypothesis regarding efficacy variables
- unidentified primary efficacy endpoint and primary analysis method for assessing this endpoint
- effect of multiple comparisons on the estimate of the size and determination of a treatment effect, e.g., multiple comparisons between treatment arms, multiple efficacy variables, and multiple analyses of the data
- measures taken to minimize bias in the conduct of the trial and assessment of the efficacy parameters
- insufficient description of the process and procedures for examining data, including informal and formal analyses

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Please refer to 21 CFR 314.126, and International Conference on Harmonization (ICH) Guidelines E3 and E9, for further discussion of the principles of adequate and well controlled trials that would need to be satisfied in order for the results from Part C of BRF113220 to serve as the basis of formal proof of efficacy. ICH Guideline E3 may be accessed at
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/Step4/E3_Guideline.pdf
and ICH Guideline E9 may be accessed at
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf.

GSK Email Response of 1/26/2012: To evaluate the robustness of the observed treatment effect, GSK will propose and submit to the agency, several sensitivity analyses for both PFS and overall best response. GSK also notes that should BRF113220 be submitted as primary evidence [redacted] (b) (4), a blinded independent central review (BICR) of scans will need to occur. Subsequent to the 27JAN12 meeting, GSK will provide the following documentation to FDA for comment prior to the undertaking the final analysis:

- Statistical Analysis Plan for
  - The clinical study report, including full documentation of all proposed efficacy analyses.
  - Companion diagnostic.
- Charter for the BICR committee.

Please note: the second interim analysis of this study has been removed; the next analysis of the data will be the final one for PFS and RR.

Topics for Discussion During Meeting of 1/27/2012:

With regard to BRF113220, in order to best prepare for future interactions with the Agency, GSK would like to understand if there are any additional measures that should be taken to address the issues cited above as well as outlined in the briefing document.

A consideration with regard to using BRF113220 as a potential file is the fact that the gelatin capsule form of dabrafenib was used through most of this study, while the proposed commercial capsule for dabrafenib is HPMC. As noted in the briefing document, the HPMC capsule has a higher exposure than the gelatin capsule after single dose with mono-therapy. The following types of data will be available to understand the impact of the HPMC capsule on the combination:

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Study BRF113220:

- Upon availability of the dabrafenib HPMC capsules, new supplies were provided to sites for subjects enrolled in parts B and C of BRF113220; as the change in capsule was not predicted to make a substantial difference in exposure. After discovering the higher exposure with the HPMC capsule dosed as mono-therapy, these patients in BRF113220 were transitioned to the gelatine capsule to maintain the integrity of the study.
- 31 patients in Parts B and C that received 150mg BID BRAF HPMC capsule with 2mg QD MEK starting from the first dosing day for a median of ~2 months. These data can be compared to safety data from 93 patients in Parts B and C receiving 150mg BID BRAF gelatin capsule with 2mg QD MEK from the first dosing day.
- Part D utilizes HPMC capsules and will provide the following data:
  - Serial PK for dabrafenib (HPMC) 75 and 150 mg BID alone and in combination with 2 mg trametinib in a total of 60 subjects including approximately 15 subjects at 150 mg BID dabrafenib and 2 mg QD of trametinib
  - 55 patients from Part D (30 pts from PK cohort and 25 from expansion cohort) that received 150mg BID HPMC BRAF and 2mg QD MEK
  - AE profile for the first 30 pts enrolled will be available with a median follow-up of 6 months (range 3-9 months)

Notably, the key safety finding with the combination, namely pyrexia, is often seen early on (i.e. within 2 months). It also worth noting that the follow dabrafenib mono-therapy studies utilized the HPMC capsule of dabrafenib: BRF113929 (Ph 2, brain metastases); BRF113683 (Ph 3 randomized study against dacarbazine); BRF113928 (Ph 2 NSCLC); BRF114144 Rollover (for those that received HPMC in previous study); BRF113468 (Food Effect/ Relative BA); BRF113771 Drug-Drug Interaction (DDI) Study; BRF113479 (Absolute BA).

Of particular interest to CDRH, GSK is actively pursuing all outstanding patient samples for Part C of BRF113220, and has sent letters to the clinical sites requesting these samples. The table below summarizes the current status of samples secured for Part C of the study:

# Samples Tested by RGI	Invalid Samples (NTI, QNS, SRNT, OODR)	# of Samples with a Test Result	BRAF Result	# Samples Available as Tissue	# Samples Available as DNA	Tissue Availability
139	15	124	96 V600E 26 V600K 2 wt N=124	79 V600E 21 V600K 2 wt N=102	17 V600E 5 V600K 0 wt N=22	162 Enrolled Subjects 124 Available Tissues **76.5% Tissue Availability**

(QNS) quantity not sufficient; (OODR) out of detectable range; (NTI) no tumor identified; (SRNT) sample received not testable

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Once all available samples have been secured, GSK will work with their diagnostic partner bioMerieux (bMx) to perform a retrospective bridging study to establish the BRAF mutation status of the samples using the bMx THxID BRAF IUO Assay under the current IDE (G120011). Concordance between the original BRAF mutation result and the result obtained using the bMx THxID BRAF IUO will be established, and statistical analyses will be performed to establish the relationship of the bMx THxID BRAF mutation result and clinical endpoints (ORR and PFS). All statistical analyses will be outlined in advance in a Statistical Analysis Plan.

GSK would like to have an initial discussion regarding HPMC and the companion diagnostic within the context of BRF113220 potentially serving as an early file. The intent of this conversation is to explore if there is any additional work that should be considered at this point in time.

Discussion during 1/27/2012 Meeting: GSK summarized the number of patients receiving BRF113220 (dabrafenib) as the gelatin capsule form and those receiving it as the HPMC capsule, the proposed form. GSK noted that, based on cross-study PK comparisons, the HPMC caspsue formulation gave a 1.8-fold increase in AUC compared with the same dabrafenib dose in the gelatin capsule formulation.

FDA advised that, in addition to providing safety and efficacy data with the two formulations, GSK provide information on drug interactions between the BRF113220 and MEK 115306for the intended commercial formulation for dabrafenib.

With regard to the proposed assay development for the companion diagnostic for detection of BRAF mutations, GSK stated their intent to submit the PMA in mid-2012. The CDRH review staff advised that the clinical data from the primary trial supporting registration would need to be reviewed as part of the clinical validation of the PMA. Both positive and negative samples from the IUO device should be provided to support the PMA. In addition. multiple sensitivity analyses should be conducted and should demonstrate consistent findings across these multiple analyses.

With regard to the clinical trial results, FDA agreed to meet with GSK at the time of the definitive analysis of the combination trial. FDA stated that an application based on the combination trial should contain information indicating that combination therapy is better than sequential therapy.

Finally, FDA noted that there are deficiencies in the trial design and conduct that undermine confidence in the results and requested a firm understanding that if confirmatory trials are negative, GSK should withdraw the indication if not confirmed.

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2. Rationale for not including a trametinib mono-therapy arm in combination studies

On February 24, 2011 GSK and FDA met to discuss the initial trial design for MEK115306 (see final meeting minutes attached in Appendix 4). It was agreed that a study design in which the combination of dabrafenib and trametinib was compared to dabrafenib single-agent with the primary endpoint of Overall Survival would be acceptable to demonstrate clinical benefit and the relative contribution of trametinib. It was further agreed that the secondary endpoint of PFS comparing the combination of dabrafenib and trametinib compared to single-agent trametinib would be acceptable to demonstrate the relative contribution of dabrafenib.

Since that meeting, significant amounts of data have become available with dabrafenib and trametinib used as mono-therapy for the treatment of BRAF mutation-positive metastatic melanoma. These data provide a much clearer characterization of the safety and efficacy of each drug as mono-therapy and are very informative in understanding the relative contribution each agent will provide. In addition, the results of randomized Phase III studies involving dabrafenib and trametinib as mono-therapy treatments for BRAF V600 mutation positive metastatic melanoma will be available early 2012.

The table below outlines the high-level efficacy data from the Phase II studies of dabrafenib and trametinib monotherapy studies in BRAF V600 unresectable metastatic melanoma. These results are similar to those seen in the mono-therapy Phase I studies of each agent.

Summary of High-Level Results from Monotherapy Studies

b-raf Targeted Agent	Study	Patient Population	N	ORR	Median PFS
dabrafenib	BRF113710	BRAF V600E mutant metastatic melanoma (primary efficacy population)	76	59% (95% CI:48, 70)	6.3 months (95% CI 4.6, 7.6)
trametinib	MEK113583	BRAF V600E mutant metastatic melanoma (subpopulation without brain metastases)	36	28% (95% CI 14, 45)	5.3 months (95% CI 3.6, 7.4)

In addition, vemurafenib was approved by the Agency this year, based primarily on the results of BRIM3: randomized, open-label trial comparing vemurafenib to dacarbazine in patients with previously untreated metastatic or unresectable melanoma with the BRAFV600E mutation. The study demonstrated an improvement in overall survival (HR=0.44; 95% CI: 0.33, 0.59; $p< 0.0001$, log-rank test) as well as an improvement in progression-free survival (HR=0.26; 95% CI: 0.20, 0.33; $p<0.0001$, log-rank test). The median PFS was 5.3 (95% CI: 4.9, 6.6) and 1.6 months (95% CI: 1.6, 1.7) in the vemurafenib and dacarbazine arms, respectively. Overall response rate was 48.4% (95% CI: 41.6%, 55.2%) and 5.5% (95% CI: 2.8%, 9.3%) in the vemurafenib and dacarbazine arms, respectively. As noted in the table above, GSK has observed similar clinical

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activity from dabrafenib in terms of overall response rate and median progression-free survival.

GSK believe the information above clearly establish the following: 1.) BRAF inhibitors will become the standard of care for the BRAF mutation-positive metastatic melanoma population 2.) The proposed benefit of the combination will likely not be solely due to the activity of trametinib.

With regard to the first point, while the results of BREAK-3 have yet to be reported GSK believes that the data for dabrafenib contained in this briefing document are consistent with the data from vemurafenib, with consistently similar ORR and PFS reported for the two agents. We expect these results will be confirmed when the results of BREAK-3 are reported in 1Q2012. Given the large advantage in both PFS and OS seen with vemurafenib compared to the standard therapy DTIC, (b) (4)

With regard to the second point, the data in this briefing document on trametinib mono-therapy in patients (b) (4) also clearly establish that trametinib is not more clinically active than a BRAF inhibitor when compared to the totality of evidence from vemurafenib and dabrafenib mono-therapy studies. Indeed, clinical data from study BRF113220 suggest that combinations with complementary mechanisms of action are likely to be more effective than mono-therapy, particularly in a setting where resistance is known to develop. As such, GSK believe these data obviate the need to include a trametinib single-agent arm in any combination study of dabrafenib+trametinib, as the proposed benefit of the combination over BRAF mono-therapy will very likely not be solely due to the activity of trametinib.

Given the data generated to-date from the Phase I and II studies (i.e. BRF112680, BRF113710, MEK111054, MEK113583), as well as the soon to be available phase 3 data for each agent (BRF113683 and MEK114267), the single agent activity of dabrafenib and trametinib has been adequately studied. From these data it is clear that the proposed benefit of the combination is unlikely to be solely due to activity of trametinib. Therefore, GSK believes that it is no longer necessary to include a trametinib mono-therapy arm, in either of the proposed Phase III study designs. Does the Agency agree?

FDA RESPONSE: FDA agrees that other data sources may suffice to provide the necessary data and that GSK will not be required to include a trametinib monotherapy arm in either of the proposed trials for the sole purpose of demonstrating the contribution of dabrafenib to the effect of dabrafenib/trametinib combination treatment. However, in an NDA submission seeking approval of this combination, GSK should provide data from clinical trials or from nonclinical studies that adequately demonstrates the contribution of dabrafenib to the effect of the combination.

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Data that is limited to clinical outcomes in Phase I, II, and III studies (i.e., BRF112680, BRF113710, MEK111054, MEK113583, BRF113683, and MEK114267) evaluating only dabrafenib and trametinib as single agents would not be sufficient to demonstrate the contribution of each component of the combination.

Please refer to the FDA guidance "Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf.

GSK Email Response of 1/26/2012: GSK would like greater clarity regarding the following sentence: "Data that is limited to clinical outcomes in Phase I, II, and III studies (i.e., BRF112680, BRF113710, MEK111054, MEK113583, BRF113683, and MEK114267) evaluating only dabrafenib and trametinib as single agents would not be sufficient to demonstrate the contribution of each component of the combination". Does the Agency mean that GSK will need to justify the lack of a trametinib arm in a future NDA not only based on clinical data, but also nonclinical data demonstrating synergistic or additive effect of the combination compared to the individual therapies?

Discussion during 1/27/2012 Meeting: FDA stated that GSK needs to demonstrate the contribution of each component to the effect of the combination for initial approval of two previously unmarketed investigational products. This may be adequately demonstrated through nonclinical studies or through clinical studies. Cross study comparisons evaluating the individual components separately is not sufficient to adequately satisfy this requirement. GSK acknowledged FDA's response.

3. Proposed Development Program for the Combination of dabrafenib+trametinib in Metastatic Melanoma

While the introduction of BRAF inhibitors represent a significant advance in the treatment of BRAF V600 mutation-positive metastatic melanoma patients, resistance to BRAF inhibitors as single agents develops rapidly and there is a critical need to develop combination therapies which can delay or overcome resistance. The proposed development plan for the combination of dabrafenib and trametinib is intended to address this unmet need. Interim efficacy data showed a clinical compelling early efficacy signal of dabrafenib 150 mg BID in combination with trametinib at 2 mg QD arm relative to dabrafenib mono-therapy. Specifically, the study demonstrates improvements in confirmed Overall Response Rates; including higher Complete Response rates and lower Progressive Disease events with the combination compared to dabrafenib mono-therapy. There is a statistically significant improvement in PFS with dabrafenib in combination with 2 mg QD GSK112012 over dabrafenib mono-therapy. The median progression-free survival for dabrafenib 150 mg BID in combination with trametinib at 2 mg QD arm is yet to be reached.

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Due to the rapidly evolving clinical landscape and emerging data noted above Question 1, GSK now proposes a development program for the combination of dabrafenib+trametinib that includes two Phase III studies of the combination versus a BRAF inhibitor.

- MEK115306 is a Phase III, randomized, double-blinded study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to dabrafenib and placebo in subjects with unresectable (Stage IIIc) or metastatic (Stage IV) BRAF V600E/K mutation-positive melanoma.
    - This study will provide independent confirmation of the results from BRF113220.
    - In the event that results from BRF113220 are not sufficiently robust, then this study will serve as a pivotal study for the combination in the treatment of BRAF mutation-positive melanoma.
- MEK116513 is a Phase III, randomized, open-label study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to the BRAF inhibitor vemurafenib in subjects with unresectable (Stage IIIc) or metastatic (Stage IV) BRAF V600E/K mutation-positive melanoma.
    - This comparative study is being conducted primarily to support global reimbursement of the combination outside of the US.
    - This study will also provide Overall Survival data comparing the combination to the current standard of care for patients BRAF mutation-positive metastatic melanoma; i.e. vemurafenib. If the magnitude of benefit on PFS is not sufficiently robust from BRF113220 and MEK115306, then MEK116513 will provide evidence of clinical benefit.

It should be noted that GSK has considered conducting a single three arm study including dabrafenib and vemurafenib, but there may be logistical issues in procuring vemurafenib to begin such a global study in a timely manner. Notably, given the impressive interim results from BRF1133220, GSK believe it is imperative to begin a phase III program for the combination expeditiously to ensure complete enrolment; should compelling efficacy results from BRF1133220 present challenges in conducting further randomized studies. To avoid any delay in the initiation of a phase III study to evaluate the combination, GSK is proposing two separate studies.

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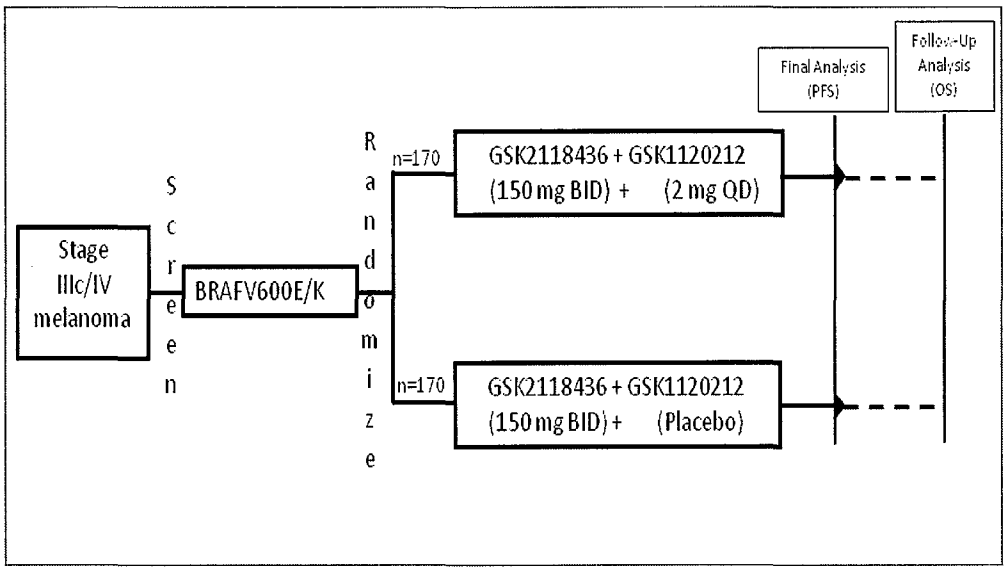
MEK115306

MEK115306 is a Phase III, randomized, double-blinded study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to dabrafenib and placebo in subjects with unresectable (Stage IIIc) or metastatic (Stage IV) BRAF V600E/K mutation-positive melanoma. The primary objective of this two-arm study is to establish the superiority of dabrafenib and trametinib combination therapy over dabrafenib and trametinib-placebo (BRAFi mono-therapy) with respect to progression-free survival (PFS) for subjects with unresectable/metastatic BRAF V600E/K mutation-positive melanoma.

MEK115306 Study Schema



Rational for Study MEK115306

MEK115306 will compare the combination of dabrafenib and trametinib to dabrafenib mono-therapy with primary endpoint of PFS. GSK proposes that this study will provide independent confirmation of the results seen in BRF113220. Additionally, in the event that results from BRF113220 are not sufficiently robust, then this study will serve as a pivotal study for the combination in the treatment of BRAF mutation-positive melanoma.

GSK notes previous interactions with the FDA, and the Agency's stated position that the relationship between progression-free survival and overall survival has not been established in melanoma. GSK also acknowledges the Agency's position that a PFS benefit of a sufficient magnitude, which is statistically significantly and clinically meaningful, may be considered clinical benefit.

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The preliminary results of BRF113220 provide evidence that the combination of dabrafenib and trametinib may demonstrate a large effect in terms of PFS versus dabrafenib mono-therapy. GSK believes that PFS is an appropriate endpoint in this setting based on the following:

(1) PFS is a direct measure of anti-tumor effect. GSK believes this lack of correlation exists historically because there have been no effective therapies for metastatic melanoma, and clinically significant PFS effects have not been demonstrated with standard cytotoxic agents. The past year has marked a turning point in this dearth of effective therapies and the emerging data provides evidence that targeted therapies with high clinical activity (i.e. BRAF inhibitors) can translate into large effects on PFS which in turn translates into improvement in Overall Survival. Recently, this has been demonstrated in the phase 3 trial of the BRAF inhibitor vemurafenib, which demonstrated high overall response rate (48%), a large PFS benefit against DTIC (median PFS 5.3m vs. 1.6 m; HR 0.26) and a corresponding large effect on OS (median NR for vemurafenib; HR 0.44)

(2) GSK believes that a large PFS effect, as the proposed phase 3 is designed to detect, is itself clinical benefit in this aggressive malignancy which is frequently associated with clinical symptoms and rapid clinical deterioration. Approximately two-thirds of subjects on the GSK studies in BRAF V600 mutation positive metastatic melanoma, including the BRF113220 study, have M1c disease; these patients have significant clinical co-morbidity and have poor prognosis.

With regard to the first point above, GSK acknowledges that ipilimumab has demonstrated an effect on overall survival with little to no effect on PFS. Efficacy endpoints such as response rate and progression-free survival are not as relevant to therapies that require time to stimulate the immune system and indirectly affect tumor cell biology. In the clinical studies evaluating ipilimumab, only a small fraction of patients received a durable benefit from ipilimumab therapy and the rate of tumor response as well as disease control was not significantly improved. This is most probably due to the distinct mode-of-action of ipilimumab in activating a host anti-tumor immune response, which frequently results in a delayed tumor size reduction even after initial radiographic tumor progression (Eggermont, Eur. J. Cancer, 2011). Thus well established surrogate efficacy markers such as overall response rate or progression-free-survival based on the commonly used RECIST criteria are of very limited value in describing the risk-to-benefit ratio of ipilimumab. In contrast, small molecule BRAF inhibitors (i.e. vemurafenib and dabrafenib, as well as the MEK inhibitor trametinib, have demonstrated clinical activity by inducing objective tumor response and by prolonging progression-free survival in a majority of melanoma patients whose tumors harbor $BRAF^{V600}$-mutations, and thus are more applicable and appropriate efficacy endpoints for these types of molecules. As demonstrated by the data from the BRIM-3 study of vemurafenib, a significant improvement in PFS predicted a significant improvement in OS.

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GSK believes that MEK115306, with the primary endpoint of progression-free survival, can provide substantial evidence of clinical benefit and provide this evidence in a more timely manner than a study with an Overall Survival endpoint; thus allowing for earlier access of the combination to patients. The study is designed as a double blind study to address potential bias in assessments of progression and the PFS endpoint will be subjected to an independent review, and powered to detect a large effect on overall survival against BRAF directed therapy. Patients will not be allowed to cross-over upon progression. Overall Survival, the secondary endpoint is 80% powered and will require 192 OS events to detect HR of 0,667, approximately 26 months from the start of the study.

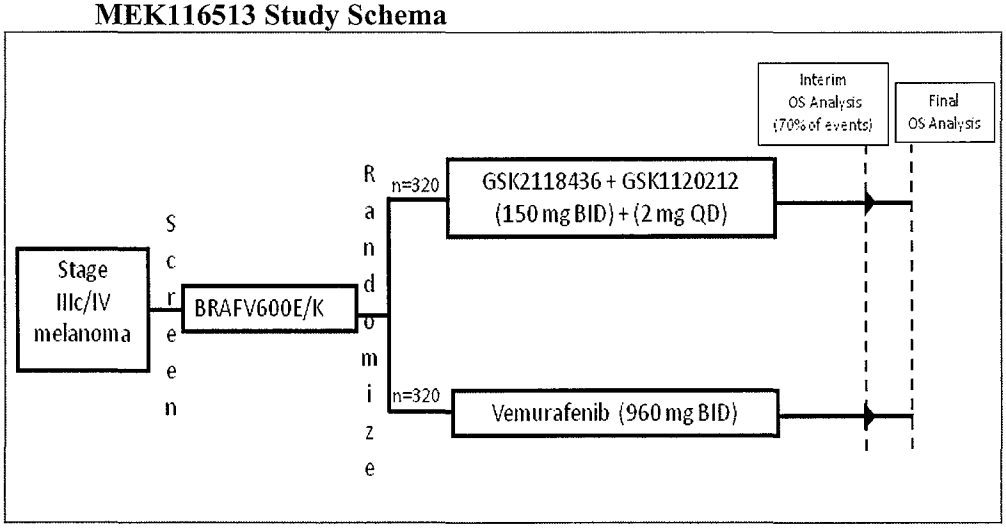
GSK acknowledges that should the benefit in PFS not prove robust enough, and effect on Overall Survival will be necessary. The study MEK116513 will provide Overall Survival against the currently approved standard of care.

MEK116513

MEK116513 is a Phase III, randomized, open-label study comparing the combination of the BRAF inhibitor, dabrafenib and the MEK inhibitor, trametinib to the BRAF inhibitor vemurafenib in subjects with unresectable (Stage IIIc) or metastatic (Stage IV) BRAF V600E/K mutation-positive melanoma.

The primary objective of this two-arm study is to establish the superiority of dabrafenib and trametinib combination therapy over vemurafenib with respect to overall survival (OS) for subjects with advanced/metastatic BRAF V600E/K mutation-positive cutaneous melanoma.

MEK116513 Study Schema



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Rational for Study MEK116513

MEK116513 will compare the combination of dabrafenib and trametinib to vemurafenib mono-therapy with the primary endpoint of OS. This adequate and well-controlled comparative study is being conducted primarily to support global reimbursement of the combination. Notwithstanding, GSK fully acknowledges that should BRF113220 and/or MEK115306 fail to provide evidence of a large, clinically meaningful effect on PFS, the overall survival data from this study will be needed to definitely establish clinical benefit.

Summary

GSK proposes a comprehensive development program for the combination of dabrafenib and trametinib for the treatment of BRAF mutation-positive unresectable or metastatic melanoma. This program includes an ongoing randomized Phase II study (BRF113220) and two randomized Phase III studies (MEK115306 and MEK116513). As noted in the Executive Summary, the clinical development landscape for emerging therapies in melanoma presents new challenges to the traditional development paradigm. GSK is proposing a global clinical development program that addresses the emerging development paradigm for highly active agents, as well as providing the most meaningful program to ensure global access of the combination therapy to patients as soon as possible. MEK115306 with the primary endpoint of progression-free survival can provide substantial evidence of clinical benefit and provide this evidence in a more timely manner than a study with an Overall Survival endpoint; thus allowing for earlier access of the combination to patients. MEK116513 is a comparative study and is being conducted primarily to support global reimbursement of the combination outside of the US, but will also provide Overall Survival data comparing the combination to the current standard of care for patients BRAF mutation-positive metastatic melanoma; i.e. vemurafenib. If the magnitude of benefit on PFS is not sufficiently robust from BRF113220 and MEK115306, then MEK116513 will provide evidence of clinical benefit.

The concept protocol for MEK115306 is provided in Appendix 2. GSK believes that a robust effect on PFS, which is clinically meaningful and statistically significant as demonstrated in this study, would be sufficient to support a filing and registration for the treatment of BRAF mutation-positive unresectable or metastatic melanoma, in the event that the data from BRF113220 is not sufficiently robust. Does the Agency Agree?

FDA RESPONSE: Yes, (b) (4) based primarily on the results of MEK115306 would require demonstration of a robust effect on PFS and the PFS effect should be of sufficient magnitude to permit a positive risk-benefit determination. MEK115306 should be adequately powered to rule out a clinically important, detrimental effect on survival and an interim analysis of survival should be provided in the application for assessment of safety. Whether the minimally detectable statistically significant PFS difference of two months as proposed for this trial constitutes clinical benefit would be a review issue.

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GSK may consider alternative analysis plans to perform an interim analysis for efficacy, designed to detect a very large effect on PFS, in order to limit the number of patients receiving a potentially less effective therapy. In addition, GSK should include the incidence of squamous cell carcinoma as a secondary endpoint of the trial.

Please be aware that for a single randomized trial [redacted] (b) (4) the trial should be well-designed, well-conducted, internally consistent, and provide statistically persuasive efficacy findings such that a second trial would be ethically or practically impossible to perform. Please refer to FDA guidances "Providing Clinical Evidence of Effectiveness for Human Drug and Biological products" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072008.pdf and "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics" at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071590.pdf.

Please also see additional FDA comment # 13.

GSK Email Response of 1/26/2012: GSK acknowledges the Agency comments and will address the suggestions with regard to an interim analysis in the Special Protocol Assessment submission.

Discussion during 1/27/2012 Meeting: FDA acknowledged GSK's response. There was no discussion during the meeting.

4. **The concept protocol for MEK116513 is provided in Appendix 3. While GSK does not believe data from MEK116513 would be required for regulatory approval, should the study demonstrate a statistically significant, and clinically meaningful, improvement in Overall Survival of the combination (dabrafenib+trametinib) over mono-therapy vemurafenib, this information would be important to patient and prescribers and therefore the data would warrant inclusion into the clinical study section of a future label. Does the Agency agree?**

FDA RESPONSE: FDA encourages Sponsors to perform adequate and well-controlled trials that help practitioners in clinical decision making concerning the safe and effective use of a drug(s).

GSK Email Response of 1/26/2012: GSK would like greater clarity. Assuming both MEK115306 and MEK116513 are positive, GSK believes these data would be appropriate for a future label. Does the Agency concur that study MEK116513, given its design, could warrant inclusion in the label.

Discussion during 1/27/2012 Meeting: FDA stated that to include information in the Clinical Studies Section of the label that makes, or implies, a comparative efficacy claim, the trial must provide substantial evidence of that claim. Determination that results from a single trial, i.e., MEK116513, would provide substantial evidence to make a

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comparative efficacy claim would be subject to the same criteria required of a new drug approval in Oncology based on a single trial. In addition, the labeling in the Clinical Studies Section should provide information that oncologists consider important to clinical decision making. GSK acknowledged FDA's response.

5. Proposed Development Program for the Combination of dabrafenib+trametinib in Adjuvant Melanoma

As described in Section 4.5 of the briefing document, GSK is considering a two-arm study comparing the combination of dabrafenib + trametinib to placebo in the adjuvant setting for patients with stage III resectable V600E/K mutation positive melanoma.

> It is well documented that BRAF mutations are present in primary lesions and are preserved in corresponding metastatic lesions, indicative of a common clonal origin thus demonstrating early and continued involvement in melanoma pathogenesis. In patients with high risk melanoma, the rate of disease recurrence following complete surgical resection of lymph nodes ranges between 40-80%. The median time to relapse in these patients is quite rapid occurring within approximately 12 months, with more than 50% of the relapses occurring at a distant anatomical location, suggestive of the presence of micrometastatic disease as the source of future relapse. Overall survival rates of less than 50% are seen in these high-risk patients (Balch JCO 2009). Despite multiple clinical trials, no adjuvant therapies have been shown to be an acceptable standard of care (Dummer et al. 2010; NCCN Guidelines V3.2012). Based on the preservation of the V600 mutation throughout melanoma disease progression, BRAF mono-therapy would be expected to provide similar responses on V600 mutant cells in the adjuvant setting, but the overall clinical benefit may still be limited by the development of resistance or an unacceptable safety profile.

Potential benefits of combining dabrafenib (BRAF inhibitor) with trametinib (MEK inhibitor) in the adjuvant setting is supported by *in vitro* and *in vivo* preclinical data which has demonstrated that the combination can enhance the levels of apoptosis, abrogate the onset of resistance, and prevent the development of proliferative skin lesions compared to BRAF mono-therapy. This combination has demonstrated enhanced activity against parental (non-drug-resistant) as well as dabrafenib-resistant cell lines, suggesting that potential benefits of combination may result from overall improved activity relative to single agents as well as an attenuation of tumor growth resulting from acquired resistance. Although the mechanisms of resistance to BRAF treatment are not completely understood, emerging data has demonstrated MEK activation is commonly found at the time of relapse, despite various MEK-independent mechanisms. Cell line data generated by GSK is similar to *in vitro* data with other BRAF/MEK inhibitor combinations (Corcoran, 2010; Emery, 2009). Similar to cell line data, in mouse xenograft studies with A375 cells which harbor a BRAFV600E mutation, the combination of dabrafenib and trametinib was significantly better than either agent alone.

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An added benefit of this combination in the adjuvant setting is prevention of MEK activation in normal tissues, a mechanistic side effect of BRAF mono-therapy, which could overcome the development of low-grade squamous-cell carcinomas that occurs in some patients. A combination of BRAF/MEK inhibitors prevented the development of proliferative skin lesions (epithelial hyperplasia and hyperkeratosis of the skin, nonglandular stomach and/or footpads) observed in rats following treatment with a BRAF inhibitor alone, suggesting that the addition of MEK to BRAF may potentially mitigate the risk of developing epithelial proliferative effects (i.e., cutaneous SCC) as observed in the clinic. Observations on proliferative skin effects are similar to those published with another BRAF/MEK inhibitor combination (Carnahan 2010).

As noted by Lacouture et al. (2011), hyperproliferative skin effects seen with exposure to BRAF inhibitors are easily cured via surgical removal and therefore do not pose a major concern in either the adjuvant or metastatic setting. But there remains a concern of RAF inhibitor induced secondary malignancies in earlier-stage patients, as it is unknown whether RAF inhibitors will promote growth of dormant RAS mutant tumors of the lung or pancreas, or other sites. Due to this risk, the authors maintain that RAF inhibitors cannot currently be recommended for use as mono-therapy in adjuvant treatment of high-risk, surgically resected patients. Importantly, the authors note that cotreatment with a MEK inhibitor may attenuate this risk in addition to improving antitumor effects.

The data from BRF113220 provide evidence to support the principles noted above. Specifically the results from BRF113220 demonstrates a higher Overall Response Rate, higher proportion of Complete Reponses, fewer Progressive Disease events and longer progression-free survival seen with the combination compared to BRAF mono-therapy. Additionally, the results from BRF113220 demonstrate a reduction in incidence of hyperproliferative skin effects associated with BRAF inhibition; substantiating the results seen in nonclinical experiments and hypothesized by Lacouture et al.

GSK believes that the data derived from the advanced setting (i.e. BRF113220, MEK115306 and MEK116513) is transferable and relevant to the early setting in terms of relative contribution and superiority of the combination over single-agent therapy. Taken together, there is strong scientific rationale and encouraging preclinical/clinical data that the combination may prevent or delay the development of resistance with the potential to provide a more favorable risk-benefit profile in the adjuvant setting.

Given the results of nonclinical experiments and the substantiation of these results from clinical data in BRF113220, GSK believes that the totality of evidence strongly suggests the combination of dabrafenib and trametinib is the optimal investigational choice for the adjuvant setting. Specifically, the combination may provide superior efficacy versus BRAF mono-therapy [redacted] (b) (4) [redacted] **In addition, the results phase 3 combination study in the metastatic setting (MEK115306) will provide robust evidence of the superiority of the combination versus dabrafenib mono-therapy in unresectable or metastatic melanoma, thus precluding the need to establish superiority to a BRAFi mono-therapy again in resectable melanoma. As such, GSK proposes a study of the**

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combination versus placebo, without a BRAF mono-therapy arm. Does the Agency agree?

FDA RESPONSE: There is insufficient information to provide specific guidance for the proposed design of the adjuvant trial. FDA recommends that GSK submit a separate meeting request to discuss the development program for the combination dabrafenib/trametinib as adjuvant therapy. Please provide detailed information in that pre-meeting briefing document summarizing the results of the non-clinical pharmacology and toxicology program supporting the proposed design and patient population, updated clinical data from the dabrafenib/trametinib combination development program including studies demonstrating the contribution of each agent to effect of the combination, and a draft protocol or concept protocol.

GSK Email Response of 1/26/2012: GSK will follow up with the Agency to schedule an additional interaction to discuss this question and additional details concerning the adjuvant study.

Discussion during 1/27/2012 Meeting: FDA acknowledged GSK's response. There was no discussion during the meeting.

(b) (4)

[redacted]

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(b) (4)

NONCLINICAL QUESTIONS

7. The toxicity profile of orally administered dabrafenib and trametinib as single agents has been established in safety pharmacology studies, repeat dose toxicity studies of up to 13 weeks duration in adult rats and dogs and in *in vitro* and *in vivo* genetic toxicology studies. For dabrafenib, an oral 2-week toxicity study in mice and an oral combined female fertility, early embryonic and embryofetal development studies in rats have also been conducted. For trametinib, a definitive embryofetal development study in rats has been performed and one is in progress in rabbits. Juvenile tolerability/dose range studies in rats are also ongoing with dabrafenib and trametinib with definitive juvenile toxicity studies planned to be completed in late 2012 and 2013 (as single agents) (b) (4) (b) (4)

The ICH S9 Guidance (Nonclinical Evaluation for Anticancer Pharmaceuticals) does not generally recommend combination toxicity studies when both agents are in late stage development with adequate clinical experience of each single agent and co-administration. However, to explore potential toxicological concerns with combination therapy of these agents, GSK is conducting a 1-month repeat dose combination toxicity study in dogs (study in reporting phase). Preliminary findings indicate no exacerbation of known toxicities with each agent alone, nor were novel adverse toxicities or significant change in dabrafenib or trametinib toxicokinetic profiles noted in dogs following co-administration.

Based on the nonclinical safety profile established from these studies, GSK does not consider that any additional nonclinical toxicology studies are warranted to support both the planned Phase III combination study and registration of this combination therapy.

Does the agency agree that the completed and ongoing safety assessment studies with trametinib and dabrafenib (administered as single agents) supports the planned Phase III combination study, registration and marketing for the treatment of (b) (4)

FDA RESPONSE: The completed and ongoing non-clinical studies appear adequate to support the proposed Phase 3 trial, and may be adequate to support (b) (4) for the drug combination (b) (4) A final determination regarding the adequacy of the data to support the proposed Phase 3 trial will be a review issue when the final protocol is submitted to the IND. Additional comments on the adequacy of the nonclinical data to support registration and marketing the drug combination would be premature at this time.

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Discussion during 1/27/2012 Meeting: GSK acknowledged FDA's response. There was no discussion during the meeting.

8. GSK plans to conduct additional single agent nonclinical safety studies with dabrafenib and trametinib to support the adjuvant combination indication. A list of planned studies and their respective timings is presented in the table below.

Planned Single Agent Toxicology Studies with dabrafenib and trametinib

Type of Study/[A] Duration of Dosing	Route of Administration	Species	Planned Study Start
Repeat Dose Toxicity			
6-month	Oral	Mouse	~1Q 2012 prior to PhIII start
			(b) (4)

A = for each study listed, dabrafenib and trametinib will be administered as single agent
B = final species selection for carcinogenicity study with dabrafenib contingent on 3-month interim data from 6 month mouse study

For each agent, a 6-month toxicity study in mice will be conducted to support the adjuvant indication. In the case of dabrafenib, the mouse has been selected based on the potential for achieving higher exposures to both parent and metabolites GSK2298683 (M4) and GSK2167542 (M8). In a 2-week repeat dose toxicity study in mice with dabrafenib, gender-averaged mean AUCs at 1000 mg/kg/day were approximately 2X, 3X, 1.4X and 14X human clinical exposure (based on AUC) for parent and metabolites GSK2298683 (M4), GSK2285403 (M7), and GSK2167542 (M8), respectively. To directly compare the toxicity profile in mice to rats (based on the 3-month rat toxicity study), an interim assessment will be performed at 3 months including toxicokinetic and histopathology evaluations. This interim assessment will aid in confirmation of rodent species and maximum tolerated dose (MTD) (b) (4) For trametinib, the mouse is selected based on the potential for achieving higher exposures to parent (there is minimal metabolism observed for this compound) relative to the clinical exposure. In 13-week repeat dose toxicity studies in rats and dogs, gender-averaged mean AUC values at the MTD were approximately 0.33X and 0.37X, respectively, human clinical exposure (gender-averaged mean AUC of 126 ng.h/mL in rats versus 376 ng.h/mL in patients). In repeat dose pharmacology studies lasting at least 80-days, athymic nude mice tolerated doses yielding exposures in excess of clinical levels (approximately 2-4X).

In nonclinical embryofetal development studies in rats given dabrafenib, developmental toxicities were observed that included reduced fetal body weight, embryo-lethality, cardiac ventricular septal defects, delayed skeletal development and variation in thymic shape. Additionally, testicular toxicity was observed in repeat dose toxicology studies in adult animals given dabrafenib for up to 13 weeks, with no clear evidence of recovery

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following an off-treatment period of up to 4 weeks. In a 13-week repeat dose toxicity study with rats given trametinib, increases in ovarian cystic follicles and decreases in cystic corpora lutea were observed in female rats. Given these male and female reproductive and embryofetal development effects with dabrafenib and trametinib, GSK does not consider that performing additional fertility and pre-postnatal developmental toxicity studies would provide additional toxicology results that would affect the benefit/risk assessment for the combined use of these products in the adjuvant setting.

There is high risk of metastasis in Stage III melanoma patients with few treatment options presently in the adjuvant setting. Because improvement in survival rates are expected for Stage III melanoma patients following co-administration of trametinib and dabrafenib, [redacted] (b) (4)

Cutaneous squamous cell carcinoma and hyperkeratotic lesions have been observed in patients given BRAF kinase inhibitors, including dabrafenib and vemurafenib. Proliferative lesions have been observed in dogs (skin) and in rats (skin and forestomach mucosa) in repeat dose toxicology studies with dabrafenib of up to 3 months duration. In the 1-month combination toxicity study in dogs with dabrafenib and trametinib, no proliferative or hyperkeratotic skin lesions were observed. Nonclinical investigations in rats using tool BRAF and MEK inhibitors in combination suggest lower potential for development of proliferative epithelial lesions when these agents are coadministered. These nonclinical findings suggest potential benefit of co-administration of BRAF and MEK inhibitors in mitigating risk of developing proliferative lesions in humans.

Assuming comparable findings (between available 3-month repeat dose rat data and 3-month interim data from the 6-month mouse study), [redacted] (b) (4) GSK does not recommend performing a rat carcinogenicity study with trametinib due to low systemic exposure at the MTD in rats relative to human exposure. The 6-month repeat dose toxicity study in mice given trametinib, also including an assessment at 3 months to bridge to the rat toxicity results, is planned to start January 2012 to enable dose selection for this study.

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Does the agency agree with the proposed nonclinical studies with trametinib and dabrafenib (administered as single agents) that will support combination Phase III clinical trials, registration and marketing for the treatment of Stage III, BRAF V600 mutation positive, resectable melanoma in the adjuvant setting?

FDA RESPONSE: The proposed nonclinical development plan appears adequate to support the trametinib/dabrafenib drug combination in the adjuvant setting for this advanced cancer patient population. The adequacy of the nonclinical data to support the development of the combination in the adjuvant setting will be a review decision.

Additional comments on the adequacy of the nonclinical data to support registration and marketing the drug combination would be premature at this time.

Discussion during 1/27/2012 Meeting: GSK acknowledged FDA's response. There was no discussion during the meeting.

ADMINISTRATIVE/REGULATORY QUESTIONS

9. GSK proposes to include the following documents in the new IND submission for IND 113557 for dabrafenib and trametinib used in combination:
   - Form FDA 1571
   - Cover Letter
   - Form FDA 3674
   - Module 1.13.9 General Investigational Plan for dabrafenib and trametinib used in combination
   - Module 5.3.5.1
     - Study Protocol BRF113220 (Latest Version: Amendment 003)
     - Study Protocol MEK115306
     - Study Protocol MEK116513

Forms FDA 1572 will follow in a subsequent submission once principle investigators have been identified. Also, note that currently Study Protocol BRF113220 is filed under both IND 105302 and IND 102175. The proposal is to file the most recent version and all future amendments of this protocol under IND 113557; and not to file any future amendments to IND 105032 or IND 102175.

All additional information for dabrafenib and trametinib will be incorporate into IND 113557 by cross-reference to the respective mono-therapy IND applications (i.e. (b) (4), (b) (4), IND 102175).

Does the Agency agree with the proposed contents of the Combination IND 113557?

FDA RESPONSE: Please withdraw protocol BRF113220 from IND 105302 and IND 102175 following submission of the protocol to IND 113557 and FDA notification that IND 113557 may proceed.

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Discussion during 1/27/2012 Meeting: GSK acknowledged FDA's response. There was no discussion during the meeting.

10. GSK proposes to synchronize the Development Safety Update Reports (DSUR) for all three IND applications: i.e. for IND 105032, IND 102175 and the future IND 113557. The following table outlines the proposal.

	IND 105032	IND 102175	IND 113557
Current DSUR Development International Birthdates	June 23	December 19	Not established
Reporting period for initial synchronized DSUR	24-Jun-2011 through 23-Jun-2012	20-Dec-2011 through 23-Jun-2012	IND initiation through 23-Jun-2012
Proposed future DSUR Anniversary Date	June 23	June 23	June 23

GSK proposes to align these Development International Birthdates starting in 2012; this will ensure that every IND provides a DSUR covering a year or less. Naturally, following 2012 the DSUR reports for each IND will cover the period of a full year. This proposal will serve two purposes:

1. As each DSUR will contain data from studies conducted under the other IND, synchronizing the anniversary date will limit the amount of times GSK has to cut data for annual reports.

2. A synchronized anniversary date will provide the Agency with a robust annual assessment of each agent alone and in combination based on a single data-cut.

Does the Agency agree with the proposal to synchronize the DSUR (Development Safety Update Reports) for IND 105032, IND 102175 and the future combination IND 113557?

FDA RESPONSE: Yes

Discussion during 1/27/2012 Meeting: GSK acknowledged FDA's response. There was no discussion during the meeting.

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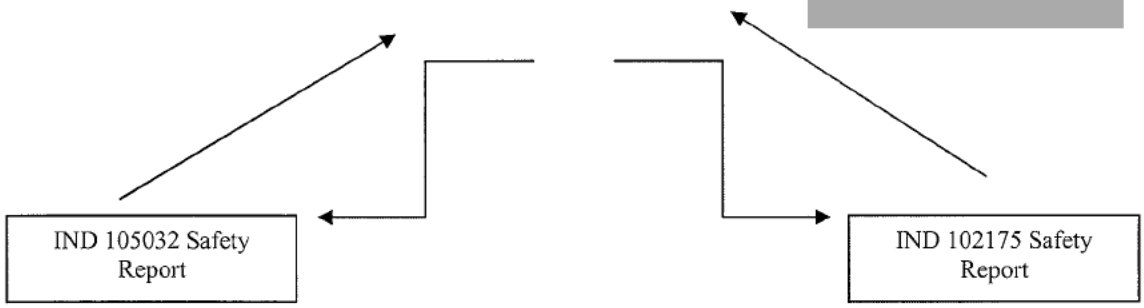
11. GSK proposes the following reporting scheme for safety reports amongst the three IND applications:

    - Safety reports from studies with trametinib go to the IND 102175 and combination IND
    - Safety reports from studies with dabrafenib go to IND 105032 and the combination IND
    - Safety reports from the trametinib+dabrafenib studies go to the combination IND and the individual INDs

    The schematic below illustrates the reporting scheme:

    Flow of IND Safety Reports among the three IND Applications

APPEARS THIS WAY ON ORIGINAL



Does the Agency agree the GSK proposal regarding the reporting of safety reports?

FDA RESPONSE: Yes

Discussion during 1/27/2012 Meeting: GSK acknowledged FDA's response. There was no discussion during the meeting.

ADDITIONAL FDA COMMENTS:

Clinical

12. FDA has the following recommendations concerning the design of trials MEK115306 and MEK116513:

    a. consider including V600 mutation type (V600E versus V600K) as a randomization stratification factor

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b. designate the occurrence of all cutaneous squamous cell carcinomas (cuSCC) as SAEs and design relevant case report forms to collect the following information :

- tumor location
- tumor thickness and/or depth
- tumor diameter
- high-risk histological features such as degree of differentiation, perineural invasion, or vascular involvement
- staging evaluation results
- treatment(s) administered
- follow-up performed

c. include safety assessments to monitor for the development of non-cutaneous squamous cell carcinomas at high risk sites.

GSK Email Response of 1/26/2012:

- V600 mutation type will be added as a randomization stratification to the design of both trials.
- Both Phase III protocols will clearly state that cuSCC is considered an SAE
- The Phase III protocols will make thorough physical examinations including a genitourinary exam with visual inspection of the cervix in female patients and a rectal exam in all patients mandatory during the screening- and the last study visit (e.g. treatment discontinuation). In addition, regular physical examinations are requested every 4 weeks while subjects are on study and participating investigators will be advised to direct their attention to the skin and other anatomical sites at high risk of SCC development.

Discussion during 1/27/2012 Meeting: FDA acknowledged GSK's response. FDA recommends that protocols MEK115306 and MEK116513 require participating investigators to examine anatomical sites at high-risk of SCC development, e.g., thorough head and neck examinations at baseline and periodically during treatment as well as at the end of study. FDA also requested that GSK include in an SPA submission all sample case report forms pertaining to cutaneous squamous cell carcinomas and non-cutaneous second malignancies. GSK acknowledged FDA's response.

13. FDA requests that GSK clarify the timing of the planned final OS analysis in Protocol MEK115306. The briefing document does not identify whether the final OS analysis is planned after 192 death events or after 70% of enrolled subjects have died (i.e., 238 death events) as suggested in Appendix 2 of the briefing document, page 10.

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GSK Email Response of 1/26/2012: A final OS analysis will be performed when 70% of enrolled patients have died or are otherwise lost to follow-up. The study will be closed at this time, which is estimated to be approximately 3 years after the start of the study.

Discussion during 1/27/2012 Meeting: FDA acknowledged GSK's response. There was no discussion during the meeting.

14. GSK states that if the magnitude of benefit on PFS is not sufficiently robust from BRF113220 and MEK115306, then MEK116513 will provide evidence of clinical benefit. Please be advised that positive results from MEK116513 in the setting of marginal or inconsistent results from MEK115306 might not provide substantial evidence of effectiveness of the dabrafenib/trametinib combination; any differences in outcomes of studies that do not favor the combination of dabrafenib and trametinib must be examined and thoughtfully discussed in the Integrated Summary of Effectiveness (ISE) submitted in an NDA.

    In addition, if the magnitude of benefit demonstrated in MEK115306 is not sufficiently robust and GSK intends to submit data from MEK116513 to support filing and registration of the dabrafenib/trametinib combination, then MEK116513 must be designed to demonstrate the contribution of trametinib to the combination.

15. FDA recommends that GSK submit the protocol and statistical analysis plan for MEK115306 to IND 113557 for a Special Protocol Assessment.

    GSK Email Response of 1/26/2012: GSK will submit a Special Protocol Assessment for MEK115306.

    Discussion during 1/27/2012 Meeting: FDA acknowledged GSK's response. There was no discussion during the meeting.

16. FDA requests submission of high-level efficacy results from the BRF113683 trial immediately following the completion of the high-level analyses.

    GSK Email Response of 1/26/2012: High-level efficacy results from BRF113683 will be available within the first quarter of this year. GSK will work with the Project Manager to schedule a meeting/teleconference to share these results with the Agency.

    Discussion during 1/27/2012 Meeting: FDA acknowledged GSK's response. There was no discussion during the meeting.

Clinical Pharmacology

17. FDA recommends that GSK include sparse pharmacokinetic sample collection for dabrafenib and trametinib in the combination treatment arm in the proposed Study MEK116513.

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In addition, explore exposure-response (measures of effectiveness, biomarkers and toxicity) relationships for the combination use of dabrafenib and trametinib in the targeted patient population. Refer to Guidance for Industry found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf and http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf for more information.

GSK Email Response of 1/26/2012: PK sampling is already planned for MEK115306. GSK does not intend to include PK sampling in MEK116513, as this data will already be gathered from MEK115306 in the same population, dose and formulation.

Discussion during 1/27/2012 Meeting: FDA acknowledged GSK's response. FDA continues to recommend sparse pharmacokinetic sample collection for dabrafenib and trametinib in the combination treatment arm in the proposed Study MEK116513 to better explore exposure-response (measures of effectiveness, biomarkers and toxicity) relationships for the combination use of dabrafenib and trametinib in the targeted patient population. There was no discussion during the meeting. GSK acknowledged FDA's response.

4. ACTION ITEM:

GSK will request a brief teleconference to discuss trial designs for adjuvant combination therapy to be followed by a request for a more detailed meeting upon development of the draft protocol.

5.0 ATTACHMENTS AND HANDOUTS:

- GSK Slide Presentation of January 27, 2012
- Meeting Attendance List

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27JAN12 Pre-IND Meeting
Pre-IND 113557
dabrafenib and trametinib

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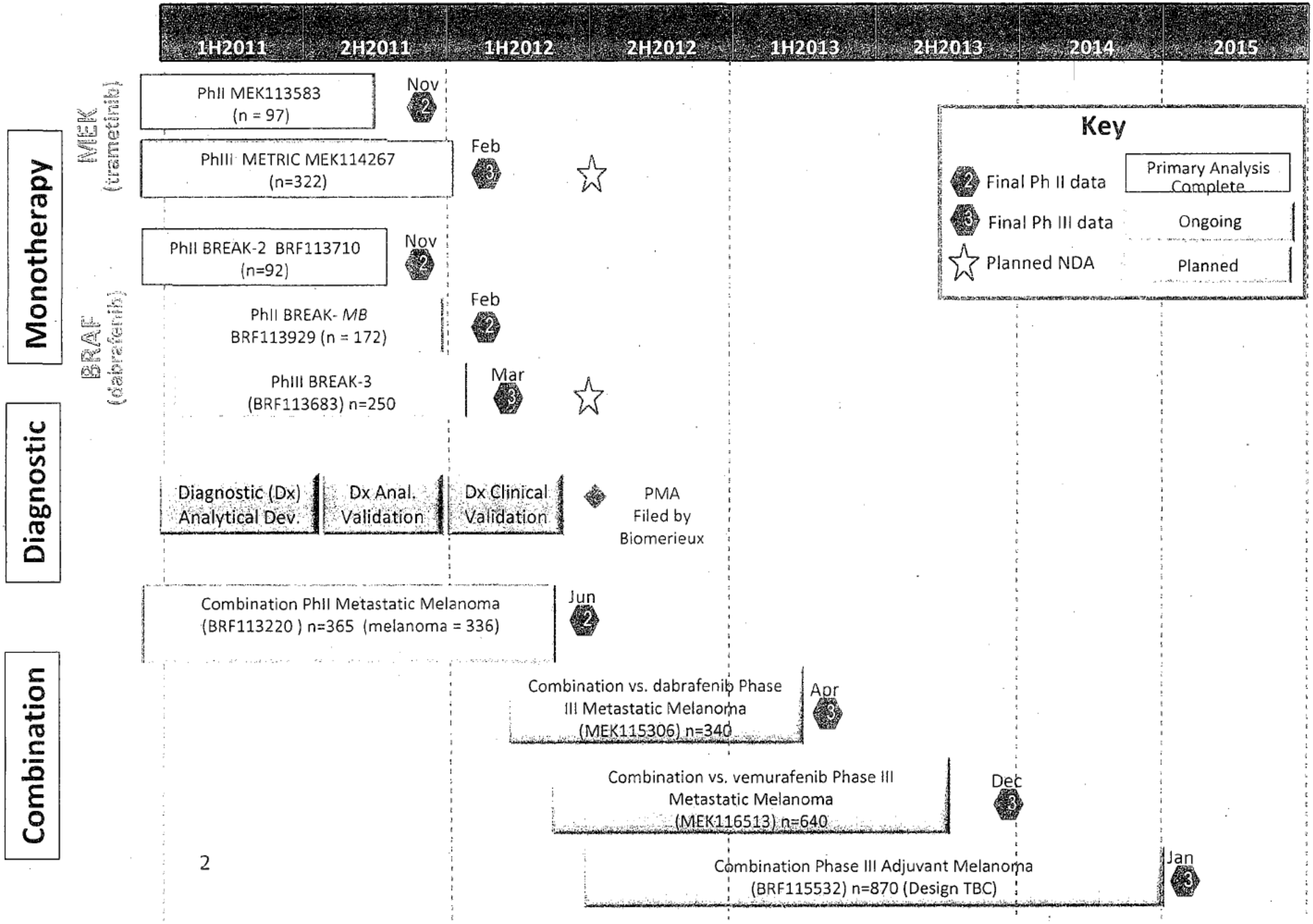
GSK Melanoma Development



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Summary of Phase II Monotherapy Data

BRAF Targeted Agent	Study	Patient Population	N	Efficacy		Safety
				ORR (confirmed)	Median PFS	Adverse Events (%)
dabrafenib (BRAFi)	BREAK-2 BRF113710 (Single arm open label P2 study) [1]	BRAF V600E mutant metastatic melanoma (primary efficacy population)	76	59% (95% CI:48, 70)	6.3 months (95% CI 4.6, 7.6)	Arthralgia (33) Hyperkeratosis (27) Pyrexia (24) SCC (10)
trametinib (MEKi)	MEK113583 (Single arm open label P2 study) [2]	BRAF V600E mutant metastatic melanoma (subpopulation without brain metastases)	36	28% (95% CI 14, 45)	5.3 months (95% CI 3.6, 7.4)	Skin Related Tox (87) Rash (54) Dermatitis Acneiform (30) Diarrhea (52) Ocular: CSR/RVO (<2) LVEF Dys (8-15)

[1] Trefzer et al. Society for Melanoma Research. 2011.
[2] Kim et al. Society for Melanoma Research. 2011

Reference ID: 3444185

BRF113220 - Study Design and Objectives

Part A

Drug-drug interaction (N= 8)

Objective

- Determine the effect of trametinib on dabrafenib PK

Part B

Dose escalation

Expansion cohorts (N=77)

Objectives

- Assess safety/tolerability
- Determine RP2D
- Characterize steady-state PK
- Evaluate clinical activity

Colorectal BRAF+ (N=25)

Prior BRAF inhibitor (N=25)

Objective

- Evaluate clinical activity

Part C

Randomized Phase II Trial (N=162)

Objectives

- Clinical activity (RR, PFS) of combo vs dabrafenib
- Assess safety/tolerability

Part D

PK Study dabrafenib (HPMC) + trametinib (N= 60 and still enrolling)

Objectives

- Assess safety/tolerability
- Characterize PK with dabrafenib (HPMC)

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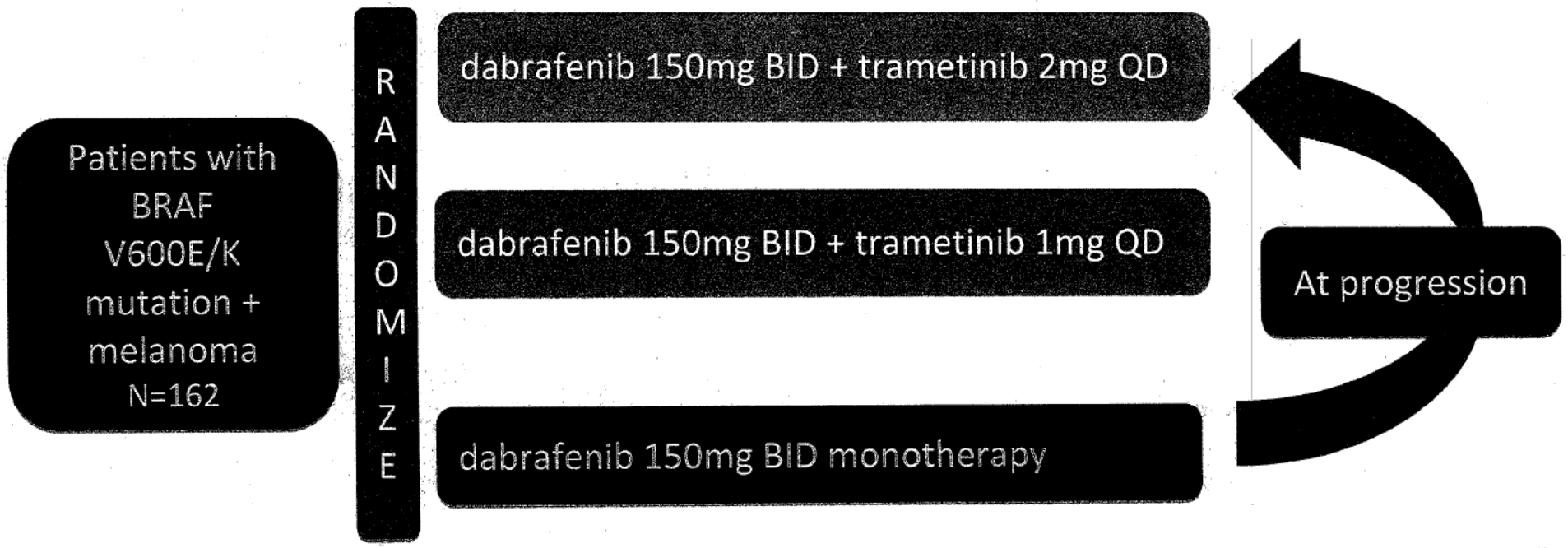
BRF113220 - Randomized Phase 2 (Part C)



- Open-label; Investigator assessed
- Interim analysis planned followed by final analysis
  - 50% of patients - at least 6 month follow-up
  - Final analysis planned at the time of 70% of progression events

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BRF113220: Part C - Best Confirmed Response BRAF V600 E/K Metastatic Melanoma

Best Confirmed Response	Dose level (dabrafenib BID/ trametinib QD)		
	150 mg Mono (N=47) *	**150 mg/1 mg (N=50)***	**150 mg / 2 mg (N=49)***
CR	**0**	**1 (2%)**	**3 (6%)**
PR	23 (49%)	21 (42%)	34 (69%)
SD	20 (43%)	24 (48%)	12 (24%)
PD	4 (9%)	2 (4%)	0
NE	0	2 (4%)	0
Response Rate (95% CI)	23 (49%) (34.1%, 63.9%)	22 (44%) (30.0%, 58.7%)	**37 (76%) (61.1%, 86.7%)**
Difference in Response Rate (95% CI) P-value		-5% (-24.8%, 14.9%) P-value =0.6261	**27% (7.9%, 45.3%) P-value = 0.0072**

* Subject who are still on study and have not progressed with less than 2 post-dose lesion assessment were excluded from the analysis.

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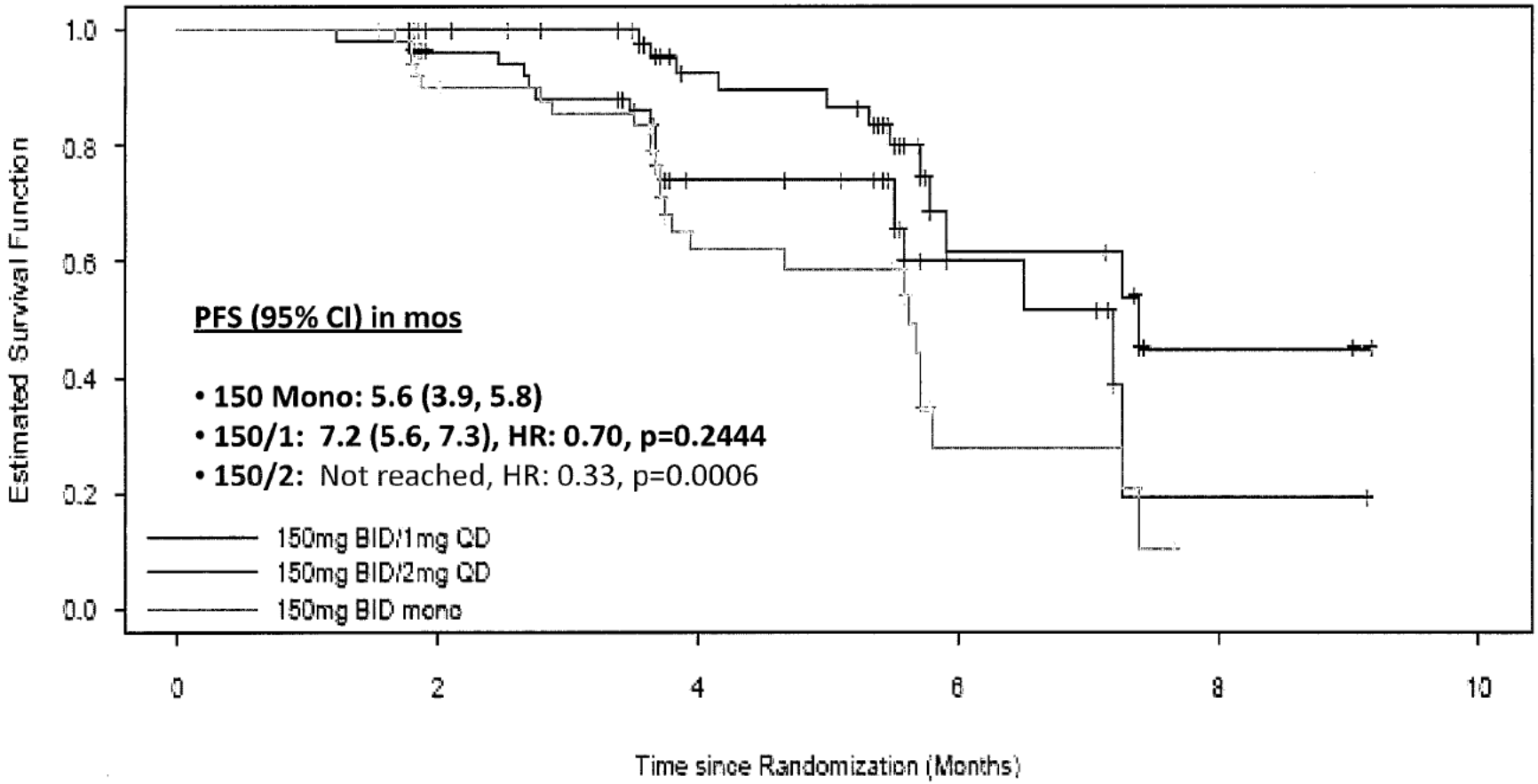
BRF113220: Part C – Interim Progression-Free Survival (PFS)



Subjects At Risk					
150mg BID/1mg QD	64	47	24	7	1
150mg BID/2mg QD	65	49	32	9	2
150mg BID mono	[illegible]	[illegible]	[illegible]	4	

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BRF113220: Part C - Adverse Events Overview

Adverse Events	Dose level (dabrafenib BID/ trametinib QD)		
	150 mg Mono (N=53)	**150 mg/1 mg (N=54)**	**150 mg / 2 mg (N=55)**
Fatigue	21 (40%)	28 (52%)	24 (44%)
Pyrexia	**10 (19%)**	**31 (57%)**	**30 (55%)**
Chills	**8 (15%)**	**23 (43%)**	**24 (44%)**
Nausea	11 (21%)	22 (41%)	15 (27%)
Headache	14 (26%)	17 (31%)	14 (25%)

Adverse Events	Dose level (dabrafenib BID/ trametinib QD)		
	150 mg Mono (N=53)	**150 mg/1 mg (N=54)**	**150 mg / 2 mg (N=55)**
Serious Adverse Events **Pyrexia**	13 (25%) **0**	12 (22%) **1 (2%)**	21 (38%) **8 (15%)**
AEs of Grade 3 and Above **Pyrexia**	21 (40%) **0**	19 (35%) **1 (2%)**	26 (47%) **2 (4%)**
AEs Resulting Dose Reduction **Pyrexia**	3 (6%) **0**	10 (19%) **2 (4%)**	8 (15%) **5 (9%)**
AE Resulting Dose Interruption **Pyrexia**	13 (25%) **2 (4%)**	27 (50%) **14 (26%)**	25 (45%) **13 (24%)**

[8]The dose modification and management guidelines for pyrexia are implemented

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Phase III Combination Study Design

	MEK115306				
1	Unresectable **Stage IIIc or IV Melanoma**	**V600 E/K MUT**	N= 170	**dabrafenib : 150 mg BID + trametinib : 2 mg QD**	PFS
			N=170	**dabrafenib: 150 mg BID**	
	MEK116513				
2	Unresectable **Stage IIIc or IV Melanoma**	**V600 E/K MUT**	N=320	**dabrafenib : 150 mg BID + trametinib : 2 mg QD**	OS
			N=320	**vemurafenib : 960 mg BID**	

- Primary: Study 1) PFS - Combination Vs. dabrafenib (n=340); 90% power; HR 0.59
  - Secondary OS: interim at PFS; >80% power at study close; HR 0.67

  Study 2) OS- Combination Vs. vemurafenib (n=640); 90% power; HR 0.67

Back-Up

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Reference ID: 3444185

Part C - Patient Characteristics

Characteristics	Dose level (dabrafenib BID/ trametinib QD)		
	150 mg Monotherapy (N=53)	150 mg/1 mg (N=54)	150 mg / 2 mg (N=55)
Mean age, yrs	52.0	50.0	55.7
Gender, Male	29 (55%)	30 (56%)	34 (62%)
ECOG 0	33 (62%)	38 (70%)	36 (65%)
Prior brain metastases	4 (8%)	6 (11%)	3 (5%)
BRAF Mutation Status			
V600E	44 (83%)	45 (83%)	48 (87%)
V600K	9 (17%)	9 (17%)	7 (13%)
M status at Screening – M1c	33 (62%)	30 (56%)	36 (65%)
LDH - > ULN	26 (49%)	25 (46%)	23 (42%)

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Part C - Adverse Events of Interest

Adverse Events		Dose level (dabrafenib BID/ trametinib QD)		
		150 mg Mono (N=53)	150 mg/1 mg (N=54)	150 mg / 2 mg (N=55)
Pyrexia		**10 (19%)**	**31 (57%)**	**30 (55%)**
Cardiac	**↓Ejection Fraction**	**0**	**3 (6%)**	**3 (5%)**
	Hypertension	**2 (4%)**	**3 (6%)**	**2 (4%)**
Ocular Events*		**9 (17%)**	**8 (15%)**	**13 (24%)**
Chorioretinopathy		0	0	1 (2%)
Skin Related Toxicities*		**32 (60%)**	**21 (39%)**	**31 (56%)**
Rash		16 (30%)	7 (13%)	12 (22%)
Dermatitis Aceneiform		2 (4%)	6 (11%)	7 (13%)
Squamous Cell Carcinoma*		**7 (13%)**	**0**	**3 (5%)**
Skin Papiloma		**7 (13%)**	**1 (2%)**	**1 (2%)**
Actinic Keratosis		**2 (4%)**	**1 (2%)**	**4 (7%)**
Hyperkeratosis		**14 (26%)**	**0**	**2 (4%)**
Hepatic Disorders*		**5 (9%)**	**13 (24%)**	**6 (11%)**
AST Increase		4 (8%)	11 (20%)	6 (11%)
ALT Increase		2 (4%)	10 (19%)	5 (9%)

* Include multiple terms.

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Part C Updated - SAEs Pyrexia

- 13 patients with 17 episodes
  - 12 (Combination, n= 109, 11%)
  - 1 patient on monotherapy
    - Crossed over to combination (fever 61 days hence)
- 11 patients hospitalized
  - No documented hypotension *
  - Many patients required IV fluids
  - 1 patient admitted to ICU
    - Short stay (had high fever with epistaxis)
  - 1 patient with renal failure (? Secondary to antibiotics)
  - 1 patient rise creatinine (0.8 to 1.2 mg/dL)

*Patients in cohort B with pyrexia and hypotension (~5/125)

Reference ID: 3444185

Pyrexia

- Typically presents within first 2 months
- Majority patients respond to standard anti-pyretics
- Standard management and treatment guidelines
  - Importance of medical evaluation and infection workup
  - Updated: include steroids if resistant standard anti-pyretics
    - Effectiveness of steroids:
      - Anecdotal reports from investigator—effective in many patients
      - Formal analyses not conducted as yet
  - Dose interruptions for temperature > 39 C
  - Education will be key for the phase III trial
    - Current investigators seem well versed on management
- Mechanism being evaluated
- Association with drug exposure being investigated

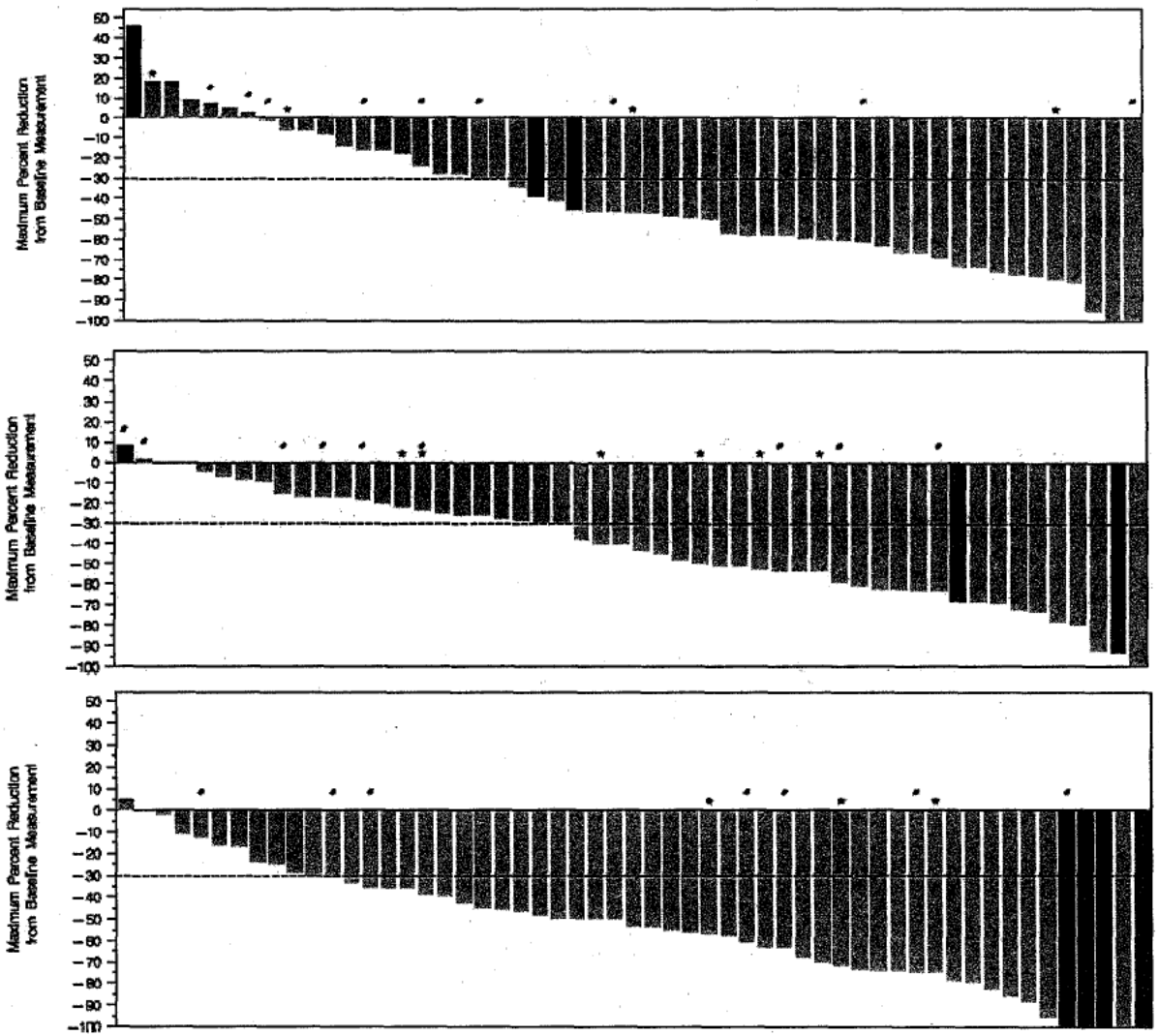
Reference ID: 3444185

Part C - Waterfall Plot

Monotherapy

150 mg/1mg

150 mg/2mg



Best Unconfirmed Response

- Complete response
- Partial response
- Stable disease
- Progressive disease
- Not evaluable

* Prior brain met

\# V600K

MEETING ATTENDANCE LIST

Meeting between Glaxo SmithKline LLC (IND 113557) and the Center for Drug Evaluation and Research.

DATE: January 27, 2012 TIME: 2:30-3:30 P.M. ROOM: 1313

NAME - Please print	AFFILIATION
Norma Griffin	DOP2/OHOP/CDER/FDA
MARGIT BRAUER	DOP2/OHOP
Eric Richards	GSK
Rafael Amador	GSK
Vicki Goodman	GSK
DANIELE OUELLET	GSK
Steve Lane	GSK
JEFF Legos	GSK
Ellen Cutler	GSK
Anne-Marie Martin	GSK
DOUGLAS J. DeMARINI	GSK
Michael Streit	GSK
MARK CORNFORD	GSK
Jennifer Dudinak	GSK
Kiran Patel	GSK
Marc Theoret	DOP2/OHOP
RICHARD PAZDUR	OHOP
Joe Gootenberg	DOP2/OHOP/CDER/FDA
ANTHONY J. MURGO	OHOP
Jian Wang	FDA/CDER/OCP/DCP5
Lilian Zhang	FDA/CDER/OCP/DCP5
DONNA ROSCOE	FDA/CDRH/OIVD/DIHD
Kun He	FDA/CDER/OB/DB5
Weishi Yuan	FDA/CDER/OTS/OB/DB5
Andrew McDougal	FDA/CDER/OHOP/DHOT
PATRICIA KEEGAN	FDA/CDER/OHOP/DOP2

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/s/

NORMA S GRIFFIN
02/23/2012