CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204114Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	204,114
Priority or Standard	Standard
Submit Date(s)	August 2, 2012
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Division / Office	DOP2 / OHOP
Reviewer Name(s)	Marc Theoret Suzanne Demko, Team Leader
Review Completion Date	May 23, 2013
Statistical Team	Huanyu Chen Ke Hun, Team Leader
Established Name	Trametinib
(Proposed) Trade Name	Mekinist
Therapeutic Class	Kinase inhibitor
Applicant	GlaxoSmithKline
Formulation(s)	0.5 mg, 2 mg Tablets
Dosing Regimen	2 mg orally once daily
Indication(s)	Unresectable or metastatic melanoma with BRAF V600E or V600K mutation as detected by an FDA-approved test.

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

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

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.

Limitation of use: MEKINIST is not indicated for treatment of patients who have received a prior BRAF-inhibitor therapy.

1.2 Risk Benefit Assessment

Melanoma develops at a relatively early age which results in a substantial number of years of life lost per person (Ekwueme, Guy, et al. 2011), and once metastatic carries a grim prognosis—the five year survival rate is historically less than 10% for patients. Melanoma harbors BRAF mutations in approximately 40-60% of patients (Davies, Bignell, et al. 2002; Jakob, Bassett, et al. 2012; Long, Menzies, et al. 2011). The most common of these BRAF mutations is V600E although patients with melanoma harboring BRAF V600K mutations are a substantial proportion of patients with BRAF V600 mutation-positive melanoma, approximately 5-30% (Rubinstein, Sznol, et al. 2010). There are few FDA-approved treatments for metastatic melanoma—vemurafenib, ipilimumab, aldesleukin, and dacarbazine (DTIC)—and only vemurafenib, an inhibitor of some mutant forms of BRAF kinase, including BRAF V600E, was specifically studied in patients with BRAF V600E mutation-positive melanoma. In this molecularly defined subgroup of melanoma patients, vemurafenib demonstrated a prolongation of investigator-assessed progression-free survival (PFS) from a median of 1.6 months [95% confidence interval (CI): 1.5, 1.7] with DTIC to 5.3 months (95% CI: 4.8, 6.6) with vemurafenib with a hazard ratio (HR) of 0.26 (95% CI: 0.20, 0.33). Vemurafenib also demonstrated improved OS (OS) compared to DTIC with a HR of 0.44 (95% CI: 0.33, 0.59; $p < 0.0001$). Vemurafenib is not FDA-approved for treatment of patients with BRAF V600K mutation-positive melanoma.

The recommendation for approval of NDA 204114 (trametinib) is primarily based on the results of the MEK114267 trial which demonstrated a statistically persuasive and robust, clinically meaningful prolongation in PFS. The MEK114267 trial was an open-label, multicenter, international, randomized (2:1), active-controlled trial comparing single agent trametinib, an inhibitor of the MEK1/2 kinases, to chemotherapy in 322 patients with previously untreated or treated, histologically confirmed, unresectable (Stage IIIc) or metastatic (Stage IV) cutaneous melanoma determined to be BRAF V600E or V600K mutation-positive based upon centralized testing. Patients were allocated to receive trametinib 2 mg orally once daily (n=214) or investigator choice of chemotherapy (n=108), dacarbazine 1000 mg/m^2 intravenously or paclitaxel 175 mg/m^2 intravenously once every 3 weeks, until disease progression or intolerable

toxicity. The MEK114267 trial met its primary endpoint of investigator-assessed PFS demonstrating a statistically significant 53% reduction in the hazard rate of progression of disease or death [HR 0.47 (95% CI: 0.34, 0.65); 2-sided p-value <0.0001 (unstratified log-rank test)] on the trametinib arm compared to the chemotherapy arm. The median PFS on the trametinib arm was 4.8 months (95% CI: 4.3, 4.9) compared to 1.5 months (95% CI: 1.4, 2.7) on the chemotherapy arm. Analyses based on a blinded, independent central review assessment of PFS supported the primary efficacy analysis using investigator assessments. The results of the OS analysis based on data that are not mature (20% deaths occurred in the intent-to-treat population at the time of data cutoff) do not raise concerns for a detriment in OS with trametinib and suggest a positive impact on OS [HR of 0.56 (95% CI: 0.33, 0.95); 2-sided nominal p-value of 0.0136]; however, the trial was not powered for OS and the statistical analysis plan (SAP) did not adjust the significance level for multiplicity. The investigator-assessed, confirmed objective response rates (ORR) were 22% (95% CI: 17%, 28%) on the trametinib arm, including 4 (2%) complete responders, and 8% (95% CI: 4%, 15%) on the chemotherapy arm, all partial responders. The median duration of response was 5.5 months (95% CI: 4.1, 5.9) for the objective responders to trametinib and was not reached (95% CI: 3.5 months, not reached) for the objective responders to chemotherapy. Currently under FDA review by the Center for Devices and Radiological Health (CDRH) is a premarket approval application for the in vitro companion diagnostic test for trametinib, the BioMerieux THxID BRAF Kit (PMA P120014) to detect BRAF V600 (E or K) mutations in melanoma.

The primary safety risks of trametinib are cardiomyopathy, interstitial lung disease and pneumonitis, ocular toxicity, and rash. The incidence of cardiomyopathy defined as cardiac failure, left ventricular dysfunction, or decreased ejection fraction was 7% in trametinib-treated patients and nil in the chemotherapy-treated patients in the MEK114267 trial. Risk of cardiomyopathy requires routine monitoring of left ventricular ejection fraction (LVEF). The incidence of the other major safety risks in trametinib-treated patients across clinical trials (n=329) were, in order of decreasing frequency, 87% for skin toxicities, 6% for serious infections in the skin, 2% for interstitial lung disease/pneumonitis, 1% for retinal vein occlusion, and approximately 1% for retinal pigment epithelial detachments. Management of these risks requires dose interruption, dose reduction, or permanent discontinuation of trametinib.

Approximately 9% of trametinib-treated patients experienced adverse events (AE) leading to treatment withdrawal. Dose reductions for AEs occurred in 27% of trametinib-treated patients, most commonly for rash (9%) and decreased ejection fraction (3%). Adverse events led to withholding treatment without dose reduction in 20% of trametinib-treated patients, most commonly for rash (4.3% in the trametinib treatment group vs. 0 in the chemotherapy treatment group), diarrhea (2.4% vs. 0), peripheral edema (1.9% vs. 0), ALT/AST increase (1.4% vs. 0), and ejection fraction decreased (1.4% vs. 0). Grade 3 or 4 AEs occurred in 48% of trametinib-treated patients—the most frequent were hypertension (12.8% of trametinib-treated patients vs. 4% of chemotherapy-treated patients) and rash (8.1% vs. 0%).

The most frequent (≥20%) adverse reactions of trametinib were rash, diarrhea, fatigue, peripheral edema, and acneiform dermatitis. Additional clinically significant adverse reactions of trametinib were hypertension, hepatotoxicity, bradycardia, and rhabdomyolysis.

Trametinib has a favorable benefit-risk profile for treatment of patients with BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma when compared to available treatment. Trametinib is the first drug to demonstrate efficacy in an important subgroup of patients with BRAF V600 mutation-positive melanoma, those whose melanoma harbor the BRAF V600K subtype, and it represents a new therapeutic option with a novel mechanism of action for treatment of the indicated patient population. Trametinib demonstrated superiority to chemotherapy—a clinically relevant comparator at the time of initiation of the MEK114267 trial—with a prolongation of PFS of sufficient magnitude, when compared to treatment effects of available therapy, to be considered clinical benefit. It is uncertain whether the prolongation in PFS with trametinib will also result in an improvement in OS, similar to the treatment effects observed with vemurafenib, also an inhibitor of kinases within the mitogen-activated protein kinase (MAPK) pathway but at a level upstream of the MEK1/2 kinases, the target of trametinib. In this reviewer's opinion, the role of trametinib administered as monotherapy to patients with BRAF V600E mutation-positive unresectable or metastatic melanoma is limited because direct inhibition of this mutant form of BRAF with a BRAF inhibitor, rather than downstream inhibition of the MEK1/2 kinase with trametinib, appears to result in greater magnitude of anti-tumor activity—limitations of cross study comparisons notwithstanding. Sequential use of trametinib following disease progression on a BRAF inhibitor is not a viable treatment strategy based on the results of MEK113583 trial—there were no confirmed objective tumor responses with trametinib administered at the to-be-marketed dose in a cohort of 40 patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. Importantly, the development program for trametinib is evaluating the efficacy of trametinib as combination therapy with dabrafenib, an inhibitor of the mutant BRAF V600E kinase, for treatment of patients with BRAF V600 mutation-positive melanoma— (b) (4) Cardiomyopathy—a common toxicity encountered by prescribers of oncology drugs/biologics—is one of the major safety risks of trametinib and requires appropriate monitoring and early intervention by clinicians to mitigate serious sequelae of this toxicity. This reviewer recommends that, as postmarketing requirements, the Applicant define and characterize the serious risks of cardiotoxicity and ocular toxicity with trametinib.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

The reviewer recommends the following post-marketing requirements:

1. Submit cumulative safety analyses annually, and for one year after the last patient has completed clinical trial treatment, to identify and characterize the risk of serious sequelae of cardiomyopathy, including safety evaluations adequate to inform labeling of patient populations at a highest risk for developing these toxicities and to provide evidence-based dose modification and monitoring recommendations, in all ongoing and subsequently initiated randomized controlled clinical trials through 2020 that use trametinib alone or in combination with other anti-cancer drugs.

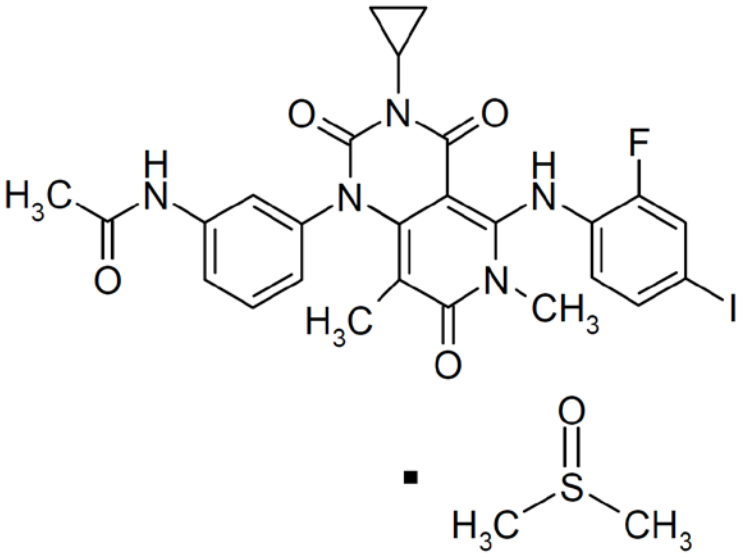
2. Submit integrated safety analyses from an adequate number of randomized controlled clinical trial(s) to identify and characterize the risk of retinal pigmented epithelial detachments (RPED), including safety evaluations adequate to inform labeling of patient populations at highest risk and to provide evidence-based dose modification and monitoring recommendations in labeling of RPED events.

2 Introduction and Regulatory Background

2.1 Product Information

The chemical name for trametinib dimethyl sulfoxide is 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). The molecular formula is $C_{26}H_{23}FIN_5O_4.C_2H_6OS$ and the molecular mass is 695.53 (DMSO solvate of parent). The structural formula of trametinib is presented in Figure 1.

Figure 1: Structural Formula of Trametinib



2.2 Tables of Currently Available Treatments for Proposed Indications

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

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

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

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

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

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

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

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

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

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

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

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

2.3 Availability of Proposed Active Ingredient in the United States

Trametinib is not available in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Trametinib, if approved by FDA, will be the first selective MEK inhibitor marketed in the U.S. Review of safety information for seven MEK inhibitors under IND—other than trametinib—identified the following important clinical safety issues common to two or more MEK inhibitors:

- Cardiac disorders—LVEF decrease, syncope
- Eye disorders— retinal vein occlusion (RVO), central serous retinopathy (CSR), and other retinal events
- Skin and subcutaneous disorders —rash (acneiform dermatitis, maculopapular rash)
- 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

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following summarizes the presubmission regulatory activity for trametinib:

- The Applicant submitted IND 102175 on April 14, 2008, and received notification from FDA that the first-in-human trial (MEK111054) was allowed to proceed on May 15, 2008.
- On July 30, 2010, FDA held a Type B, end-of-phase 1 (EOP1)/Pre-Phase 3 meeting to discuss the development program for trametinib in the proposed indication treatment of patients with B-RAF V600E/K (b) (4) mutation positive advanced or metastatic cutaneous melanoma (i.e., unresectable Stage IIIC or Stage IV). The Applicant proposed to conduct the MEK114267 trial, a randomized, open-label Phase III trial comparing trametinib to chemotherapy (dacarbazine or paclitaxel) in patients with unresectable or metastatic melanoma with BRAF V600 mutation (E/K (b) (4) that received up to one prior therapy, to support the proposed indication. The key agreements and comments from this meeting were:
  - FDA recommended that the Applicant enroll BRAF wild-type patients in MEK114267 to collect more data in this subgroup before concluding a lack of efficacy, but acknowledged that it was the Applicant's decision whether to include mutation-positive patients only in the proposed trial
  - FDA agreed with the proposed comparator arm but stated that whether product labeling will include both treatment-naïve patients (b) (4) would be a review issue
  - FDA did not agree with the proposed co-primary endpoints of PFS and OS and recommended that the Applicant evaluate OS as the sole primary endpoint
  - FDA acknowledged that it would be willing to discuss the results of study MEK114267, including the magnitude of the difference between arms and the clinical relevance of this difference, if it were to be designed using PFS as the primary endpoint

  - FDA stated that the companion diagnostic to select the proposed patient population must be approved by the time of drug approval
  - FDA agreed that the Applicant may initiate a prospective QTc study in cancer patients for GSK1120212 with results available after submission of an NDA. FDA stated that the Applicant should continue to collect routine ECGs at steady state post-dose in ongoing clinical studies and that the Applicant perform central tendency analysis and categorical analysis for submission in the original NDA
- On November 8, 2010, FDA held a Type C meeting to discuss a food effect study and an absolute Bioavailability study
- On November 9, 2010, FDA held a Type B, EOP1/Pre-Phase 3 Chemistry Manufacturing, and Controls (CMC) meeting to discuss the acceptability of the proposed CMC development plan to support the Phase 3 clinic studies, and ultimately the filing of the NDA
- On February 15, 2012, FDA held a Type B, pre-NDA CMC meeting to discuss and obtain Agency consensus on the acceptability of the proposed CMC information package supporting the planned NDA
- On May 9, 2012, FDA held a Type B, pre-NDA meeting to discuss the contents and planned NDA/eCTD submissions. The key agreements and comments from this meeting were:
  - FDA acknowledged that the design and reported results of the MEK114267 trial together with the proposed supportive data appear sufficient to support the filing of an NDA from a clinical perspective
  - FDA stated that it agreed to consider labeling that is inclusive of V600K and V600E mutational status (b) (4) if safety and efficacy in the subgroups are adequately supported by clinical study results and mechanism of action of trametinib
  - FDA stated that the Applicant's proposal (b) (4) is not acceptable. FDA agreed that the Applicant (b) (4) The Applicant agreed to provide a tabular summary of the incidence of AEs grouped by toxicity severity as well as the corresponding pooled datasets limited to clinical trials conducted using the same NCI CTCAE version
  - FDA agreed that the text portion of the integrated summary of efficacy (ISE) and integrated summary of safety (ISS) in modules 2.7.3 and 2.7.4, respectively, would be acceptable if sufficiently detailed to serve as the narrative portions of the ISS and ISE as per 21 CFR 314.50
  - FDA agreed with the Applicant's proposal for submission of patient narratives and case report forms (CRF)s
  - FDA agreed with the timing of the 120-day-safety update using a data cutoff date of June 23, 2012

- FDA agreed that the Applicant should submit, as soon as available, the independent analysis by (b) (4) of the five cases of sudden death/cardiac arrest reported coincident with the administration of trametinib

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

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

- Missing components of the electronic common technical document (eCTD) in the original NDA submission
- Data discrepancies resulting from, at least in part, incongruous data cutoffs between information captured in the datasets based on electronic case report forms (eCRF)s entries following data cleaning and that used to create the pdf versions of case report forms, and errors in the eCTD submission documents
- Dataset definition files did not contain definitions of multiple variables
- Dataset definition files contained an inadequate level of detail in the variable definitions to facilitate efficient review
- Inadequate and/or incorrect annotations within the annotated CRFs
- Key variables in datasets were absent, inconsistent in name or definition across datasets, and/or incomplete
- Non-functioning SAS programs for statistical analyses

Please see Dr. Chen's Statistical Review of NDA 204114 for additional details in regard to data quality and integrity.

3.2 Compliance with Good Clinical Practices

The Applicant stated the following:

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

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

OSI inspected three clinical sites as well as the Applicant (Table 2). The following was excerpted from the OSI review:

> Mohammed Milhem, M.D.
> Site #84362
> Assessment of data integrity:
> The data provided by Dr. Milhem's site for Study MEK114267 that were submitted to the Agency in support of NDA 204114 appear to be reliable and acceptable for use in support of the pending application.
>
> Lev Demidov, M.D.
> Site #86717
> Assessment of data integrity:
> The data provided by Dr. Demidov's site for Study MEK114267 that were submitted to the Agency in support of NDA 204114 appear to be reliable and acceptable for use in support of the pending application.
>
> Caroline Robert, M.D.
> Site #86614
> Assessment of data integrity:
> The data provided by Dr. Robert's site for Study MEK114267 that were submitted to the Agency in support of NDA 204114 appear to be reliable and acceptable for use in support of the pending application.
>
> GlaxoSmithKline
> Assessment of data integrity:
> The data generated, as it pertains to Study MEK114267 were inspected in accordance with the sponsor-monitor oriented BIMO compliance program, CP 7348.810. Study MEK114267 appears to have been conducted adequately by GlaxoSmithKline and the data submitted by the Applicant for this study may be used in support of the pending Application.
>
> OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS
> Based on the review of inspectional findings for the inspections of GlaxoSmithKline, Dr. Milhem, Dr. Demidov, and Dr. Robert, the data submitted by the Applicant for Study MEK114267 appear reliable in support of NDA 204114.

The preliminary classifications for the inspections of Dr. Demidov, and Dr. Robert, and the final classification for the inspections of GlaxoSmithKline and Dr. Milhem, are No Action Indicated (NAI).

Note: All observations noted above related to the inspections of Dr. Demidov and Dr. Robert are based on communications with the field investigators who conducted these inspections; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR for these inspections.

Table 2: Office of Scientific Investigations Clinical Site Inspection Results and Final Classification.

	Protocol / Site/ Subjects, N	Inspection Dates	Final Classification
Mohammed Milhem, M.D. University of Iowa Hospitals and Clinics Holden Comprehensive Cancer Center 5970Z JPP 200 Hawkins Drive Iowa City, IA 52242 US	MEK114267 Site: #84362 Subjects: 11	September 24-26, 2012	NAI
Lev Demidov, M.D. Cancer Research Center Kasirskoye Shosse, 24 Moscow, 115478 Russia	MEK114267 Site: #86717 Subjects: 10	December 3-7, 2012	Pending (Preliminary Classification NAI)
Caroline Robert, M.D. Institut Gustave Roussy Service de Dermatologie 39, rue Camille Desmoulins Villejuif, 94805 France	MEK114267 Site: #86614 Subjects: 11	November 26-29, 2012	Pending (Preliminary Classification NAI)
GlaxoSmithKline 1250 South Collegeville Road Collegeville, PA 19426	MEK114267	November 6-8, 2012	NAI

Source: FDA Clinical Inspections Summary for NDA 204114
Abbreviations in Table: NAI, no deviation from regulations; Pending, preliminary classification based on information in 483, if issued, and preliminary communication with the field; the EIR has not been received from the field and complete review of EIR is pending.

3.3 Financial Disclosures

In accordance with 21 CFR 54.2, GlaxoSmithKline submitted a list of the MEK114267 and MEK113583 trial investigators attached to FDA form 3454 certifying that the investigators had no financial arrangements as defined in 21 CFR 54.2(a, b, and f) that could affect the outcome of the study. No investigator had a financial interest in the Applicant at the time they started their participation in the covered study. If the Applicant was unsuccessful in collecting updated

financial information at the end of the trial from investigators despite acting with due diligence, which is up to three documented attempts to collect this information, the Applicant listed these investigators on Form 3454b "Data not obtained." Of 111 investigators (principal and subinvestigators) in the MEK113583 trial, the Applicant listed 11 on List (B) to Form 3454. Of 526 investigators (principal and subinvestigators) in the MEK114267 trial, the Applicant listed 26 on List (B) to Form 3454.

One subinvestigator (b) (6) at Study Site (b) (6) recruited (b) (6) patients out of the (b) (6) patients accrued in trial MEK115383. This subinvestigator received a significant payment, i.e. > $25,000, consisting of grants to fund ongoing research ($65,632), retainers for ongoing consultation ($1,750), and other ($263.61). The Applicant conducted analyses of the MEK113583 trial with and without the data from study site (b) (6); the AE rate, patient disposition, baseline demographic profiles, and best confirmed response rates are, in general, consistent for each cohort with or without inclusion of data from Study Site (b) (6).

REVIEWER COMMENT:
Financial arrangements with the investigators, based on the information reported by the Applicant, did not raise questions about the integrity of the covered trials MEK113583 and MEK114267.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The Applicant submitted a major amendment to NDA 204114 on April 13, 2013, to support alternate storage conditions of trametinib than those proposed in the original NDA. Please refer to the CMC Review of NDA 204114.

4.2 Clinical Microbiology

The drug product is a non-sterile tablet for oral administration. Product Quality Microbiology did not identify any microbiology deficiencies. Refer to Dr. Metcalfe's Product Quality Microbiology review for details.

4.3 Preclinical Pharmacology/Toxicology

The Applicant conducted 13-week toxicity studies in Sprague Dawley rats and Beagle dogs. The main target organs of toxicity in rats were skin, gastrointestinal tract, lymphoid and hematopoietic organs, liver, and adrenal gland. In dogs, the primary target organs of toxicity were also skin and gastrointestinal tract as well as lymph nodes and lungs. The following lung

toxicity information is excerpted from the FDA Pharmacology/Toxicology review of NDA 204114:

> Gross findings of pale, raised, or dark areas in the lungs corresponded with histopathological findings of minimal hemorrhage, mononuclear infiltration, pleural fibrosis, and macrophage accumulation. All findings in the lung were classified as minimal to mild; however, clinically, treatment with trametinib has been associated with cases of interstitial lung disease and pneumonitis.

Trametinib was not genotoxic based on in vitro and in vivo studies. The Applicant did not conduct carcinogenicity studies of trametinib based on the intended use in patients with advanced cancer.

In cardiac safety pharmacology studies, trametinib demonstrated low potential for causing QT prolongation. However, repeat dose studies in mice demonstrated decreases in left ventricular function. The following summary of cardiac safety pharmacology studies is excerpted from the FDA Pharmacology/Toxicology review:

> ECG monitoring was included in the 13-week dog toxicology study and in separate single dose studies in both anesthetized and conscious dogs. No [treatment]-related effects were observed. *In vitro*, trametinib inhibited hERG channel activity in a concentration dependent manner in assays conducted on CHO-K1 and HEK293 cells but with IC50 values of 3.7 μM and 1.54 μM, respectively, suggesting low potential for causing QTc prolongation at physiologically relevant levels. Trametinib had no effect on QT prolongation when tested in the rabbit left ventricular wedge preparation though there was a decrease in contractility in wedges at high concentrations of the drug. In an attempt to further characterize the cardiac toxicity noted during the clinical development of trametinib, the Applicant conducted a study using male mice administered GSK1120212B at dose levels of 0.25 and 0.5 mg/kg given by oral gavage once daily for 21 days. Trametinib-dependent decreases in mean heart rate and lower mean absolute and relative heart weights were observed, regardless of dose level. In addition, trametinib-treated mice had lower left ventricular functional parameters, though the contractility response to dobutamine was preserved in these animals. The decrease in left ventricular function was similar to that reported in humans though mice tolerated trametinib at exposures higher than either humans or other animal species tested and the cardiac findings in this study occurred at exposures 3- to 7-fold higher than the clinical exposure at the recommended dose.

The FDA Pharmacology/Toxicology reviewers recommend the designation of trametinib as Pregnancy Category D based on the submitted reproductive toxicology studies of trametinib.

According to the FDA Pharmacology/Toxicology NDA review and evaluation, the review of nonclinical studies supports a recommendation for approval of the marketing application for trametinib tablets. Please refer to the review of Pharmacology/Toxicology by Drs. Khasar, Weis,

and Brower for additional details of the nonclinical studies submitted by the Applicant in support of NDA 204114.

4.4 Clinical Pharmacology

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

4.4.1 Mechanism of Action

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

Administration of a 1 mg and 2 mg dose of trametinib to patients with BRAF V600 mutation-positive melanoma resulted in dose-dependent changes in tumor biomarkers including inhibition of phosphorylated ERK, inhibition of Ki67 (a marker of cell proliferation), and increases in p27 (a marker of apoptosis). The following is excerpted is from the FDA NDA Clinical Pharmacology Review:

> Baseline and post-dose (day 15) paired tumor biopsies were obtained for IHC analysis in 22 patients who received trametinib at doses of 0.5, 1.0, or 2.0 mg QD in Study MEK111054. Higher doses resulted in greater inhibition of pERK and Ki67 and increase in p27, with the magnitude of change appearing more pronounced in patients with BRAF V600 mutation-positive melanoma versus patients with all tumor types and mutation status, although the sample size is small.

Table. Median percent change from baseline in H scores of exploratory biomarkers by dose

	All tumor types and mutation status[b]				BRAF V600 mutation positive melanoma		
	pERK	**Ki67**	**p27**		**pERK**	**Ki67**	**p27**
0.5 (n=8)	2.6	-3.9	3.6	0.5 (n=0)	N/A[a]	N/A[a]	N/A[1]
1.0 (n=4)	3.8	-2.1	35.2	1.0 (n=2)	7.5	12.5	46.1
2.0 (n=10)	-30.0[c]	-54.4	83.0	2.0 (n=4)	-61.5[d]	-83.0	171

[a] No patients with BRAF V600 mutation-positive melanoma in the 0.5 mg dose group
[b] Source: Study MEK111054 final study report, Table 12.1, Pages 1514-5
[c] n=9; [d] n=3

4.4.3 Pharmacokinetics

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

> ***ADME:*** The mean absolute bioavailability of a single 2 mg oral dose of trametinib is 72%, with median time to achieve peak concentrations (T_{max}) of 1.5 hours. The increase in exposure is greater than dose proportional after a single dose of 0.125 to 10 mg, and dose-proportional following repeat doses of 0.125 to 4 mg. Following oral administration of 2 mg trametinib daily (QD), geometric mean C_{max}, C_{trough} (pre-dose concentration), and $AUC_{(0-\tau)}$ at day 15 are 22.2 ng/mL, 12.1 ng/mL, and 370 ng·hr/mL, respectively. Inter-patient variability at steady state is 22% in AUC and 28% in C_{max}. Trametinib is highly protein bound (97.4%).
>
> Trametinib undergoes non-CYP450 mediated metabolism predominantly via deacetylation to form M5 or in combination with hydroxylation to form M7. Following repeat doses of trametinib, the parent drug is the major component (≥ 75%) in plasma, with M5 and M7 each constituting approximately 10% of drug-related material. Following oral administration of [^{14}C]- trametinib, > 80% of excreted radioactivity was recovered in the feces while < 20% of excreted radioactivity was recovered in the urine with < 0.1% of the excreted dose as parent drug in urine. The estimated elimination half-life based on the population pharmacokinetic (popPK) analysis is 3.9 to 4.8 days. The accumulation ratio on day 15 relative to day 1 is approximately 6.
>
> ***Food Effect:*** Administration of a single 2 mg dose of trametinib with a high-fat, high-calorie meal resulted in a 70% decrease in C_{max} and a 24% decrease in AUC_{0-168h}, compared to fasted conditions. The Applicant recommends that trametinib be administered one hour before or two hours after a meal, similar to the fasted conditions in clinical trials. Considering the approximately lower peak to trough ratio at steady state (2) as compared to that after a single dose (4 to 5), a 70% decrease in C_{max} observed after a single dose would be less pronounced after repeat dosing, and a 24% decrease in AUC is not considered clinically important as efficacy was also achieved in patients whose dose was reduced to 1.5 mg (a 25% dose reduction due to intolerability) in the registration trial. However, given that a single dose of trametinib taken with a high-fat meal resulted in a 24% decrease in systemic exposure and the clinical efficacy of trametinib was established under fasted conditions, the review team recommends avoiding administration of trametinib with a high-fat meal to preserve clinical efficacy while providing a less restricted dosing condition for better compliance.

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

Organ Impairment: Formal clinical studies have not been conducted to evaluate the effect of organ impairment on the pharmacokinetics (PK) of trametinib. A popPK analysis showed that mild and moderate renal impairment and mild hepatic impairment did not influence the apparent clearance of trametinib, hence no dose adjustment is recommended for patients with mild or moderate renal impairment and for patients with mild hepatic impairment. No data is available in patients with severe renal impairment and in patients with moderate or severe hepatic impairment. Based on the results of a mass balance study and the popPK analysis suggesting that hepatic elimination is the major route while renal excretion is a minor route of elimination for trametinib, the Applicant is requested to conduct a clinical trial to determine the appropriate trametinib dose in patients with hepatic impairment under a post marketing requirement (PMR).

The Applicant has not conducted formal drug interaction studies with trametinib. Based on in vitro studies, trametinib is not a substrate of CYP450 or efflux transporter P-gp or BCRP, is not an inhibitor of the CYP enzymes tested (see below), but is a potential inducer of CYP3A4. The following is excerpted from the FDA Clinical Pharmacology NDA Review:

Drug Interactions: Trametinib is not a substrate of CYP450 or efflux transporters P-gp or BCRP in vitro. However, it is not known if trametinib is a substrate for OATP. An IND comment will be sent to the Applicant to consider conducting an in vitro study to determine if trametinib is a substrate of OATP.

In vitro studies with human hepatic microsomes showed that trametinib (at concentrations of 0.01 to 10 μM) does not inhibit CYP enzymes including CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, and transporters including OATP1B1, OATP1B3, P-gp, and BCRP at a clinically relevant systemic concentration of 0.04 μM (calculated R1 values < 1.1). Trametinib inhibits CYP2C8 with an R1 value of 1.2, which is slightly greater than the cutoff value of 1.1.

In vitro studies with primary human hepatocytes indicated that trametinib has the potential to induce CYP3A4, but not CYP2B6 or CYP2C8. Based on cross-study comparisons, oral administration of trametinib 2 mg QD with everolimus (sensitive CYP3A4 substrate) 5 mg QD had no clinically important effect on the exposure (AUC and Cmax) of everolimus.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3 lists clinical trial data submitted by the Applicant in support of this NDA. The Applicant states that the melanoma program consisted of three clinical trials to demonstrate that trametinib was safe and effective for the treatment of patients with BRAFV600 mutation-positive melanoma: the primary trial, MEK114267, and two supportive trials, MEK113583 and MEK111054.

Table 3: Clinical Studies of Trametinib.

Trial ID	Purpose	Centers N	Countries	Subjects N
MEK114267[a]	Efficacy/Safety	86	Argentina, Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Greece, Italy, Norway, Poland, Russia, Sweden, Switzerland, Ukraine, United Kingdom, United States, New Zealand.	322
MEK113583[a]	Efficacy/Safety	10	Australia, United States	97
MEK111054[a]	Efficacy/Safety/ PK	12	United States	206
BRF113220	Safety/ PK / PD	16	Australia, United States	74[b]
P3K113794	Safety/ PK/PD / Efficacy		Canada, Italy, United States	48
TAC113886	Safety/ PK/PD Efficacy	NR	United States	63
TAC115829	Safety/ PK/PD/ Efficacy	NR	United Kingdom, United States	20
MEK114784	Safety/ PK/PD/ Efficacy	NR	Japan	18
MEK113487	Efficacy/ Safety/ PK/PD	NR	Australia, Belgium, Canada, Germany, Korea, Poland, Spain, Taiwan, United States	160
MEK111759	Efficacy/Safety/ PK/PD	NR	Belgium, France, Germany, United States	95
MEK114653	Efficacy/ Safety/ PK/PD	NR	France, Greece, Hungary, Italy, Netherlands, Spain, South Korea, United States,	128
MEK114375	Rollover	NR	United States	38
MEK113486	PK	NR	United States	120
MEK113177	PK	NR	United States	75
MEK112111	PK	2	United States	31
MEK112110	PK	NR	Belgium, France, Germany, Spain, South Korea, United States	67
MEK115064	BP-Absolute bioavail-ability	1	United States	4
MEK113709	BP-food effect	3	United States	24
MEK113708	BP-ADME	1	United States	2

Abbreviations in Table: BP, biopharmaceutic trial; ID, identifier; NR, not reported; PD, Pharmacodynamic trial, PK, pharmacokinetic trial,
[a] Trial reviewed in the clinical review of efficacy and/or safety.
[b] Subgroup of patients in the PK population.

5.2 Review Strategy

The clinical review of safety and efficacy focused on data from three trials to support the proposed indication (see Section 2.1); the NDA contains a single randomized, active-controlled trial which serves as the primary evidence of efficacy. The primary clinical review includes a joint clinical-statistical review of efficacy. The FDA statistician was the primary reviewer of efficacy portion of the MEK114267 trial. The clinical review of efficacy presents the findings of the primary statistical review of the MEK114267 trial in applicable subsections within Section 6 of this review. In addition, the FDA statistician generated a separate, primary review of the NDA. One medical officer performed the primary clinical review of safety as well as completed the remaining sections of the NDA review template. Please note that Section 5.3 contains the review of the individual clinical trial methods and Sections 6 and 7 present the reviews of efficacy and safety, respectively.

The clinical review of efficacy focused on detailed review and analysis of all data from the MEK114267 trial including the clinical study reports, CRFs, and SAS datasets. The clinical review included review and analysis of the trial designs, SAP, and results of the MEK113583 and MEK111054 trials to evaluate whether these trials support the results of the MEK114267 trial.

The clinical review of safety focused on safety data from the MEK114267 trial with additional analyses focused on clinically important AEs with trametinib (e.g., deaths, non-fatal SAEs, AEs leading to treatment modifications, significant AEs) from the MEK113583 and MEK111054 trials. In addition, analyses of safety information submitted for patients who received trametinib across the trametinib development program served to identify additional safety signals with trametinib.

The review included the following:

- Evaluation of the current literature on melanoma epidemiology, diagnosis, prognostic features, and treatment
- Review of the trials listed in Table 3 including the clinical study reports, protocols, protocol amendments, SAPs, and/or synopses
- Assessment of the eCTD Module 2 summaries including the Clinical Module Overview, Summary of Clinical Effectiveness, and Summary of Clinical Safety, Integrated Summary of Efficacy, Integrated Summary of Safety, Risk Management Plan, and proposed labeling
- Analyses using the Applicant's data sets, with a focus on the data sets derived directly from the original CRFs (listings data sets), to evaluate the safety and efficacy of trametinib

- Consultations with the FDA statisticians
- Formulation of benefit/risk analysis and recommendations

5.3 Discussion of Individual Studies/Clinical Trials

Protocol No.: MEK114267

REVIEWER COMMENT: Section 5.3 of the review summarizes protocol MEK114267, Amendment 3. The Applicant submitted amendments 4 and 5 after the data cutoff date. At the end of the protocol (Amendment 3) summary, this section provides a summary of the key revisions within each amendment.

Clinical Trial Title

MEK114267, a Phase III randomized, open-label study comparing GSK1120212 to chemotherapy in subjects with advanced or metastatic BRAF V600E/K mutation-positive melanoma.

Study Sites

The Applicant conducted this study in 86 centers in North America, Europe, Australia, New Zealand, and South America.

Objectives:

The objectives specify different analyses based on the following patient subgroups (Table 4):

Table 4: Definition of Patient Subgroups. MEK114267 Protocol.

	Prior Chemotherapy	
	Yes	**No**
BRAF V600 mutation subtype / brain metastasis status		
V600E / no prior brain metastasis	A	B
V600E / prior brain metastasis	C	
V600K / No prior or prior brain metastasis	D	

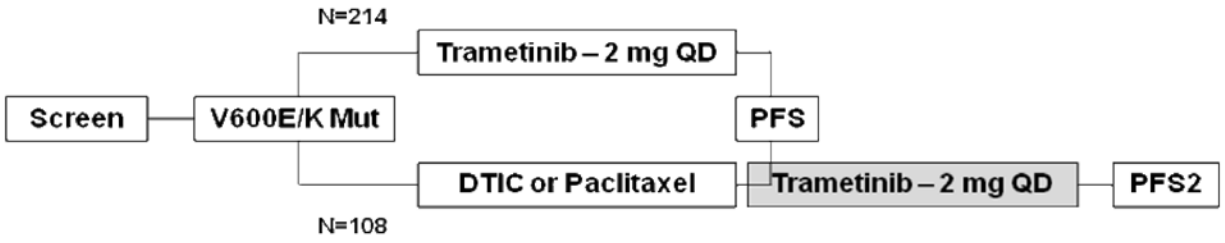
- **Primary**: to establish the superiority of GSK1120212 over chemotherapy with respect to PFS in the primary analysis population, i.e. patients with advanced/metastatic BRAF V600E mutation-positive melanoma without a history of prior brain metastases [Table 4, Subgroups A+B]

- **Secondary**:
  - to characterize PFS in two subgroups, based on receipt of prior chemotherapy in the advanced or metastatic setting, within the primary analysis population: (1) no prior chemotherapy [Table 4, Subgroup A] and (2) one prior chemotherapy [Table 4, Subgroup B]
  - to characterize OS, ORR, and DOR in the primary analysis population [Table 4, Subgroups A+B]
  - to characterize PFS, OS, ORR, and DOR in the intent-to-treat (ITT) population (i.e. regardless of BRAF mutation or history of brain metastases) [Table 4, Subgroups A+B+C+D]
  - to characterize ORR and DOR in patients with BRAF V600K mutation-positive melanoma regardless of prior history of brain metastases or prior chemotherapy[Table 4, Subgroup D]
  - to characterize ORR and DOR in patients with BRAF V600E mutation-positive melanoma regardless of prior history of brain metastases or prior chemotherapy [Table 4, Subgroups A+B+C]
  - to characterize PFS, ORR, DOR in patients following crossover from chemotherapy to GSK1120212. [Table 4, Subgroups A+B+C+D]

Study Design

This was a multicenter, open-label, randomized (2:1) two-arm, Phase 3 trial in patients with histologically confirmed, advanced or metastatic (Stage IIIc or Stage IV) BRAF V600E or BRAF V600K mutation-positive cutaneous melanoma who received either no prior chemotherapy or a maximum of one prior chemotherapy regimen for advanced of metastatic disease. Randomization strata were LDH [above institutional upper limit of normal (ULN) vs. equal or below ULN] and prior chemotherapy for advanced or metastatic disease (Yes vs. No). The trial used a central interactive voice response system (IVRS) to randomize patients to receive GSK1120212 or chemotherapy (choice of dacarbazine or paclitaxel at the discretion of the investigator provided the patient had not received that type of chemotherapy before randomization). At the time of progression of disease (PD), patients on the chemotherapy arm could crossover to receive GSK1120212 (Figure 2):

Figure 2: MEK114267 Trial Design.



Reproduced from Module 2.7.3, Page 11

Study Population

Inclusion criteria:

- Men or women ≥ 18 years of age
- Histologically confirmed diagnosis of Stage III unresectable (Stage IIIc) or metastatic (Stage IV) cutaneous melanoma which is also determined to be BRAF V600E or BRAF V600K mutation-positive by the central laboratory
- No prior treatment or up to one prior regimen of chemotherapy for advanced or metastatic melanoma. Prior treatment with immunotherapy (except ipilimumab unless given in the adjuvant setting) or sorafenib was allowed. PD must be documented for any anticancer therapy prior to randomization
- Measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1)
- All prior treatment-related toxicities must have recovered to NCI CTCAE (v 4.0) ≤ Grade 1 (except alopecia)
- Able to swallow and retain oral medication and not have any clinically significant gastrointestinal abnormalities that may alter absorption
- Women of childbearing potential (WOCBP) and men with reproductive potential must agree to use effective contraception during the study. WOCBP must have a negative serum pregnancy test within 14 days prior to randomization
- ECOG PS≤ 1
- Organ Function criteria: ANC ≥1.5 x 10^9/L, platelet count ≥ 100 x 10^9/L, Hb ≥ 9g/dL, PT/INR and PTT ≤ 1.5 x upper limit of normal (ULN), total bilirubin ≤ 1.5 x ULN, AST and ALT ≤ 2.5 x ULN, serum creatinine ≤ 1.5 mg/dL, and LVEF ≥ lower limit of normal (LLN) by Echo or MUGA
- French subjects: In France, a patient will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category

Exclusion criteria:

- Any prior use of BRAF inhibitors (BRAFi), MEK inhibitors (MEKi), or ipilimumab in the advanced or metastatic setting
- Patients who have received dacarbazine or paclitaxel prior to randomization will not be eligible to receive the same chemotherapy as study medication
- Any major surgery, extensive radiotherapy, chemotherapy with delayed toxicity, biologic therapy or immunotherapy within the last 21 days. Chemotherapy given daily or weekly without the potential for delayed toxicity within the last 14 days
- Current use of any prohibited medication
- History of another malignancy with the exception of patients who have been disease-free for 3 years or patients with a history of completely resected non-melanoma skin cancer

- Any serious and/or unstable pre-existing medical, psychiatric disorder, or other conditions that could interfere with patient safety, obtaining informed consent, or complying with study procedures
- Known Human Immunodeficiency Virus (HIV), Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection (with the exception of chronic or cleared HBV and HCV infection which was allowed)
- Brain metastases with the following exceptions that were all confirmed by the Applicant's Medical Monitor:
  - All known lesions must be previously treated with surgery or stereotactic radiosurgery (prior whole brain radiotherapy was not allowed
  - Brain lesion(s), if still present, must be confirmed stable (i.e. no increase in lesion size), or if no longer present, must be confirmed as no evidence of disease, for ≥90 days prior to randomization (must be documented with two consecutive MRI or CT scans using contrast performed at least 60 days apart)
  - Patient was asymptomatic with no requirement for corticosteroids for ≥ 30 days prior to randomization
  - No requirement for enzyme-inducing anticonvulsants for ≥ 30 days prior to randomization
- History or evidence of cardiovascular risk including any of the following:
  - QTcB ≥ 480 msec
  - History or evidence of current clinically significant uncontrolled arrhythmia with the exception of atrial fibrillation that was controlled for >30 days prior to randomization
  - History of (within 6 months prior to randomization) acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting
  - History or evidence of current ≥ Class II congestive heart failure as defined by New York Heart Association (NYHA)
- History of interstitial lung disease or pneumonitis
- History of or current evidence or risk of RVO or CSR, predisposing factors to RVO or CSR (e.g. uncontrolled glaucoma or ocular hypertension, uncontrolled hypertension, uncontrolled diabetes mellitus, or history of hyperviscosity or hypercoagulability syndromes), or visible retinal pathology as assessed by ophthalmic exam considered a risk factor for RVO or CSR such as:
  - Evidence of new optic disc cupping
  - Intraocular pressure > 21 mm Hg as measured by tonography
- Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to the study drug, or excipients or to dimethyl sulfoxide (DMSO) or to Cremophor EL (polyoxyethylated castor oil)
- Lactating female

Treatment Plan

The protocol specified stratified randomization (2:1) using the randomization strata LDH (> ULN vs. ≤ ULN) and prior chemotherapy for advanced or metastatic disease (Yes vs. No) to the following treatment arms:

- Arm A
  - GSK1120212 (trametinib) 2 mg administered orally under fasting conditions (at least one hour before a meal or at least two hours after a meal) once daily
- Arm B
  - Dacarbazine 1000mg/m^2 administered intravenously (iv) once every 21 days
  - Paclitaxel 175mg/m^2 administered iv once every 21 days

Treatment continued until PD, unacceptable toxicity, death, or withdrawal.

Patients received premedications for dacarbazine or paclitaxel as per the institutional standard of care.

The protocol allows crossover of patients randomized to the chemotherapy arm who have documented PD–confirmed by the independent radiological review committee based on RECIST 1.1—to receive GSK1120212 if patients meet the following criteria:

- All toxicities (except alopecia) due to chemotherapy must be NCI CTCAE (Version 4.0) ≤ Grade 1
- Have no known brain metastases or neurologic symptoms indicating brain metastases
- ECOG performance status 0-2
- Last ECHO/MUGA within normal limits

REVIEWER COMMENT: The eligibility criteria for crossover are dissimilar to enrollment eligibility criteria in two key baseline characteristics: (1) the protocol eligibility criteria to enroll in the trial would have excluded patients with an ECOG PS of 2 and (2) the screening evaluation included a brain MRI to exclude patients with untreated/unstable brain metastases—this evaluation was not required at the time of crossover.

Dose Modification and Supportive Care Guidelines

The protocol specified the following GSK1120212 dose levels (Table 5):

Table 5: GSK1120212 (Trametinib) Dose Levels. MEK114267 Protocol.

Dose Level	Dose/Schedule
0	2 mg once a day
-1	1.5 mg once a day
-2	1.0 mg once a day

Protocol MEK114267 provided general dose modification guidelines for GSK1120212 (Table 6) as well as specific treatment modification guidelines for rash, ejection fraction changes, visual changes, pneumonitis, and diarrhea (*see Appendix 9.4 Treatment Modification Plan for Toxicity, MEK114267 Trial).*

Table 6: General Dose Modification Guidelines for Trametinib. MEK114267 Protocol.

Toxicity Grade	Dose Modification of GSK1120212
1	Continue at current dose level
2	Temporarily interrupt dose until toxicity resolves to Grade 1 or baseline. Upon resolution, then restart at current dose
3	Temporarily interrupt dose until toxicity resolves to Grade 1 or baseline. Upon resolution, then consider dose reducing by
4	Permanently discontinue GSK1120212

The protocol permitted a maximum of two dose reductions of paclitaxel and dacarbazine according to the following dose levels (Table 7):

Table 7: Paclitaxel and Dacarbazine Dose Levels. MEK114267 Protocol.

Dose Level	Paclitaxel Dose	Dacarbazine Dose
0	175 mg/m^2	1000 mg/m^2
-1	135 mg/m^2	750 mg/m^2
-2	90 mg/m^2	500 mg/m^2

Table 8 and Table 9 show the dose modifications for clinically significant non-hematological or hematological toxicities, respectively, related to either paclitaxel or dacarbazine.

Table 8: Chemotherapy Dose Modification Guidelines for Non-Hematological Toxicity. MEK114267 Protocol.

Toxicity Grade	Action
1 or 2	Continue paclitaxel or dacarbazine therapy.
3 or 4	Hold paclitaxel or dacarbazine therapy until recovery to Grade ≤1, then decrease paclitaxel or dacarbazine dose by one dose level. Exception: for Grade 4 hypersensitivity reactions, discontinue paclitaxel or dacarbazine permanently.

Table 9: Chemotherapy Dose Modification Guidelines for Hematological Toxicity. MEK114267 Protocol.

<table>
<tr><th colspan="2">Hematologic Toxicity</th><th colspan="3" rowspan="2">Treatment Modification Instructions</th></tr>
<tr><th>ANC Nadir</th><th>Platelets Nadir</th></tr>
<tr><td>≥500 -<1500 mm^3 (or <500/mm^3 for <7 days and no neutropenic fever)</td><td>AND/OR
≥75,000 - < 100,000/mm^3</td><td colspan="3">Withhold paclitaxel or dacarbazine until ANC ≥ 1500/mm^3 and Platelets ≥ 100,000/mm^3. No dose reductions</td></tr>
<tr><td rowspan="2"><500/mm^3 (for ≥7 days and no neutropenic fever) OR with neutropenic fever</td><td rowspan="2">AND/OR
<75,000/mm^3</td><td colspan="3">Withhold paclitaxel or dacarbazine until ANC ≥ 1500/mm^3 and Platelets ≥ 100,000/mm^3</td></tr>
<tr><td>First Occurrence: Reduce the paclitaxel dose to 135 mg/m^2 or dacarbazine dose to 750 mg/m^2</td><td>Second Occurrence: Reduce the paclitaxel dose to 90 mg/m^2 or dacarbazine dose to 500 mg/m^2</td><td>Third Occurrence: Discontinue paclitaxel or dacarbazine permanently</td></tr>
</table>

Monitoring Plan

The monitoring plan and study scheduled tests and evaluations are summarized in Table 10.

Table 10: Schedule of Assessments. MEK114267 Trial.

			AT ALL CYCLES	PLUS AT THESE SPECIFIC CYCLES							
Study Assessments	**Screening[1]**	**Day 1 Cycle 1**	**Day 1 Cycle 2- Cycle X [4]**		**Day 1 Cycle 5**	**Day 1 Cycle 8**	**Day 1 Cycle 11**	**Day 1 Every 4 Cycles (starting with Cycle 15)**	**Treatment Dis-continuation**	**Follow- up Post Treatment Dis-continuation**	**Conclusion**
Informed consent[2]	X										
Demographic data	X										
Serum pregnancy test[3]	X										
Randomize subject		X									
Disease characteristics	X										
Prior therapy	X										
Ophthalmologic Exam[17]	X										
Past and current medical conditions including cardiovascular familial history	X										
Dispense oral medication and assess compliance [5]		X	X								
Administer IV dacarbazine or paclitaxel[5]		X	X								
Lesion assessment (including photography for skin lesions)[6]	X	Week 6, Week 12, Week 21 and Week 30 and then every 12 weeks (± 7 days)									
Brain MRI[6,20]	X										
Quality of life assessment[18]	X	Week 6, Week 12, Week 21 and Week 30 and then every 12 weeks (±7 days) until determination of progressive disease, at disease progression, and 6 weeks following disease progression.									
Vital signs (including Height/Weight)[7]	X		X						X		
Performance status (ECOG)	X		X						X		
Physical examination[8]	X		X						X		
ECG[9]	X		X (only at Cycle2)		X	X	X	X	X		
Echocardiogram (ECHO)/MUGA[10]	X		X (only at Cycle2)		X	X	X	X			
Concomitant medications	X	X	X						X		
Chemistry and Hematology[12]	X		X						X		
Coagulation	X										
Sample collection for cardiac markers[12] (Blood collection ONLY)		X	X (only at Cycle2)		X						
Adverse events[11]	X	X	X						X	X	X
Blood sample for PK[19]			X (only at Cycle 2)		X	X					
Blood sample for PGx[13]		X									
Plasma sample for circulating free DNA[14]	X								X		
Mandatory tumor tissue sample for V600 E/K (T1799A) testing[15]	X										
Optional tumor tissue for biomarkers[15]	X								X		
Follow up contact[16]										X	
Follow up anti-cancer therapy										X	
Subject completion or death											X

PGx = pharmacogenetics; IP = investigational product; MRI = magnetic resonance imaging; ECOG = Eastern Cooperative Oncology Group; ECG = electrocardiogram; ECHO = echocardiogram

1. All screening procedures may be performed 14 days prior to randomization, except for tumor assessments, ECG, ECHO/MUGA scans and Ophthalmologic Exam which may be performed within 28 days prior to randomization.
2. Informed consent for PGx research is to be obtained before any PGx-related procedures. Only subjects consented for the main clinical study are eligible for consent for PGx.
3. Serum pregnancy test will be required in women of child-bearing potential within 14 days prior to randomization. Subsequent tests may be urine tests, and should be performed as clinically indicated.
4. These assessments apply to all cycles and should be performed on Day 1 of EACH cycle unless otherwise specified in this column. For other cycles listed in this table the Cycle 2 – Cycle X assessments must be performed in conjunction with those listed out separately for specific named cycles.
5. Subjects should start treatment as soon as possible after randomization up to a maximum of 72 hours post-randomization. For subjects randomised to receive GSK1120212 dispense a 3 week supply with instructions. Record dose reductions and/or dose interruptions/delays, dose escalations.
6. Lesion assessment by contrast CT or MRI of chest, abdomen and pelvis, including photography of skin lesions must be performed within 28 days prior to randomization. Target and non-target lesions must be identified at time of screening scan and the same lesions must be re-assessed at each timepoint in a consistent way. Assessments must be performed on a calendar basis (i.e. not delayed due to delays in administering study medication). A window of ± 7 days is allowed for scheduling. The same diagnostic method, including use of contrast when applicable, must be used throughout the study to evaluate each lesion. Lesion assessment [contrast CT (preferred) or MRI of chest, abdomen and pelvis], including photography for skin lesions with callipers should occur at times shown until disease progression (even if the patient withdraws from treatment). If Brain MRI is contraindicated then CT with and without contrast is acceptable. If the last radiographic assessment was more than 6 weeks prior to subject discontinuation from study and progressive disease has not been documented, a disease assessment should be obtained at the time of study discontinuation and continued thereafter until determination of progressive disease.
7. Record blood pressure, pulse rate and body weight. Height measured only at screening. Measurements should be in Metric scale.
8. Physical examination: Full physical exam at screening, then brief physical exam at the start of each cycle.
9. ECG assessments must be performed within 28 days prior to randomization. Two copies of the ECG tracing should be obtained at the time of the ECG, one to be kept in the study file for retrospective collection by the sponsor if necessary.
10. ECHO (preferred)/ MUGA assessments must be performed within 28 days prior to randomization. An ECHO/MUGA should be performed on (±3 days) Day 1 of Cycle 2 (week 3). ECHO/MUGA should be performed on Day 1 (±7 days) on Day 1 of Cycles 5 (week 12), 8 (week 21), 11 (week 30) then every 4 cycles (every 12 weeks) thereafter until discontinuation of IP. 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) must follow the LVEF guidelines for study drug management and requirements for subsequent ECHO/MUGA.
11. Adverse event assessment should be continuous until 30 days post-treatment.
12. Haematology, Chemistry and cardiac markers: Evaluations will be performed by the central laboratory. Screening labs performed within 14 days prior to randomization do not need to be repeated. Unscheduled labs (i.e. hematology), if required may be conducted at the local laboratory. Cardiac marker samples will be stored for possible retrospective analysis.
13. Blood sample for PGx: To be obtained only if the informed consent for PGx research has been obtained. Sample can be collected at any timepoint during the study, however collection at the first opportunity following randomization is preferred.
14. A plasma sample for circulating free DNA is mandatory at screening and an optional sample may be assessed at the time of disease progression.
15. Tumor tissue sample (mandatory) to be obtained from most recent tissue available to assess for V600E/K(T1799A) DNA mutation using the central BRAF mutation assay at screening.; An optional tumour tissue sample from a lesion not required for disease assessment may be collected at screening or baseline, and at the time of disease progression for biomarker analyses.
16. Follow up contact: Record the date of last contact in follow up. Contact includes clinic visits, telephone contacts, and e-mail. Subjects should be contacted for follow-up every 12 weeks post disease progression.
17. Ophthalmologic exam will include indirect fundoscopy and tonometry. Color fundus photos are also recommended at screening if available. After screening, additional Ophthalmologic exams and photos (if available) will be performed only as symptomatically warranted.
18. The quality of life assessment will consist of the EORTC QLQ-C30 and EQ-5D and will be conducted at times shown.
19. PK samples for subjects taking GSK1120212 are to be obtained during the study visit at Day 1 of Cycles 2, 5, and 8. Subjects with morning clinic visits will be instructed to withhold their morning dose, and samples will be collected prior to GSK1120212 administration; for subjects with afternoon clinic visits, subjects will take their morning dose as usual, and samples will be collected 4-8 hours following GSK1120212 administration. Date and exact time of PK sample and of most recent dose will be recorded.
20. Brain lesion(s), if still present at baseline, must be confirmed stable (i.e. no increase in lesion size) for ≥90 days prior to randomization (must be documented with two consecutive MRI or CT scans using contrast)

Source: Reproduced from the Protocol MEK114267, Table 11.

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

Statistical and Analytical Plan

The primary analysis population was a subgroup of the ITT population: patients with BRAF V600E mutation-positive melanoma without a prior history of brain metastases.

REVIEWER COMMENT: Amendment 3 to the protocol revised the primary efficacy population from the ITT population to the subset of patients with BRAF V600E mutation-positive melanoma without a prior history of brain metastases based on the following rationale: to focus on the

population most likely to benefit from trametinib. The Applicant states that the revision to the primary efficacy analysis was prompted by results of the MEK113583 trial which observed prolonged PFS in the subgroup of patients with BRAF V600E mutation-positive melanoma without a prior history of brain metastases compared to that observed in the overall study population. The Applicant's revision of the primary efficacy analysis population to a subgroup of the ITT increases the potential for bias. Neither BRAF V600 mutation-subtype nor history of brain metastases were stratification factors in the MEK114267 trial; in fact, there was an imbalance between treatment arms in the proportion of the ITT population that qualified for inclusion in the revised primary efficacy population, 83% of the trametinib arm compared to 88% of the chemotherapy arm. The primary analysis population for the purposes of regulatory consideration, as agreed upon by the Applicant, is the intent-to-treat population (see Dr. Chen's Statistical Review for details).

The primary endpoint was PFS in the primary efficacy population (i.e., patients with BRAF V600E mutation-positive melanoma without a prior history of brain metastases) defined as the time from randomization until the earliest date of radiological disease progression documented by the investigator per RECIST 1.1 or death. Secondary endpoints are OS, ORR, duration of response, and additional PFS analyses (subgroup of patients with history of prior chemotherapy for advanced disease at baseline, ITT population, crossover population).

The sample size determination was based on the following assumptions:

- Exponential survival distribution
- HR 0.4286 (median PFS of 3 months in the control arm and 7 months in the experimental arm)
- A 2:1 randomization scheme
- One-sided significance level α=0.025
- Power of $\geq$ 99%
- Accrual of 6 patients in month 1; 15 in month 2; 20 in month 3; 30 in month 4 and uniform accrual of 40 patients thereafter
- A 2% and 10% dropout rate on the GSK1120212 and Chemotherapy arms, respectively
- A projection of 145 progression free survival events in the overall population at the time a minimum number of events have occurred in each of the subpopulations (i.e., prior chemotherapy and no prior chemotherapy at baseline) to provide $\geq$87% power

Under these assumptions, the statistical plan estimated that an estimated 297 patients (198 randomized to GSK1120212 and 99 to chemotherapy) would need to be enrolled to observe 145 PFS events.

The SAP specified the following analysis populations:

- Primary Efficacy Population, defined as BRAF V600E patients without a prior history of brain metastases (subset of the ITT population)
- ITT population, defined as all randomized patients regardless of whether treatment was administered

- Safety population, defined as all randomized patients who received at least one dose of study medication and allocated to a treatment group based on the actual treatment received (in the randomized phase)
- GSK1120212 crossover population, defined as the subset of patients who were randomized to the chemotherapy arm and who elected at the time of disease progression to receive GSK1120212 and subsequently received at least one dose of GSK1120212.

The protocol specified that a minimum of 40% of the total patient population would be enrolled into each subgroup (prior chemotherapy and no prior chemotherapy). The final analysis was planned once a minimum of 60 PFS events have occurred within each of the prior chemotherapy groups. No adjustments to the significance level alpha was made for these subgroup comparisons since the Applicant considered these as supportive analyses of the primary efficacy analysis.

REVIEWER COMMENT: At the time that the Applicant modified the statistical section (Amendment 3) to change the primary efficacy population, the Applicant estimated that approximately 276 patients with BRAF V600E mutation-positive melanoma without a prior history of brain metastases have been enrolled (97 with a history of prior chemotherapy use and 179 without a history of prior chemotherapy use in the advanced or metastatic setting). The revised protocol specified that with a minimum of 120 events in the revised primary efficacy population, it would be possible to detect an improvement as low as 45% (i.e., a hazard of 0.6838) with statistical significance.

According to the SAP (Submitted to IND 102175 as SDN-255 on 12/16/2011), the final analysis would be performed when at least 60 PFS events have occurred during the randomized within each of the following subgroups:

- BRAF V600E patients without a prior history of brain metastases and without prior treatment with chemotherapy in the advanced or metastatic setting and
- BRAF V600E patients without a prior history of brain metastases and with prior treatment with chemotherapy in the advanced or metastatic setting.

The Applicant's pre-specified, primary analysis of PFS, based on investigator-assessment of tumor response measurements (RECIST 1.1) in the subset of the ITT population of BRAF V600E patients without a prior history of brain metastases, was summarized using Kaplan-Meier estimates and compared between treatment arms using the stratified log-rank test [stratifying for prior treatment with chemotherapy for advanced or metastatic disease (Yes vs. No) and baseline LDH (above ULN vs. $\leq$ ULN)]. The Pike estimate of the treatment hazard ratios (HR) was provided, together with a 95% confidence interval.

The Applicant specified in the SAP that analyses of secondary endpoints and subgroups were intended to be supportive of the primary analysis of PFS and would be tested only if the PFS results were statistically significant in the overall population. No adjustments to alpha were made for analyses of secondary endpoints and subgroups.

The SAP defined OS as the interval of time (in months) between the date of randomization and the date of death due to any cause. Analyses of OS were planned in the following populations: (1) the primary efficacy population (i.e. BRAF V600E patients without a prior history of brain metastases), and (2) the ITT population. For patients who did not die, OS was censored at the date of last contact. The SAP specified use of the same analysis methods for comparison of OS as those used for PFS.

Additional analyses of secondary endpoints include the following:

- PFS (randomized phase; comparison using same analysis method as that used in the primary efficacy analysis)
  - ITT population
  - Prior chemotherapy subgroup within the primary efficacy population
  - No prior chemotherapy subgroup within the primary efficacy population
- PFS (crossover phase; summarized with 95% CI)
  - Crossover to GSK1120212 subgroup
- ORR (comparison of treatment arms using Fisher's exact test)
  - Primary efficacy population
  - ITT population
  - BRAF V600E patients (regardless of prior history of brain metastases)
  - BRAF V600K patients (regardless of prior history of brain metastases)
- ORR (crossover phase; summarized with 95% CI for tumor response rates)
- Duration of Response (randomized phase; defined as time from first documented evidence of PR or CR until the first documented sign of disease progression or death due to any cause)
  - Primary efficacy population
  - ITT population
  - BRAF V600E patients (regardless of prior history of brain metastases)
  - BRAF V600K patients (regardless of prior history of brain metastases)
- Duration of Response (crossover phase)

Following the final PFS analysis the study will remain open for further follow-up to collect additional survival and safety data. Specifically follow-up will continue until 80% of the total number of randomized patients have died or otherwise been lost to follow-up.

The Applicant performed the analysis of safety based on the as treated population (i.e., Safety population). The Applicant used Medical Dictionary for Regulatory Activities (MedDRA) to code AEs. The Applicant summarized the incidence of AEs by worst severity according to NCI CTCAE version 4.

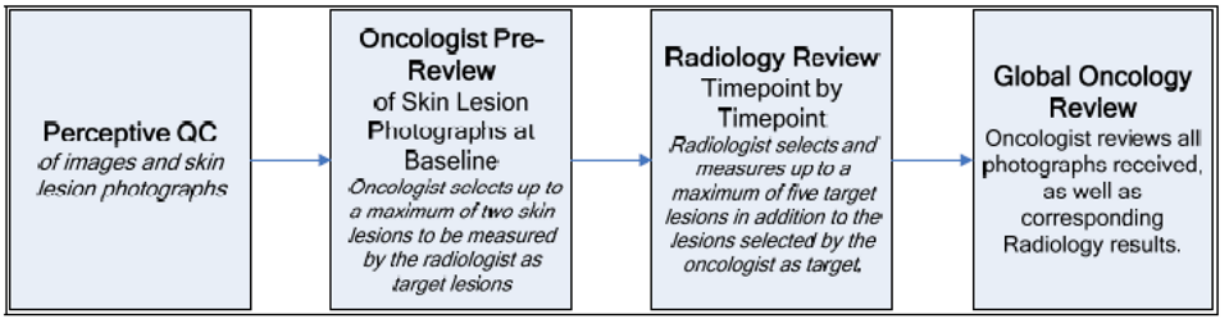
Blinded Independent Central Review (BICR)

The Applicant planned to evaluate tumor-assessment endpoints using BICR. According to the BICR charter, independent review consisted of two sequential stages of review: (1) independent radiology (IR) review, a central blinded assessment of medical imaging data by one qualified

radiologist and (2) the independent oncology (IO) review in which one independent oncologist assessed the skin lesion photographs in addition to the IR review findings to make a final efficacy endpoint determination (i.e., PFS, objective response assessment) for the case, if applicable.

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

Figure 3:Blinded Independent Central Review Process, MEK114267 Trial



Reproduced from Section 7.1 of IRC charter

The Applicant requested that the BICR amend the review charter (version 3.0, July 19, 2011) to allow the presentation to the independent oncologist of clinical measurements of subcutaneous lesions, as assessed by the site if there was no CT or MRI of the lesion(s). This amendment also removed the requirement in the charter for the independent oncologist to document an overall tumor response assessment for each timepoint. The independent oncologist-assessed PFS was captured as a PFS event date without corroborating raw data such as tumor measurements (site or IO), identification of new lesions, or overall tumor response assessment. Thus, FDA was unable to verify, based on raw data, any PFS analysis which included an assessment by the independent oncologist. Please see Dr. Chen's Statistical Review for further details.

Protocol Amendments

The Applicant submitted to IND 102175 five amendments to Protocol MEK114267. The key revisions made in each amendment included:

- Amendment 1 (October 18, 2010): The Applicant changed the primary endpoint of the study to PFS from the co-primary endpoints of PFS and OS. In addition, the amended protocol added crossover to trametinib for patients who progressed on the chemotherapy arm.

- Amendment 2 (May 2, 2011): The amended protocol required documented disease progression on prior chemotherapy (for patients who received 1 prior chemotherapy) before randomization and confirmation of stable disease/no evidence of disease for patients with prior brain metastases. Additionally, the amended protocol permitted patients who discontinued chemotherapy for reasons other than disease progression to crossover if they did not receive any other anticancer treatment, and had independent review confirmation of disease progression following study treatment discontinuation
- Amendment 3 (October 3, 2011): The Applicant changed the primary efficacy population to patients with a BRAF V600E mutational status, without a history of prior brain metastases. The Applicant stated that this change to the primary endpoint was made prior to Data Base Freeze to conduct the primary endpoint analysis of PFS
- Amendment 4 (January 27, 2012): The Applicant added to the protocol monitoring and management guidelines for hypertension based on emerging data suggesting that patients treated with trametinib may develop hypertension or experience worsening control of their pre-existing hypertension
- Amendment 5 (February 16, 2012): The Applicant amended the protocol to allow for immediate crossover (i.e., without requiring independent review confirmation of disease progression) of any patients enrolled and treated on the chemotherapy arm to trametinib.

Primary and Supportive Trials of GSK1120212 in Patients with BRAFV600 Mutation-positive Unresectable (Stage IIIc) or Metastatic Melanoma

Table 11 summarizes the trial designs and key features of the trials submitted by the Applicant intended to support the safety and effectiveness of trametinib.

Table 11: Summary of Trial Designs of Key GSK1120212 Monotherapy Trials for Melanoma.

Trial ID	Design	Population	N	Treatment Regimen	Key Endpoints
MEK 114267	OL, MC, RCT (2:1)	Stage IIIc[a] or IV, PS 0-1; BRAF V600 (E or K) by central testing; ≤1 prior chemotherapy; No prior BRAFi or MEKi	214	GSK1120212 2 mg QD	**1) PFS** Secondary: OS,ORR, DOR, PFS
			108	Dacarbazine 1000 mg/m^2 D1 q 21d OR Paclitaxel 175 mg/m^2 D1 q21d	
MEK 113583	OL, MC, two-arm	Metastatic melanoma; PS 0-1; BRAF V600 (E,D, or K) by local testing; Any # prior lines of chemotherapy; No prior BRAFi (Cohort B only) or MEKi	40	Cohort A (Prior BRAFi[b] use) GSK1120212 2 mg QD	**1) ORR** Secondary: PFS, DOR, OS
			57	Cohort B (No Prior BRAFi use) GSK1120212 2 mg QD	
MEK 111054[c]	FTIH, OL, MC, DE	Solid tumor patients not responsive to standard therapies or for whom no standard therapy exists; BRAF mutation-positive by local testing (Expansion cohort only); PS 0-1; No prior MEKi, prior BRAFi allowed; Any # prior lines of chemotherapy;	10	21/7 Regimen: Trametinib (0.125, 0.25, 0.5, 1, or 2 mg) QD for 21d on then 7d off	**1) MTD** Secondary: PK, PD, clinical tumor response
			21	Loading Dose Regimen: Trametinib (6 mg) LD on D1 or Trametinib LD (6, 8, or 10 mg) D1 and D2 then trametinib (2, 2.5, or 3 mg) continuous QD dosing	
			28	QD/QD Regimen (Pharmacodynamic Dose Range): Trametinib ≤2.5 mg QD (pharmacodynamic run-in) from D1-15 then QD dosing with 2 or 2.5 mg thereafter [i.e., (0.5/2), (1/2), (0.5/2.5), (1/2.5), (2/2.5)]	
			147	QD Regimen: Trametinib (2, 2.5, 3, or 4 mg) QD	

Abbreviations in Table: BRAFi, BRAF inhibitor; d, day; D, Study Day; DE, dose-escalation; DOR, duration of response; FTIH, first time in human; LD, loading dose; MC, multicenter; MEKi, MEK inhibitor; MTD, Maximum tolerated dose; OL, open label; ORR, overall response rate; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; PS, Eastern Cooperative Oncology Group performance status, q, every; QD, once daily; RCT, randomized controlled trial;

[a] Unresectable.

[b] Eligibility criteria for MEK113583, Cohort A required prior GSK2118436 (BRAFi) use, other BRAFi were permitted at the approval of the Applicant's medical monitor. Of the 40 patients enrolled to Cohort A, 17 patients (43%) received prior GSK2118436 and 23 (58%) received prior vemurafenib.

[c] MEK111054 enrolled 81 patients with cutaneous melanoma, 30 of the 81 had BRAF mutation-positive melanoma not previously treated with a BRAFi.

6 Review of Efficacy

Efficacy Summary

The NDA submission contained a single randomized controlled trial, MEK114267, in support of the proposed indication:

> MEKINIST™ is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutations as detected by an FDA-approved test.
>
> Limitation of use: (b) (4)

MEK114267 was a multicenter, international, open-label, randomized (2:1), active-controlled trial comparing single agent trametinib to chemotherapy (dacarbazine or paclitaxel) in 322 patients with previously treated (up to one prior chemotherapy regimen) or untreated, histologically confirmed, Stage III unresectable (Stage IIIc) or metastatic (Stage IV) cutaneous melanoma determined to be BRAF V600E or BRAF V600K mutation-positive based upon centralized testing of formalin fixed paraffin embedded tumor tissue using an investigational use only (IUO) assay. There were two randomization stratification factors: LDH (> ULN vs. ≤ ULN) and prior chemotherapy for advanced or metastatic disease (Yes vs. No).

The MEK114267 trial demonstrated a statistically significant 53% reduction in the hazard rate of progression of disease or death [HR 0.47 (95% CI: 0.34, 0.65); $p < 0.0001$] in the trametinib arm compared to the chemotherapy arm based on analysis of the ITT population using the unstratified log-rank test. The median PFS on the trametinib arm was 4.8 months (95% CI: 4.3, 4.9) compared to 1.5 months (95% CI: 1.4, 2.7) on the chemotherapy arm. Analyses of PFS based on blinded, independent central review assessment, sensitivity analyses, and demographic and prognostic baseline disease characteristic subgroups confirmed a statistically persuasive and robust, clinically meaningful prolongation of PFS in the trametinib arm. The investigator-assessed, confirmed ORR was 22% (95% CI: 17%, 28%) with 4 (2%) complete responders on the trametinib arm and 8% (95% CI: 4%, 15%) on the chemotherapy arm, all partial responders. The median duration of response was 5.5 months (95% CI: 4.1, 5.9) for the objective responders to trametinib and was not reached (95% CI: 3.5 months, not reached) for the objective responders to chemotherapy. The OS analysis performed at the time of the final PFS analysis demonstrated an estimated HR of 0.56 (95% CI: 0.33, 0.95) based on the unstratified log-rank test with a nominal p-value of 0.0136. The median OS was not estimable because the data were not mature.

Importantly, trametinib has not demonstrated anti-tumor activity in patients with BRAF V600 mutation-positive melanoma who were previously treated with a BRAF inhibitor. The MEK113583 trial was an open-label, multicenter, single arm trial evaluating the anti-tumor activity of trametinib in patients with BRAF V600E or V600K mutation-positive metastatic

melanoma who were previously treated either with or without a BRAF inhibitor. The confirmed ORR in the BRAF inhibitor-naïve cohort of patients (n=57) was 25% (95% CI: 14%, 38%) which is consistent with the ORR observed on the trametinib arm of the MEK114267 trial. However, in the cohort of patients (n=40) who were previously treated with a BRAF inhibitor, there were no confirmed objective responders.

Currently under review by CDRH is a premarket approval application for the BioMerieux THxID BRAF Kit (PMA P120014) which is intended for use as an in vitro companion diagnostic assay to detect BRAF V600 (E or K) mutations in melanoma.

6.1 Indication

The Applicant proposes the following indication:

> MEKINIST™ is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutations as detected by an FDA-approved test.
>
> Limitation of use: (b) (4)
> (b) (4)

6.1.1 Methods

The Applicant submitted data from one trial (MEK114267) that was adequately designed and conducted to test the hypothesis that administration of trametinib to patients with unresectable or metastatic, BRAF V600E and V600K mutation-positive melanoma results in an improvement in PFS compared to treatment with chemotherapy (dacarbazine or paclitaxel). The Applicant included in the SAP non-hierarchical comparative analyses of secondary endpoints intended to support efficacy of trametinib, including OS, without allocation of type I error. In addition to data from MEK114267, the Applicant provided the results from one open-label, multicenter, non-comparative trial, MEK113583, as supportive information of a treatment effect of trametinib (see Section 5.3, Table 11).

The review of efficacy focused on the analyses of the data provided for the MEK114267 trial as this is the primary trial the Applicant relied upon to demonstrate the efficacy of trametinib administered as monotherapy in the proposed patient population. This review also presents analyses of data from the MEK113583 trial to determine whether the results are supportive of a treatment effect of trametinib in the proposed patient population.

6.1.2 Demographics

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

The median age was 54.5 years on the trametinib arm and was 54 years on the chemotherapy arm. All patients randomized to treatment were white. The trametinib arm consisted of fewer females than the chemotherapy arm, 44% vs. 51%, respectively. The proportion of patients age ≥65 years was similar in both arms, 23% on the trametinib arm vs. 20% on the chemotherapy arm. The majority of patients on both arms were from Western Europe, 66% on the trametinib arm and 58% on the chemotherapy arm. At baseline, the majority of patients on both arms had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 (64% on the trametinib arm vs. 64% on the chemotherapy arm), BRAF V600E mutation subtype (86% vs. 90%), M1c disease (67% vs. 58%), normal LDH (63% vs. 62%), and visceral disease (83% vs. 79%).

Table 12 and Table 13 summarize demographics and baseline characteristics of the ITT population.

Table 12: Demographics by Treatment Arm. Intent-to-Treat Population. MEK114267 Trial.

	Trametinib N=214	Chemotherapy N=108
Age, years		
Median	54.5	54.0
Range, min-max	23-85	21-77
≥ 65, n (%)	49 (23)	22 (20)
Female, n (%)	94 (44)	55 (51)
Race: White, n (%)	214 (100)	108 (100)
Region, n (%)		
North American	22 (10)	13 (12)
West Europe	141 (66)	63 (58)
East Europe	31 (14)	17 (16)
Oceania	19 (9)	13 (12)
Latin America	1 (<1)	2 (2)
US	11 (5)	9 (8)

Source: FDA Statistical Review

Table 13: Baseline Disease Characteristics and Prior Therapy by Treatment Arm. Intent-To-Treat Population. MEK114267 Trial.

	Trametinib N=214	Chemotherapy N=108
BRAF mutation subtype, n (%)[1]		
V600E	184 (86)	97 (90)
V600K	29 (14)	11 (10)
History of brain metastases, n (%)	9 (4)	2 (2)
ECOG, n (%)		
0	136 (64)	69 (64)
1	78 (36)	39 (36)
Number of disease sites ≥ 3, n (%)	123 (57)	56 (52)
Stage, n (%)		
IIIC, IV M1a, or IV M1b	69 (32)	45 (42)
IV M1c	144 (67)	63 (58)
LDH		
≤ ULN	134 (63)	67 (62)
> ULN	75 (35)	40 (37)
Missing	5 (2)	1 (1)
Prior treatment history, n (%)		
Cancer related surgery	193 (90)	98 (91)
Chemotherapy	71 (33)	38 (35)
Immunotherapy	68 (32)	30 (28)
Radiotherapy	53 (25)	21 (19)
Biologic therapy	16 (7)	13 (12)
Histology at initial diagnosis, n (%)		
Superficial spreading melanoma	59 (28)	27 (25)
Malignant melanoma NOS	57 (27)	26 (24)
Nodular melanoma	51 (24)	24 (22)
Visceral or non-visceral disease, n (%)		
Yes	178 (83)	85 (79)
No	36 (17)	23 (21)
Had non-target lesion, n (%)	174 (81)	90 (83)
Duration (months) of metastatic disease		
Median (min-max)	7.4 (0.2-204)	6.6 (0.7-146)

Source: FDA Statistical Review
[1] One patient randomized to the trametinib arm had a BRAF V600E/V600K mutation-positive tumor

REVIEWER COMMENTS:

1. *Minor imbalances of prognostic factors (e.g. proportion of patients with M1c disease) where occurring appeared to favor the chemotherapy arm.*
2. *The pre-specified primary efficacy analysis used randomization strata based on data captured in the eCRF instead of strata captured from the IVRS. Analyses based on eCRF strata require imputation for missing baseline LDH data. The Applicant used post-randomization data in these imputations or data from the IVRS randomization. Overall, strata misclassification between IVRS and eCRF stratum was 11% . The FDA statistician*

used an unstratified efficacy analyses as the primary analysis method based on problems in verifying the stratum data.

6.1.3 Subject Disposition

Screening Phase

The MEK114267 trial screened 1059 patients to randomize 322 patients with BRAF V600E and V600K mutation-positive melanoma (Table 14). Of the 1059 patients screened for the trial, 454 (43%) were ineligible to enroll based on a wild-type BRAF V600 mutation-status. Of the 550 (52%) patients with BRAF V600E or V600K mutation-positive melanoma, 228 patients (22%) did not meet remaining eligibility criteria and did not proceed to randomization.

Table 14: Patient Disposition. Screening Population. MEK114267 Trial.

	Screening N=1059 n (%)
No tissue submitted for biomarker testing	35 (3)
Tissue submitted for biomarker testing	1024 (97)
BRAF wild type result	454 (43)
Unable to identify BRAF status[1]	20 (2)
BRAF V600 (E or K) mutation-positive	550 (52)
Eligibility criteria not met	228 (22)
Randomized	322 (30)

Source: Applicant response to information request (NDA 204114, eCTD 0051).
[1] Quantity not sufficient; no tumor identified; or out of detectable range.

REVIEWER COMMENT: The Applicant stated that it did not collect in the eCRF the reasons for not meeting eligibility criteria; it is unknown why 41% (228/550) of BRAF V600 mutation-positive patients were not eligible to participate on the trial. Thus, the reviewer cannot make specific comments about the generalizability of the findings of the MEK114267 trial based on reasons for screening failure.

Randomization/Treatment Phase

The MEK114267 trial randomized 322 patients enrolled at 86 sites in 19 countries from December 2010 to July 2011.

Twelve patients in the ITT population did not receive study treatment, three patients randomized to trametinib and nine patient randomized to chemotherapy. At the time of data cutoff, 30% in the trametinib arm and 12% in the chemotherapy arm continued on randomized treatment. Progressive disease accounted for most treatment discontinuations on the trametinib arm (54%) and on the chemotherapy arm (67%). Table 15 summarizes the treatment status and reasons for treatment discontinuation for patients in the MEK114267 trial.

Table 15: Summary of Study Treatment Status. Intent-to-Treat Population. MEK114267 Trial.

	Randomized Phase	
	Trametinib N=214 n (%)	Chemotherapy N=108 n (%)
Treatment status		
Ongoing	65 (30)	13 (12)
Discontinued	146 (68)	86 (80)
Not Treated	3 (1)	9 (8)
Primary reason for treatment discontinuation[1]		
Disease progression	116 (54)	72 (67)
Adverse event	21 (10)	6 (6)
Investigator discretion	5 (2)	4 (4)
Decision by patient / proxy	4 (2)	4 (4)

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

Study discontinuations due to death occurred in 16% of patients in the trametinib treatment arm and 27% of patients in the chemotherapy treatment arm. Study withdrawals for other reasons were infrequent as summarized in Table 16.

Table 16: Patient Disposition. Intent-to-Treat Population. MEK114267 Trial.

	Trametinib N=214 n (%)	Chemotherapy N=108 n (%)
Subject status		
Died	35 (16)	29 (27)
Ongoing	169 (79)	65 (60)
On randomized study treatment	65 (30)	13 (12)
In follow-up	104 (49)	35 (32)
On crossover study treatment[1]	0	17 (16)
Withdrawn from study	10 (5)	14 (13)
Reason for study withdrawal		
Lost to follow-up	2 (<1)	1 (<1)
Investigator discretion	2 (<1)	3 (3)
Withdrew consent	6 (3)	10 (9)

Verified using RDS.xpt, RDEATH.xpt, and RIPDISC.xpt
[1] Fifty-one patients with disease progression on chemotherapy crossed over to receive trametinib

Post-study Anti-tumor Treatment

The MEK114267 trial collected information on subsequent lines of anticancer treatment every 12 weeks following investigational product discontinuation (Table 17). The incidence of patients receiving any post-study anticancer therapy was 21% of those randomized to the trametinib treatment arm and 9% of those randomized to the chemotherapy arm (excluding crossover administration of trametinib). Chemotherapy was the main post-study anticancer therapy received by the trametinib treatment arm (11%).

Table 17: Post-study Treatment for Melanoma. Intent-to-Treat Population. MEK114267 Trial.

	Trametinib N=214 n (%)	Chemotherapy N=108 n (%)
Any anticancer therapy	46 (21)	10 (9)
Type of anticancer therapy		
Chemotherapy	23 (11)	5 (5)
Biologic therapy	1 (<1)	0
Immunotherapy	10 (5)	0
Small molecule targeted therapy	18 (8)	5 (5)

Source: RCTX.xpt

REVIEWER COMMENT: A similar proportion of patients randomized to the trametinib and chemotherapy arms received vemurafenib as post-study anticancer therapy, 18 patients (8%) and seven patients (6%), respectively. However, the Applicant reported a higher rate of post-study ipilimumab use in patients randomized to trametinib than in patients randomized to chemotherapy, 10 (5%) vs. 0 patients, respectively. These minor differences would likely not confound the interpretation of the OS analysis.

The median duration of follow-up in the randomized phase of the trial was 4.9 months (0-9 months) on the trametinib arm and was 4.8 months (0-10 months) on the chemotherapy arm (Table 18).

Table 18: Duration of Follow-Up. Intent-to-Treat and Crossover Populations. MEK114267 Trial.

	Randomized Phase		Crossover Phase N=51 (months)
	Trametinib N=214 (months)	Chemotherapy N=108 (months)	
Mean	5	4.6	2.7
SD	1.61	2.21	1.4
Median	4.9	4.8	2.7
Min.	0	0	0
Max.	9	10	6

Source: MEK114267 Clinical Study Report, Tables 7.116 and 7.126.
Abbreviations in Table: Min, minimum; Max., maximum.

6.1.4 Analysis of Primary Endpoint(s)

REVIEWER COMMENT:
At the pre-NDA meeting, FDA and the Applicant agreed upon use of the ITT population as the primary efficacy population for analysis of PFS (see Section 5.3 Discussion of Individual Studies/Clinical Trials as well as the FDA Statistical Review of NDA 204114).

The primary efficacy analysis of the MEK114267 trial demonstrated a statistically significant improvement in investigator-assessed PFS with trametinib treatment compared to treatment with chemotherapy (investigator's choice of paclitaxel or dacarbazine). The median PFS was 4.8 months (95% CI: 4.3, 4.9) on the trametinib arm and 1.5 months (95% CI: 1.4, 2.7) on the chemotherapy arm with a HR of 0.47 (95% CI: 0.34, 0.65; 2-sided p-value <0.0001). Table 19 and Figure 4 summarize the results of the primary PFS analysis.

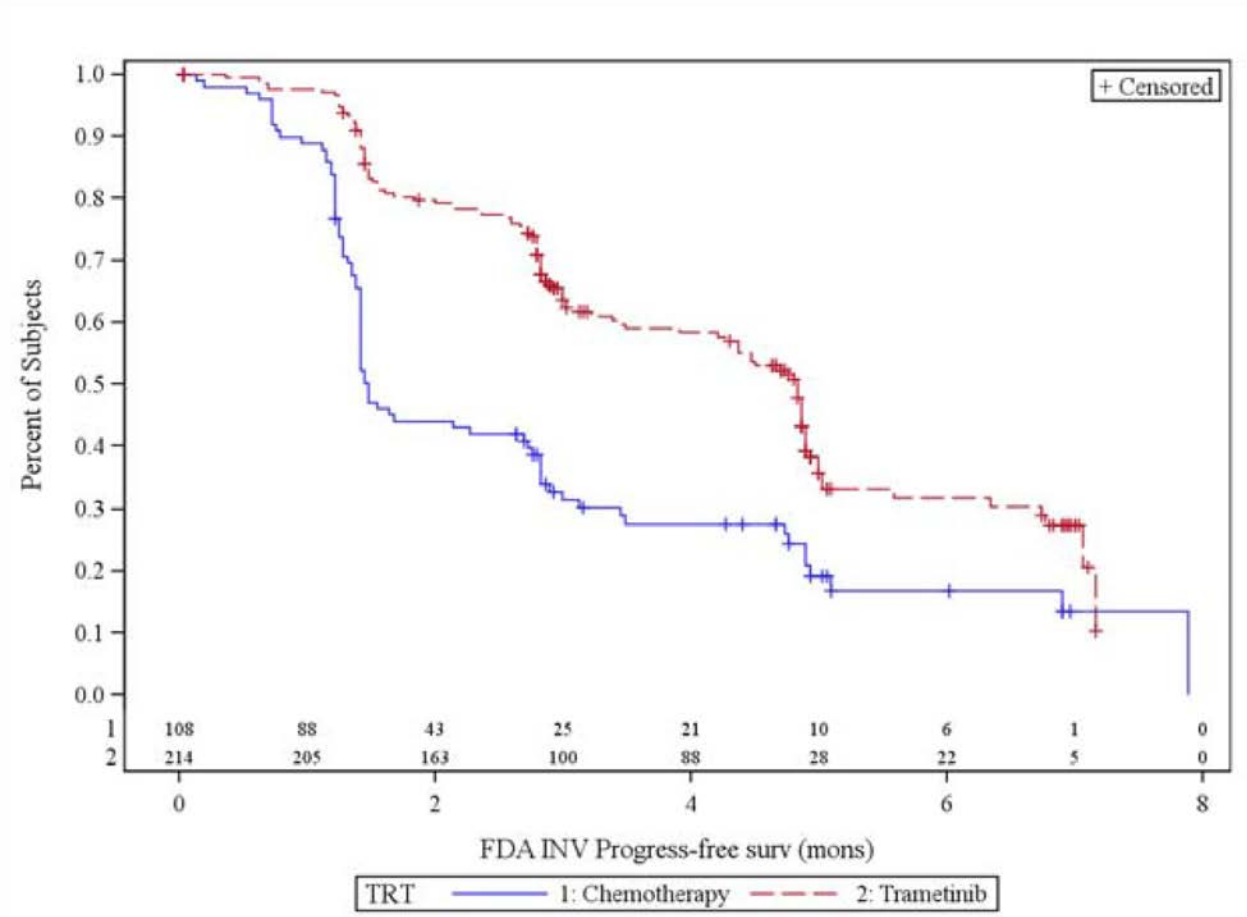
Table 19: Primary Efficacy Analysis of Progression-Free Survival. Intent-to-Treat Population. MEK114267 Trial.

	Trametinib N = 214	Chemotherapy N = 108
Number of Events, n (%)	117 (55)	77 (71)
Progressive Disease	107 (50)	70 (65)
Death	10 (5)	7 (6)
Duration of PFS, months		
Median PFS (95% CI)	4.8 (4.3, 4.9)	1.5 (1.4, 2.7)
2-sided p-value (unstratified log-rank)	< 0.0001	
HR (95% CI)[1]	0.47 (0.34, 0.65)	

Source: FDA Statistical Review
Abbreviations in Table: CI, confidence interval.
[1] by Pike

PFS analyses using methods based on the Pike estimator stratified per eCRF or IVRS as well as those using Cox proportional hazards, unstratified or stratified per eCRF or IVRS, demonstrate consistent HRs with the results of the primary efficacy analysis (see Dr. Chen's Statistical Review of NDA 204114 for details).

Figure 4: Plots of Kaplan-Meier Estimates for Progression-Free Survival by Treatment Arm. Intent-to-Treat Population. MEK114267 Trial.



Source: FDA Statistical Review

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

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

Blinded, Independent Central Review Assessment of PFS

The Applicant performed a pre-specified supportive analysis of PFS based on BICR assessments (see Section 5.3). BICR-assessed PFS (based on IR assessments or on combined IR and IO assessments) demonstrated results consistent with those of the primary efficacy analysis (Table 20).

Table 20: Supportive Analyses of Progression-Free Survival Based on Blinded Independent Central Review Assessments. Intent-to-Treat Population. MEK114267 Trial.

	IR-PFS		**IR+IO-PFS**	
	Trametinib N = 214	**Chemotherapy** N = 108	**Trametinib** N = 214	**Chemotherapy** N = 108
Number of events (%)	98 (46)	73 (68)	100 (47)	76 (70)
Progressive disease	88 (41)	66 (61)	91 (43)	69 (64)
Death	10 (5)	7 (5)	9 (4)	7 (6)
Duration of PFS, months				
Median PFS (95% CI)	4.9 (4.6, 5.0)	1.7 (1.4, 2.8)	4.9 (4.5, 5.0)	1.5 (1.4, 2.8)
p-value (2-sided, unstratified log-rank)	<0.0001		<0.0001	
HR(95% CI)[1]	0.43 (0.31, 0.62)		0.43 (0.30, 0.60)	

Abbreviations in Table: NE, not estimable; INV, investigator-assessed; IR, independent radiologist review-assessed; IO, independent oncologist review-assessed
[1] Pike unstratified HR

REVIEWER COMMENTS:

1. *The FDA analyses of the PFS, the primary efficacy analysis as well as the supportive analyses of PFS based on blinded, independent central review, provide numerically different results than those presented in the clinical study report for the MEK114267 trial. Nonetheless FDA analyses confirm the treatment effect of trametinib, i.e., an improvement in PFS compared to the chemotherapy arm. FDA could not verify—based on submission quality issues—the Applicant's derivations of tumor response data based on raw tumor measurement data. Rather than using the derived overall tumor response assessment (e.g., complete response, partial response, stable disease, etc.), FDA analyses of PFS re-derived tumor response data according to RECIST version 1.1 using raw datasets containing tumor measurements as documented by the investigator or the independent radiologist.*

2. *The data recorded by the Applicant to support an overall tumor assessment by the independent oncologist at each timepoint were not adequate for FDA to verify, using raw data, PFS analyses based on independent oncologist assessments.*
3. *Please see Dr. Chen's review for details of the submission quality issues which hindered the FDA primary efficacy analyses of PFS.*
4. *Results of sensitivity analyses, including FDA sensitivity analyses based on raw data submitted by the Applicant, support the robustness of results from the primary efficacy analysis. These sensitivity analyses included:*
    - *investigator-assessed PFS without censoring for symptomatic PD*
    - *investigator-assessed PFS without censoring for start of new anti-cancer therapy*
    - *investigator-assessed PFS without censoring for two continuous missing assessments*
5. *According to the FDA statistical review of the BICR tumor assessments, there were no between arm systematic differences, differences in substantial outlier differences, or differences in the time to scheduled visits. See Dr. Chen's Statistical Review of NDA 204114 for further details.*

6.1.5 Analysis of Secondary Endpoints(s)

Secondary endpoints were to be tested if the primary analysis of PFS was statistically significant. The Applicant considered secondary endpoints and subgroup analyses as supportive; the SAP did not include a plan to adjust the type I error rate for the secondary endpoints and subgroup analyses.

Overall Survival

The definition of OS was the time (in months) between the date of randomization and the date of death due to any cause. Censoring of OS for patients who had not died occurred at the date of last contact. The definition of OS included all deaths, including those following crossover.

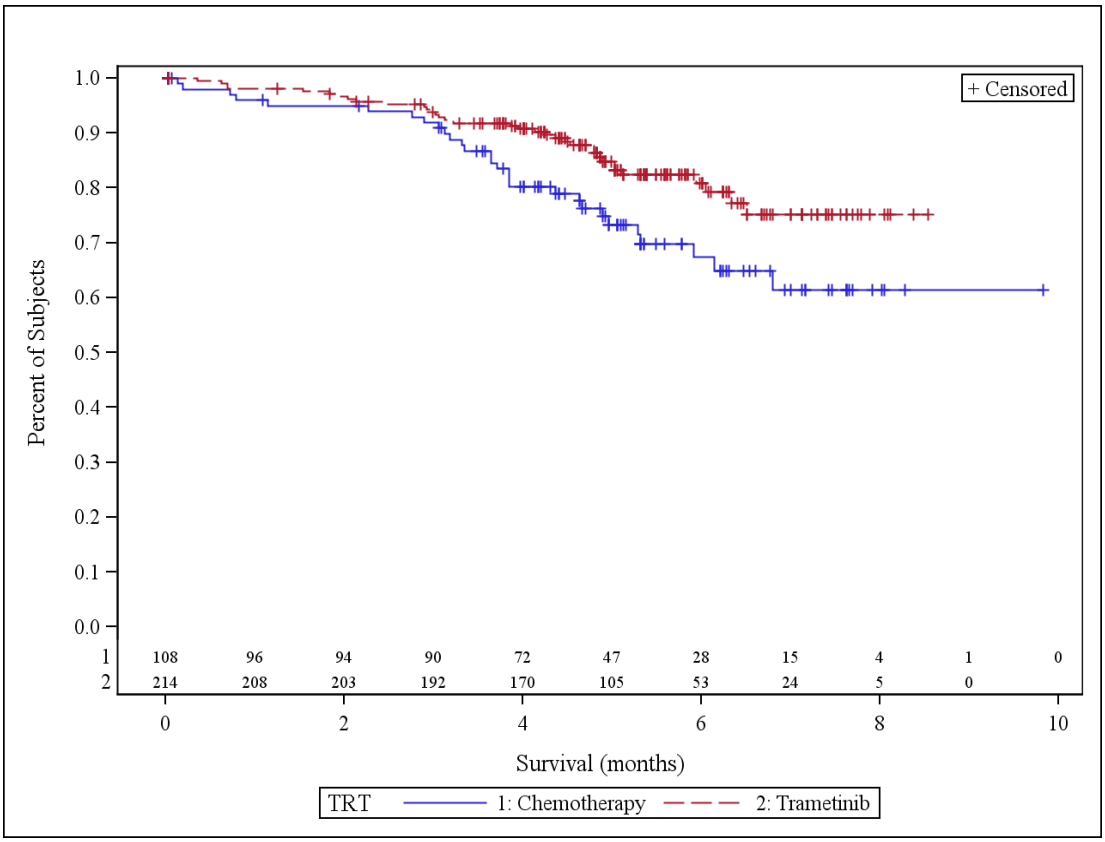
The OS data are not mature. Overall, there were 20% (64/322) death events: 16% (35/214) of patients in the trametinib arm and 27% (29/108) of patients in the chemotherapy arm died. The median survival of each study arm was not estimable. An OS analysis of the ITT population based on an unstratified, log-rank test using the Pike estimator demonstrated a hazard ratio of 0.56 (95% CI 0.33, 0.95; p=0.0136). Table 21 and Figure 5 summarize the OS analysis results.

Table 21: Analysis of Overall Survival by Treatment Arm. Intent-to-Treat Population. MEK114267 Trial.

	Trametinib N = 214	**Chemotherapy** N = 108
Number of deaths, n (%)	35 (16)	29 (27)
Duration of overall survival		
Median OS, months (95% CI)	NR (NR, NR)	NR (6.8, NR)
p-value (2 sided, unstratified log-rank)	0.0136	
HR (95% CI)		
Pike Un-Stratified (95% CI)	0.56 (0.33, 0.95)	
Pike Stratified HR Per CRF (95% CI)	0.54 (0.32, 0.92)	
Pike Stratified HR Per IVRS (95% CI)	0.53 (0.31, 0.90)	
Cox Unstratified HR (95% CI)	0.56 (0.34, 0.91)	
Cox Stratified HR Per CRF (95% CI)	0.54 (0.33, 0.89)	
Cox Stratified HR Per IVRS (95% CI)	0.53 (0.32, 0.86)	

Source: FDA Statistical Review

Figure 5: Plots of Kaplan-Meier Estimates of Overall Survival. Intent-to-Treat Population. MEK114267 Trial.



Source: FDA Statistical Review

REVIEWER COMMENTS:

1. *The results of the OS analysis do not demonstrate a detriment to OS with use of trametinib; on the contrary, these analyses show a trend toward improved OS. However, the reliability of the point estimate of the HR is uncertain because the OS data are not mature.*
2. *The SAP stated that there were no interim analyses planned for the efficacy endpoints. Table 21 represents the final OS analysis results. However, according to the SAP, the Applicant may perform additional analyses of OS once the study is closed to further follow-up.*
3. *Based on the design of the trial in the protocol and SAP, the trial was not powered to test OS, i.e., the Applicant neither hypothesized a treatment effect size of trametinib on OS nor planned to perform a final OS analysis based upon a pre-specified number of OS events to demonstrate that treatment effect.*
4. *The p-value is considered nominal based on the lack of predefined statistical criteria surrounding Type I error adjustments in the hypothesis testing of the OS secondary endpoint. Nonetheless, various analyses based on stratified and unstratified tests using Cox or Pike estimators demonstrate consistent survival HRs.*

Table 22 summarizes the analyses of OS based on BRAF V600 mutation subtype.

Table 22: Subgroup Analyses of Overall Survival. BRAF V600 Mutation Subtype. MEK114267 Trial.

BRAF Mutation Subtype	Treatment Arm	Event/ Censored	Median OS (95%CI) (Month)	Unstratified HR (95%CI)	
				Pike	Cox
V600E	Chemotherapy	26/ 71	NR(6.8, NR)	0.52 (0.30 , 0.93)	0.52 (0.31, 0.89)
	Trametinib	28/156	NR(NR, NR)		
V600K	Chemotherapy	3/ 8	NR(0.8, NR)	0.70 (0.16 , 3.04)	0.69 (0.18, 2.70)
	Trametinib	7/ 22	NR(6.3, NR)		

Source: FDA Statistical Review

REVIEWER COMMENT:
The point estimate of the hazard ratio does not suggest a detriment to OS with trametinib in the ITT population or in either BRAF V600 mutation subgroup. The 95% confidence interval of the HR for OS is wide in the BRAF V600K subgroup based on the relatively small size of this subgroup.

Overall Response Rate

The investigator-assessed, confirmed ORR was 22% (95% CI: 17%, 28%) on the trametinib arm and 8% (95% CI: 4%, 15%) on the chemotherapy arm. The median duration of response was 5.5 months (95% CI: 4.1, 5.9) for the trametinib arm and was not reached (95% CI: 3.5, not reached) for the chemotherapy arm. As summarized in Table 23, the BICR-assessed ORR rates and durations of responses were similar to those based on investigator assessment in the ITT population. In addition, the ORRs with trametinib appeared overall similar in BRAF V600E and BRAF V600K mutation subgroups, with the possible exception of investigator-assessed ORR which was lower than the BICR-assessed ORR.

Table 23: Analyses of Confirmed Objective Response Rates and Duration of Responses as Assessed by Investigator or Blinded Independent Central Review. Intent-to-Treat Population. BRAF V600E and BRAF V600K Subgroups. MEK114267 Trial.

	Investigator		Blinded, Independent Central Review			
			IR		Combined IR and IO	
	Trametinib	Chemo	Trametinib	Chemo	Trametinib	Chemo
ALL						
N	214	108	214	108	214	108
ORR, n (%)	47 (22)	9 (8)	41 (19)	6 (6)	41 (19)	5 (5)
95% CI	(17%, 28%)	(4%, 15%)	(14%, 25%)	(2%, 12%)	(14%, 25%)	(2%, 10%)
CR, n (%)	4 (2)	0	0	1 (1)	0	1 (1)
PR, n (%)	43 (20)	9 (8)	41 (19)	5 (5)	41 (19)	5 (5)
Median DoR (95%CI)	5.5 (4.1, 5.9)	NR (3.5, NR)	5.6 (3.8, 5.9)	NR (3.5, NR)	5.6 (3.8, 5.9)	NR (3.5, NR)
BRAF V600E						
N	184	97	184	97	184	97
ORR, n (%)	44 (24)	7 (7)	34 (18)	4 (4)	34 (18)	3 (3)
95% CI	(18%, 31%)	(3%, 14%)	(13%, 25%)	(1%, 10%)	(13%, 25%)	(1%, 9%)
CR, n (%)	4 (2)	0	0	0	0	0
PR, n (%)	40 (22)	7 (7)	34 (18)	4 (4)	34 (18%)	3 (3)
Median DoR (95%CI)	5.5 (3.6, 5.9)	NR (3.5,NR)	5.6 (3.8, 5.9)	NR (3.5, NR)	5.6 (3.8, 5.9)	NR (3.5,NR)
BRAF V600K						
N	29	11	29	11	29	11
ORR, n (%)	3 (10)	2 (18)	7 (24)	2 (18)	7 (24)	2 (18)
95% CI	(23%, 27%)	(2%, 52%)	(10%, 44%)	(2%, 52%)	(10%, 44%)	(2%, 52%)
CR, n (%)	0	0	0	1 (9)	0	1 (9)
PR, n (%)	3 (10)	2 (18)	7 (24)	1 (9)	7 (24)	1 (9)
Median DoR (95%CI)	4.1 (NR, NR)	NR (NR, NR)	4.1 (NR, NR)	NR (NR, NR)	4.1 (NR, NR)	NR (NR, NR)

Source: FDA statistical reviewer analysis
Abbreviations in Table: CI, confidence interval; CR, complete response; DoR, duration of response; IO, independent oncologist; IR, independent radiologist; NR, not reached, PR, partial response

The clinical review of efficacy included an exploratory analysis of confirmed ORRs based on type of chemotherapy administered on the chemotherapy arm as well as based on status of prior chemotherapy treatment for metastatic disease at baseline. Of the 37 patients randomized to the chemotherapy arm who received paclitaxel, 33 (89%) had previously received systemic chemotherapy. None of the paclitaxel-treated patients experienced an objective response (Table 24). Patients randomized to the trametinib arm experienced similar ORR regardless of prior chemotherapy use (Table 25).

Table 24: Analyses of Objective Response Rates in the Chemotherapy Treatment Group as Assessed by Investigator or Blinded Independent Central Review. Dacarbazine and Paclitaxel Subgroups. MEK114267 Trial.

	Investigator		Blinded, Independent Central Review			
			IR		Combined IR and IO	
	Dacarbazine N=62 n (%)	Paclitaxel N=37 n (%)	Dacarbazine N=62 n (%)	Paclitaxel N=37 n (%)	Dacarbazine N=62 n (%)	Paclitaxel N=37 n (%)
ORR	9 (15)	0	6 (10)	0	5 (8)	0
95% CI	(7%, 26%)	N/A	(4%, 20%)	N/A	(3%, 18%)	N/A
CR, n (%)	0	0	1 (2)	0	1 (2)	0
PR, n (%)	9 (15)	0	5 (8)	0	4 (6)	0

Source: FDA Statistical Review Addendum.
Abbreviations in Table: CR, complete response; IO, independent oncologist review; IR, independent radiologic review; N/A, not available; ORR, objective response rate; PR, partial response.

Table 25: Analyses of Objective Response Rates as Assessed by Investigator or Blinded Independent Central Review. Chemotherapy Naïve and Previously Treated With Chemotherapy Subgroups. MEK114267 Trial.

	Investigator		Blinded, Independent Central Review			
			IR		Combined IR and IO	
	Trametinib	Chemo	Trametinib	Chemo	Trametinib	Chemo
CHEMOTHERAPY NAIVE						
N	143	70	143	70	143	70
ORR, n (%)	30 (21)	9 (13)	29 (20)	6 (9)	29 (20)	5(7)
95% CI	(15%, 29%)	(6%, 23%)	(14%, 28%)	(3%, 18%)	(14%, 28%)	(2%, 16%)
CR, n (%)	3 (2)	0	0	1 (1)	0	1 (1)
PR, n (%)	27 (19)	9 (13)	29 (20)	5 (7)	29 (20%)	4 (6%)
Median DoR (95%CI)	5.5 (3.6, 5.9)	NR (3.5, NR)	5.9 (3.8, 5.9)	NR (3.5, NR)	5.9 (3.8, 5.9)	NR (3.5, NR)
PREVIOUSLY TREATED WITH CHEMOTHERAPY						
N	71	38	71	38	71	38
ORR, n (%)	17 (24)	0	12 (17)	0	12(17)	0
95% CI	(15%, 36%)	(0, 9%)	(9%, 28%)	(0, 9%)	(9%, 28%)	(0%, 9%)
CR, n (%)	1 (1)	0	0	0	0	0
PR, n (%)	16 (23)	0	12 (17)	0	12(17)	0
Median DoR (95%CI)	4.9 (3, NR)	NR (NR, NR)	5.6 (3.4, 5.6)	NR (NR, NR)	5.6 (3.4, 5.6)	NR (NR, NR)

Source: Analyses performed by FDA Statistician.

Abbreviations in Table: CR, complete response; IO, independent oncologist review; IR, independent radiologic review; NR, not reached; ORR, objective response rate; PR, partial response.

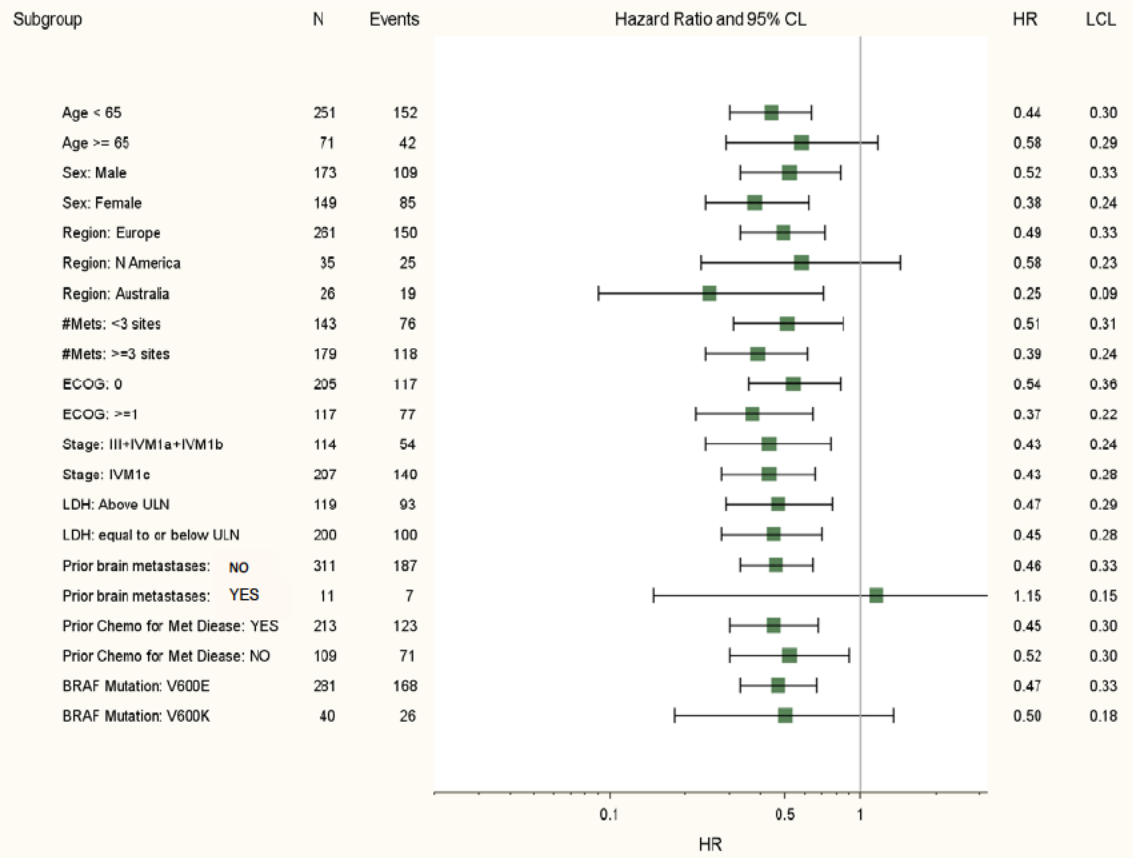
6.1.6 Other Endpoints

The review did not include an analysis of exploratory endpoints for the MEK114267 trial because the Applicant did not propose to include these results in labeling or intend to use these endpoints, as designed, to support the efficacy of trametinib.

6.1.7 Subpopulations

FDA analyses of investigator-assessed PFS by demographic and baseline characteristics are presented in Figure 6. The Applicant and FDA did not perform subgroup analyses based on race because the study population was 100% white. Subgroup analyses demonstrated consistent estimates of the PFS HR (trametinib compared to chemotherapy) and in most cases the 95% confidence intervals do not cross 1.0. In subgroups where estimates of PFS HR crossed 1, there were small numbers of patients and wide confidence intervals (e.g., North America region, history of brain metastases).

Figure 6: Subgroup Analyses of Investigator-Assessed Progression-Free Survival by Demographics and Baseline Disease Characteristics Subgroups. MEK114267 Trial.

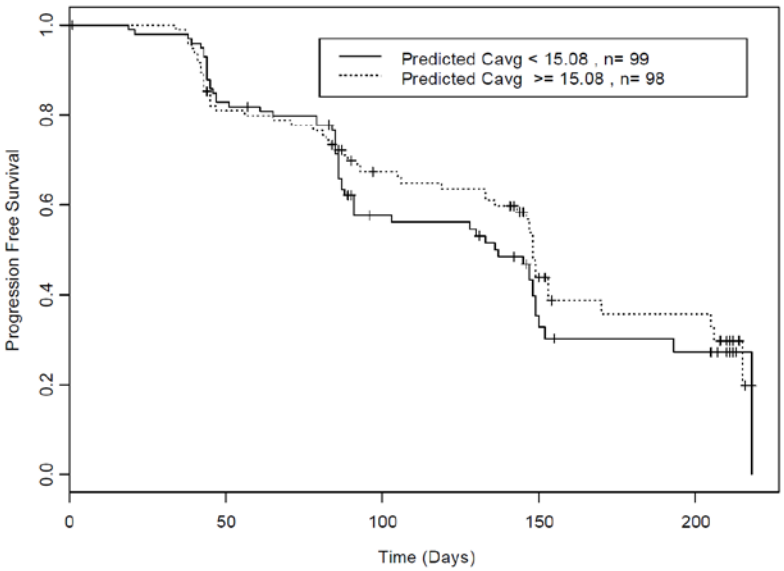


Source: Analyses performed by FDA Statistician.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The development program of trametinib contains limited data on dose-response. The Applicant has not conducted individual dose-response trials. The FDA Pharmacometrics review concluded that based on data from the MEK114267 trial, there is no evident exposure-response relationship for PFS using a multivariate Cox-proportional hazards analysis or ORR. As presented in Figure 7, plots of Kaplan-Meier estimates for patients with exposures of trametinib with a predicted $C_{avg} \geq 15.08$ ng/mL and for those with a predicted $C_{avg} < 15.0$ ng/mL do not suggest a trend toward increasing PFS with higher trametinib exposures in the MEK114267 trial. Explorations for exposure-response relationships were limited by the narrow range of exposure of trametinib when administered at the dose level of 2 mg orally once daily, the dose and schedule evaluated in MEK113583 and MEK114267 (Please see the FDA Clinical Pharmacology NDA Review for further details).

Figure 7: Plots of Kaplan-Meier Estimates of Progression-Free Survival by Trametinib Exposure Predicted Cavg ≥ 15.08 ng/mL or < Cavg 15.08 ng/mL. MEK114267 Trial.



Source: Report no. 130902, Figure 1, Page 30.

REVIEWER COMMENT:
The MEK111054 trial administered a range of doses of trametinib (see Section 5.1). According to the Applicant's Clinical Study Report for the MEK 111054 trial, 30 BRAF inhibitor-naïve patients with BRAF V600 mutation-positive melanoma received trametinib; all 30 patients enrolled in cohorts which evaluated trametinib doses ≥ 2 mg on continuous daily schedule—this included pharmacodynamic cohorts which initially administered trametinib at doses < 2 mg orally once daily only on Days 1-15 followed by trametinib once daily dosing at ≥ 2 mg thereafter. Thus, the review did not include analyses of ORRs at continuous trametinib doses < 2 mg (see Section 4.4.2).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The MEK114267 and MEK113583 protocols specified a plan to analyze biomarkers related to the activity of trametinib. Consenting patients had an optional tumor biopsy performed at baseline (if not enough archival tissue was available after meeting the BRAF assay requirements) before receiving trametinib as well as at the time of disease progression for biomarker analyses. The Applicant intends to conduct an analysis tumor samples for various biomarkers—such as BRAF, MEK1/2, PTEN, and mutations in other genes (e.g., H-, K-, and N-RAS)—and states that it will include these results in a separate report.

6.1.10 Additional Efficacy Issues/Analyses

Single Adequate and Well-Controlled Trial for Effectiveness Claim

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

- large, multicenter study
- consistency across study subsets
- multiple studies in a single study
- multiple endpoints involving different events
- statistically very persuasive finding

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

The review of efficacy examined potential limitations of the MEK114267 trial as a single trial to support the efficacy of trametinib in the proposed indication.

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

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

Second, the Applicant designed the trial to evaluate multiple secondary endpoints, including ORR and OS. The SAP, however, did not include a plan to adjust the significance level for multiplicity based on testing of multiple secondary endpoints. Thus, comparative analyses of secondary endpoints are considered exploratory (see Dr. Chen's Statistical Review for details).

Nonetheless, a PFS treatment effect of trametinib is supported by a nominally significant increase in the ORR on the trametinib arm compared to the chemotherapy arm in the ITT population—objective responses, including two complete responses, with trametinib which were associated with moderate response durations in this disease (see Section 6.1.5). Additionally, the ORR of 25% (95% CI: 14%, 38%), including 1 CR, and median duration of response of 5.7 months (95% CI: 3.7, 9.2), observed in 57 patients with BRAF V600E or V600K mutation-positive unresectable or metastatic melanoma enrolled in the BRAF inhibitor-naïve cohort of the activity-estimating trial (MEK113583) provides external evidence and replication of the anti-tumor activity of trametinib in the proposed indication. Furthermore, the analysis of OS, which is based on 20% deaths in the ITT population, suggests a trend toward increased OS with trametinib. The statistical significance of the OS results is uncertain based on deficiencies in the design of the trial to evaluate OS as a comparative endpoint (see Dr. Chen's Statistical Review). In this OS analysis it is important to note that 47% of patients randomized to chemotherapy crossed over to receive trametinib at the time of the data cutoff.

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

Trametinib Use After Prior Use of BRAF Inhibitor Therapy

The Applicant evaluated the anti-tumor activity of trametinib in patients with BRAF mutation-positive, unresectable or metastatic melanoma who have received prior treatment with BRAF-inhibitor therapy.

The MEK113583 trial titled "an open-label, multicenter study to investigate the objective response rate, safety, and pharmacokinetics of GSK1120212, a MEK inhibitor, in BRAF mutation-positive melanoma subjects previously treated either with or without a BRAF inhibitor" enrolled patients simultaneously into two cohorts: Cohort A (n=40) enrolled patients who had previously received BRAF-inhibitor therapy, and Cohort B (n=57) enrolled patients who had previously received only prior standard therapy (chemotherapy and/or immunotherapy). Patients in both cohorts received trametinib 2 mg orally once daily until disease progression or unacceptable AEs. The primary analysis of ORR, defined as the percentage of patients with a confirmed CR or PR by investigator assessment per RECIST version 1.1, was tested in each cohort separately to determine if the response rate was ≤10% (null hypothesis) or was ≥25% (alternative hypothesis), which the Applicant considered of clinical interest.

In Cohort A, the median age of patients was 58 years (range 23 to 76). The majority of patients were male (63%) and all were white. The majority of patients also had the BRAF V600E mutation subtype within their tumor specimen (83%), M1c disease (73%), three or more sites of metastatic disease (70%), and elevated LDH (55%). Sixty-three percent of patients received prior chemotherapy. All patients received prior BRAF inhibitor therapy: 58% (23/40) of patients

received vemurafenib and 43% (17/40) received dabrafenib (GSK2118436). The Applicant reported that 45% (18/40) of the patients experienced an objective response with the prior BRAF inhibitor regimen with a median duration of response of 3 months; all but three patients had stopped prior BRAF inhibitor therapy for progression of disease. Approximately half of patients received BRAF inhibitor therapy for ≥ 24 weeks.

None of the 40 patients in Cohort A experienced a confirmed PR or CR. The unconfirmed response rate was 5% (95% CI: 1%, 17%) with one unconfirmed PR and one unconfirmed CR.

REVIEWER COMMENTS:
Sequential administration of BRAF inhibitors followed by MEK inhibitors does not appear to be a viable therapeutic strategy based on the data from Cohort A of the MEK113583 trial. Patients with melanoma who experience disease progression on BRAF-inhibitor therapy appear to develop cross-resistance to MEK inhibitors. Although not fully characterized, several mechanisms of resistance of melanoma to BRAF inhibitors have been described in the literature, including: (1) intrinsic resistance factors such as Cyclin D1 amplification, PTEN loss, and hepatocyte growth factor product; (2) acquired resistance factors leading to ERK activation such as receptor tyrosine kinase upregulation, NRAS mutations, splice variants of mutant BRAF, secondary mutations in MEK, and acquired resistance mutations; and (3), acquired resistance factors leading to activation of non-ERK pathways such as the PI3K pathway through platelet derived growth factor receptor beta or insulin-like growth factor 1 receptor (reviewed by Sullivan and Flaherty 2013). Several of these mechanisms or resistance would be expected to confer resistance to MEK inhibitors as well.

7 Review of Safety

Safety Summary

The review of safety primarily focused on analyses of data submitted for the MEK114267 trial because it is the only randomized, comparative trial submitted by the Applicant to support the safety of trametinib. The size of the ISS database and duration of trametinib exposure were sufficient to characterize the safety of trametinib for treatment of a serious and life-threatening condition, i.e., advanced melanoma. Across three clinical trials (MEK114267, MEK113583, MEK111054), 329 patients with metastatic melanoma received a median daily dose of trametinib 2 mg with a median time on study treatment of 3.84 months (minimum 0.03 months, maximum 24.5 months). One hundred and seven patients (33%) were on study treatment longer than 6 months. In the ISS database, the most common adverse reactions (≥20%) for trametinib were rash, diarrhea, fatigue, peripheral edema, and acneiform dermatitis.

The MEK114267 trial was an open-label, multicenter, international, randomized (2:1) controlled trial of 322 patients with previously untreated, unresectable or metastatic BRAF V600E or V600K mutation-positive melanoma who were allocated to receive trametinib 2 mg orally twice daily (n=214) or investigator's choice of chemotherapy [n=108; dacarbazine 1000 mg/m^2 intravenously every 3 weeks or paclitaxel 175 mg/m^2 intravenously over 3 hours every 3 weeks)] administered until disease progression or intolerable toxicity. The median duration on treatment was 4.3 months in the trametinib treatment group (n=211 patients) and vs. 2.1 months in the chemotherapy treatment group (n=99 patients). The mean daily dose intensity for trametinib was 92% for trametinib, 98% for dacarbazine, and 99% for paclitaxel. Twenty-seven percent of trametinib-treated patients required at least one dose reduction and 9% required treatment withdrawal for AEs.

Overall, the most frequent (≥20%) AEs with trametinib were rash (57% of trametinib-treated patients vs. 10% of chemotherapy-treated patients), diarrhea (43% vs. 16%), and peripheral edema (26% vs. 3%).

Serious adverse events occurred in 18% of trametinib-treated patients and 20% of chemotherapy-treated patients. The most frequent SAEs in the trametinib treatment group compared to the chemotherapy treatment group were those related to skin-related toxicities or infectious sequelae thereof (6% vs. 0), cardiomyopathy (1.4% vs. 0), pulmonary embolism (1.4% vs. 0), pneumonitis/interstitial lung disease (0.9% vs. 0),

Additional clinically significant adverse reactions of trametinib were ocular toxicity (retinal pigmented epithelial detachments, retinal vein occlusion), hepatotoxicity (no Hy's Law cases), hypertension, bradycardia, and rhabdomyolysis.

The rate of AEs leading to treatment withdrawal was similar between treatment groups, approximately 9%. Adverse events led to dose reductions more frequently in the trametinib treatment group (27%) than in the chemotherapy treatment group (10%). The most frequent

cause of dose reductions of trametinib was rash (9%) and decreased LVEF(3%). Adverse events leading to treatment interruptions/delays occurred in 20% of trametinib-treated patients and 16% of chemotherapy-treated patients. Adverse events leading to withholding treatment in more than 1% of the trametinib-treated patients were rash (4.3% in the trametinib treatment group vs. 0 in the chemotherapy treatment group), diarrhea (2.4% vs. 0), peripheral edema (1.9% vs. 0), ALT/AST increase (1.4% vs. 0), and ejection fraction decreased (1.4% vs. 0).

The reviewer does not recommend a REMS based on the information provided in the submission.

7.1 Methods

The ISS database comprises safety data from the MEK114267 trial (n=209 patients), MEK113583 (n=96 patients), and MEK111054 (n= 21 patients). The review of safety is primarily based on the MEK114267 trial data based on the following:

- The MEK114267 trial is the only randomized, comparative trial submitted by the Applicant to support the safety of trametinib
- The MEK114267 trial accounts for approximately two-thirds of the trametinib-treated patients in the ISS database

For the MEK114267 trial, at the baseline/screening visit, safety assessments included documentation of medical history including concomitant medications and cardiovascular familial history; oncologic history including prior therapy; organs involved with metastatic disease; physical examination; vital signs assessment; blood sampling for laboratory safety variables; blood sample collection for cardiac markers; documentation of an ECOG performance status (PS); ECG testing; echocardiogram testing, ophthalmologic examination (included fundoscopy and tonometry); serum pregnancy testing (if applicable); and documentation of AEs. Safety assessments performed on day one of each chemotherapy cycle included documentation of concomitant medications, brief physical exam, vital signs, ECOG PS, blood sampling for laboratory safety variables (hematology and clinical chemistry), blood sample collection for cardiac markers; echocardiogram and ECG (Cycle 2 Day 1; Cycle 5, Day 1; Cycle 8, Day 1, Cycle 11, Day 1; Cycle 15, Day 1 and every 4th Cycle thereafter), and documentation of AEs. Follow-up post-treatment discontinuation included collection of AEs until 30 days post-treatment discontinuation.

REVIEWER COMMENT:
Following the scheduled screening ophthalmologic examination, the MEK114267 protocol specified that ophthalmologic examinations were to be performed only if symptomatically warranted.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The Applicant submitted three trials as listed in Table 11 to evaluate the safety of trametinib for treatment of patients with unresectable or metastatic melanoma with the BRAF V600 mutation.

The safety data submitted by the Applicant includes information from 329 patients with melanoma treated with 2 mg trametinib monotherapy once daily. The FDA clinical review of safety primarily depended on review of the data from the MEK114267 trial because it was the only trial submitted to the NDA which would allow a comparison of AEs to a control group. The review also evaluated major safety findings (deaths, SAEs) and AEs of interest using pooled data (ISS database) from the three trials based on the data cutoff date used in the 120-day safety cutoff date, i.e., June 23, 2012 (MEK114267 and MEK113583) and January 13, 2012 (MEK111054). The review did not include an analysis of pooled data to evaluate the severity of specific AEs because the primary trial used NCI CTCAE version 4 and the supportive trials, MEK113583 and MEK111054, used NCI CTCAE version 3 to grade toxicities. The review evaluated SAE data from the trametinib development program as a whole which includes data from 1749 patients who received at least one dose of trametinib at various doses, either as monotherapy or in combination with approved drugs or experimental compounds (data cutoff date June 23, 2012).

7.1.2 Categorization of Adverse Events

The Applicant mapped and coded verbatim AE terms for the MEK114267 trial using the Medical Dictionary for Regulatory Activities (MedDRA) version 14.1. The Applicant graded the severity of AE toxicities encountered on the MEK114267 trial using NCI CTCAE version 4.

REVIEWER COMMENT:
The FDA clinical review of safety included an audit of AE case report forms as well as an assessment of the coding of AE verbatim terms to MedDRA preferred terms (PT) to assess the completeness and verify the accuracy of the raw AE datasets. In an audit of 5% of trial population, minor differences between the information captured on the CRFs and that included in the AE datasets were due to the AE occurring after the data cutoff date of October 26, 2011, or exclusion of AEs present at baseline. In addition, the review of safety assessed the adequacy of the Applicant's mapping of AE verbatim terms to MedDRA PTs for 100% of the MEK114267 raw AE dataset. Of the 2770 AE line listings in the rAE.xpt dataset (MEK114267), the review used programmatic matching of identical verbatim terms (n=1008 line listings) as well as manual evaluation of the remaining verbatim terms (n=1762 line listings) to assess the acceptability of the Applicant's mapping from the verbatim term to MedDRA PTs. The MedDRA preferred terms contained in the datasets adequately represented the investigator recorded term (i.e., verbatim term) in nearly all cases. Minor differences did not alter the reliability and interpretation of the safety data.

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

The ISS database included AE data from three trials (see Section 7.1.1 and Table 11). The review of safety included an analysis of the rates of the most common (>10% of patients) treatment-emergent adverse events (TEAE)s in trametinib-treated patients on MEK114267 compared to event rates in the entire ISS database. The incidence of TEAEs by severity of

toxicity grade was not analyzed in the ISS database based on use of a different version of the NCI CTCAE to grade AEs for trials MEK111054 and MEK113583 (NCI CTCAE version 3.0) than the version used to grade toxicity severity for the MEK114267 trial (NCI CTCAE version 4.0). Overall, the incidences of the most common TEAEs occurring on the primary trial, MEK 114267, were similar to the incidences in the ISS database. Diarrhea, fatigue, peripheral edema, nausea, and vomiting occurred at a higher incidence (>5% difference) in the ISS database than in MEK114267. This analysis is summarized in Table 26.

Table 26: Incidence of Common (≥10%) Treatment-Emergent Adverse Events in Trametinib-Treated Patients. MEK114267 Trial and ISS Database.

	Trametinib Group (MEK114267 Trial) N=211 n (%)	ISS Database N=329 n (%)
Rash	121 (57)	191 (58)
Diarrhea	91 (43)	162 (49)
Fatigue	54 (26)	109 (33)
Peripheral edema	54 (26)	109 (33)
Acneiform dermatitis	40 (19)	74 (22)
Nausea	38 (18)	99 (30)
Alopecia	36 (17)	51 (16)
Hypertension	32 (15)	48 (15)
Constipation	30 (14)	61 (19)
Vomiting	27 (13)	66 (20)
Headache	26 (12)	38 (12)
Dry skin	24 (11)	57 (17)
Pruritis	21 (10)	54 (16)
Paronychia	21 (10)	27 (8)
Abdominal pain	16 (8)	43 (13)
Decreased appetite	15 (7)	42 (13)
Cough	18 (9)	37 (11)
Increased AST	18 (9)	32 (10)
Dry mouth	17 (8)	34 (10)
Dyspnea	12 (6)	35 (11)
Arthralgia	15 (7)	33 (10)

Source: RAE.xpt datasets (MEK114267 Trial and ISS, 120-day safety update)

7.2 Adequacy of Safety Assessments

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

In the MEK114267 trial, 211 patients received treatment with GSK1120212 and 99 patients received treatment with chemotherapy [Dacarbazine (n=62), Paclitaxel (n=37)]. Patients treated with GSK1120212 remained on treatment longer than patients treated with either chemotherapy (median of 4.34 vs. 2.07 months). The mean relative dose intensity was 1.83/2 mg (92%) for GSK1120212, 977.13/1000 mg/m^2 (98%) for dacarbazine, and 173.27/175 mg/m^2 (99%) for paclitaxel. The median number of cycles of chemotherapy administered was higher with dacarbazine treatment (median of 3 cycles) than with paclitaxel treatment (median of 2 cycles). Table 27 summarizes the exposure for each treatment group in the MEK114267 trial.

Table 27: Exposure to Study Drug. Safety Population. MEK114267 Trial.

	Chemotherapy (N=99)		**Trametinib (N=211)**
Time on study treatment (months)[1]			
Mean	2.9		4.14
SD	1.96		2.027
Median	2.07		4.34
Min.	0.1		0.3
Max.	7.9		8.7
Number of Subjects (%)			
≤2 months	46 (46)		39 (18)
>2 to ≤4 months	25 (25)		57 (27)
>4 to ≤6 months	20 (20)		76 (36)
>6 months	8 (8)		39 (18)
	Dacarbazine (N=62)	**Paclitaxel (N=37)**	
Trametinib daily dose (mg)[2] or Chemotherapy dose intensity (mg/m^2/cycle)			
Mean	977.13	173.27	1.83
SD	72.938	6.242	0.285
Median	1000.00	175.00	2.00
Min.	571.4	147.5	0.8
Max.	1000.0	175.0	2.0
Number of Cycles, n (%)			
Min.	1	1	NA
1st quartile	2	2	NA
Median	3.0	2.0	NA
3rd quartile	6	5	NA
Max.	12	8	NA
Number of Subjects (%)			
1-2 cycles	27 (44)	19 (51)	NA
3-4 cycles	11 (18)	7 (19)	NA
5-6 cycles	10 (16)	3 (8)	NA
> 6 cycles	14 (23)	8 (22)	NA

Source: ISS Table 8.1, MEK114267 Table 8.1 and Table 8. Reviewer spot verified the numbers in this table using REXPOSUR.xpt
Abbreviations in Table: SD, standard deviation; NA, not applicable.
[1] Time on study treatment is the time from the first dose date to last dose date including interruptions.
[2] Daily dose is the cumulative dose divided by the duration of exposure.

In the MEK114267 crossover population (n=51 patients), the mean daily trametinib dose was similar at 1.91 mg. At the time of data cutoff, the median duration of trametinib exposure in the crossover population was 1.9 months.

Within the ISS database, a total of 329 patients received a median daily dose of trametinib 2 mg with a median time on study treatment of 3.84 months (minimum 0.03 months, maximum 24.5 months). One hundred and seven patients (33%) were on study treatment longer than 6 months.

As summarized in Table 28, demographics and baseline characteristics within each treatment group were well matched. As expected, within the chemotherapy treatment group, patients who received dacarbazine compared to those who received paclitaxel had a shorter median time since metastatic diagnosis, 4.7 months compared to 10.6 months, respectively, as well as a larger proportion of excellent ECOG performance status (ECOG PS 0, 74% vs. 46%). Of note, the demographics and baseline characteristics of the MEK114267 trial safety population were similar to those of the ITT population (Table 12 and Table 13).

Table 28: Demographics and Baseline Characteristics. Safety Population. MEK114267 Trial.

	Chemotherapy			
	Dacarbazine N=62	**Paclitaxel N=37**	**All N=99**	**GSK1120212 N=211**
Age, years				
Median	56	52	55	54
Min - Max	21-77	24-77	21-77	23-85
Age≥ 65, n (%)	14 (23)	7 (19)	21 (21)	47 (22)
Gender, n (%)				
Male	28 (45)	20 (54)	48 (48)	118 (56)
Female	34 (55)	17 (46)	51 (52)	93 (44)
Race/Ethnicity, n (%)				
White/Caucasian	61 (98)	37 (100)	98 (99)	209 (99)
White-Arabic/North African	0	0	0	2 (1)
Mixed	1 (2)	0	1 (1)	0
ECOG PS, n (%)				
0	46 (74.2)	17 (45.9)	63 (63.6)	135 (64)
1	16 (25.8)	20 (54.1)	36 (36.4)	76 (36)

	Chemotherapy		All N=99	GSK1120212 N=211
	Dacarbazine N=62	Paclitaxel N=37		
BRAFV600 Mutation Type, n (%)				
V600E, n (%)	57 (92)	33 (89)	90 (91)	182 (86)
V600K, n (%)	5 (8)	4 (11)	9 (9)	29 (14)
Time since Metastatic Diagnosis (months)				
N	61 (98)	37 (100)	98 (99)	210 (99.5)
Mean	12.6	23.4	16.7	17.1
SD	23.7	32.4	27.7	25.5
Median	4.7	10.6	6.6	7.4
Min - Max	0.7-117.0	0.9-145.7	0.7-145.7	0.2 – 204.2
Time since Last Progression (months)				
N (%)	1 (2)	30 (81)	31 (31)	64 (30)
Mean	1.35	2.21	2.2	3.2
SD	NA	1.8	1.8	4.8
Median	1.3	1.6	1.5	1.6
Min - Max	1.3-1.3	0.3-8.4	0.3-8.4	0.5-30.1
Stage of disease at study entry, n (%)				
Stage IIIc	3 (5)	4 (11)	7 (7)	10 (5)
Stage IV	59 (95)	33 (89)	92 (93)	201 (95)
M1c	37 (60)	23 (62)	60 (61)	142 (67)
LDH, n (%)				
≤ ULN	41 (66)	19 (51)	60 (61)	133 (63)
>ULN	21 (34)	18 (49)	39 (39)	76 (36)
Missing	0	0	0	2 (1)
Metastasis, n (%)				
Any Visceral Disease	50 (81)	28 (76)	78 (79)	175 (83)
History of Brain Mets	1 (2)	0	1 (1)	8 (4)
Prior Chemotherapy, n (%)	2 (3)	33 (89)	35 (35)	70 (33)

Source: POP.xpt, DEMOBASE.xpt, DISCHA1.xpt
Abbreviations in Table: NA, not applicable

7.2.2 Explorations for Dose Response

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

7.2.3 Special Animal and/or In Vitro Testing

See the summary of pharmacology/toxicology in Section 4.3.

7.2.4 Routine Clinical Testing

Please refer to sections 7.4.2-7.4.4.

7.2.5 Metabolic, Clearance, and Interaction Workup

See the summary of clinical pharmacology in Section 4.4.

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

GSK1120212 (trametinib) is a new molecular entity and the first in the class of MEK inhibitors for which an NDA has been submitted.

7.3 Major Safety Results

7.3.1 Deaths

Individual deaths will not be listed in a table because OS was an effectiveness outcome for the primary trial, MEK114267.

Table 29 summarizes the primary causes of death for patients in the MEK114267 study population and in the entire ISS database. Overall, 34 patients in the trametinib treatment group (16%) and 13 patients (13%) in the chemotherapy treatment group died during the randomized phase of the MEK114267 trial. Disease under study was the most commonly reported primary cause of death for the trametinib treatment group and the chemotherapy treatment group for all deaths (85% vs. 92%) in the MEK114267 trial. Overall, the Applicant reported treatment-emergent deaths (within 28 days of investigational product dosing) in 8% of trametinib-treated patients and 2% of chemotherapy-treated patients in the MEK114267 trial. In the ISS database, the Applicant reported that 91 patients (28%) of the 329 patients died; 82 of the 91 patients (90%) were reported to have died from progression of disease.

Table 29: Subject Follow-up Status. Primary Cause of Death. Safety Population. MEK114267 Trial.

	Chemotherapy N=99 n (%)	Trametinib (N=211) n (%)
Subject status		
Dead	13 (13)	34 (16)
Alive at last contact, follow-up ended	4 (4)	8 (4)
Alive at last contact, follow-up ongoing	31 (31)	169 (80)
Primary cause of death		
Disease under study	12 (12)	29 (14)
SAE possibly related to study treatment	0[a]	1 (<1)[a]
Other, specify	1 (1)[b]	4 (2)[b]
Time to death from last dose		
≤28 days	2 (2)	17 (8)
>28 days	11 (11)	17 (8)

Three trametinib-treated patients on the MEK114267 trial experienced a Grade 5 TEAE within 28 days of the last dose of study drug (Table 30).

Table 30: All Grade 5 Treatment-Emergent Adverse Events Occurring In Trametinib Treatment Group. MEK114267 Trial.

Patient ID	Age / Sex	Adverse Event	Last dose (Day)	Onset AE (Day)	Death (Day)	Investigator Reported Primary Cause of Death
MEK114267.0400379	77/M	Myocardial infarction	63	65	65	Intercurrent illness
MEK114267.0402007	61/F	Kidney Infection	10	10	20	SAE, possibly related to study treatment
MEK114267.0402110	74/M	Perforation of Duodenum	48	49	54	Sepsis

Source: MEK114267 Clinical Study Report
Abbreviations in Table: AE, adverse event; F, female; M, male

The following provides additional details of the Grade 5 TEAEs which occurred in the trametinib treatment group:

- Patient MEK114267.0400379, a 77 year old man with metastatic melanoma and a past medical history (PMH) otherwise notable for cardiac shock status post cardioversion and lit tobacco use, experienced syncope requiring hospitalization on Day 11. Although the syncope was attributed to vomiting, he experienced a myocardial infarction (MI) on Day 15 and underwent PTCA with stent placement and concomitant medical management. The echocardiogram demonstrated decreased LVEF from 65% at baseline to 40-45% on Day 16. Trametinib was held on Days 12-25 and reinitiated on Day 26 with an ongoing decrease in LVEF. On Day 63, the patient suffered a second MI. Comfort measures were implemented and he died on Day 65.

- Patient MEK114267.0402007, a 61 year old woman with metastatic melanoma and PMH otherwise notable for hypothyroidism, fatigue, congenital solitary kidney, and prior cisplatin chemotherapy, was hospitalized on Day 6 with a Grade 3 pleural effusion and again on Day 10 for gastroenteritis and syncope, secondary to dehydration. While hospitalized the patient was diagnosed with kidney failure, abdominal hematoma, urinary tract infection (E.coli, Klebsiella pneumonia, and E. faecalis), massively enlarged liver with metastasis, and worsening of general condition.
- Patient MEK114267.0402110, a 74 year old man with metastatic melanoma and PMH otherwise notable for extensive peritoneal carcinomatosis, experienced a perforation of duodenum which was confirmed at laparoscopy on Study Day 50. The patient's post-operative course was complicated by septic shock after developing pneumonia.

Review of the raw AEs dataset (RAE.xpt) for the MEK114267 trial identified one additional patient (MEK114267.0402229) who experienced a Grade 5 AE:

- Patient 402229 experienced Grade 5 renal and liver failure on Study Day 115 that resulted in death on Study Day 119. The last dose of trametinib prior to occurrence of the AEs was on Study Day 104. The patient had been hospitalized on Study Day 104 for Grade 2 vomiting and on Study Day 105, an imaging evaluation identified new liver metastases. The patient received chemotherapy (carboplatin/paclitaxel) for progression of disease on Study Day 109. The timing of onset of liver failure and renal failure, both Grade 2 at onset, as Study Day 115. The investigator attributed the death of this patient to the disease under study.

Two chemotherapy-treated patients experienced Grade 5 SAEs, both considered unrelated to treatment: pneumonia (MEK114267.0402446) and pseudomembranous colitis (MEK114267.0403664). No patient who crossed over to trametinib experienced a fatal SAE.

Of the 157 (48%) deaths reported in the ISS database (n=329), the primary cause of death was disease under study for 147 patients (94%). Thirty-seven of the 157 deaths (23.6%) occurred within 28 days of trametinib dosing. Five patients in the ISS database experienced six total Grade 5 SAEs. Of note, in the 120-Day safety update, the Applicant removed patient MEK114267.0402110 from the list of patients with Grade 5 SAEs because the patient's cause of death was reported as the disease under study. Table 31 provides details of the five patients with Grade 5 AEs.

Table 31: All Grade 5 Adverse Events. ISS Database.

Patient ID	Age / Sex	Grade 5 AE MedDRA Preferred Term(s)	Last dose (Day)	Onset AE (Day)	Death (Day)	Investigator Reported Primary Cause of Death
MEK113583.0201003	62/M	Gastrointestinal Fistula	60	57	67	Disease under study
MEK114267.0400263	78/M	Death	107	132	132	Other specify: Unknown at this time
MEK114267.400379	77/M	Myocardial infarction	63	65	65	Intercurrent illness
MEK114267.402007	61/F	Kidney Infection	10	10	20	SAE, possibly related to study treatment
MEK114267.0402229	M	Liver failure Renal failure	104	119	119	Disease under study

Source: 120-Day Safety update: EXPOSUR.xpt, DEATH.xpt, AE.xpt
Note: the Applicant excluded Patient MEK114267.0402110 (see Table 30) from the listing of fatal SAEs in the 120-Day safety update . The Applicant stated that this patient's death was listed as due to the disease under study and therefore not required to be reported as an SAE.

All Grade 5 AEs were considered unrelated to the study drug with the exception of liver failure and renal failure, both experienced by Patient MEK114267.0402229. The following are descriptions of the two additional cases of Grade 5 AEs reported in the trametinib treatment group in the 120-Day safety update:

- Patient MEK113583.0201003, a 62 year old male with melanoma metastatic to the abdomen/abdominal wall and liver and past medical history otherwise significant for abdominal distension, abdominal pain, anemia, diabetes, hypoalbuminemia, and small bowel resection related to the melanoma (3 months prior to start of study), developed a gastrointestinal fistula on Day 60 and subsequently died due to disease under study on Study Day 67.
- Patient MEK114267.0400263, a 78 year old man with nodular melanoma metastases involving the lymph nodes, liver, spleen, and lung with a significant PMH of former tobacco use, hyperlipidemia, Grade 1 emphysema, and syncope, died on Study Day 132 while on home hospice. The patient's treatment course was complicated by hospitalizations for orthostatic hypotension and cellulitis (Day 19; trametinib continued), Grade 3 symptomatic interstitial pneumonitis (Day 60; trametinib interrupted Days 61-87 and reduced to 1 mg on Day 88), Grade 3 pneumonitis and heart failure (Day 108; trametinib discontinued on Day 108), and Grade 2 shortness of breath and pulmonary embolism (Day 120). The second occurrence of Grade 3 pneumonitis had improved to Grade 2 by Study Day 114. The patient's LVEF on echocardiogram had improved from 35% on Study Day 108 to 48% by Study Day 119. Adverse events considered related to study treatment by the investigator, which were ongoing at the time of death, included fatigue, chest pain, cardiac failure, and pneumonitis. Shortness of breath and pulmonary embolism were also ongoing but were considered by the investigator to be unrelated to trametinib.

REVIEWER COMMENTS: Review of the data provided for the six patients with Grade 5 SAEs—four patients identified in the review of MEK114267 and two additional patients reported in the 120-day safety update—suggests that in five cases the deaths were likely related to the

underlying metastatic melanoma, including sequelae thereof, or underlying comorbidities. Although liver failure and renal failure were recorded as related to study treatment in one of these five patients, the primary cause of death for Patient MEK114267.0402229 was recorded as disease under study. As described in the previous reviewer comment, the onset of liver failure and renal failure AEs began after initiation of chemotherapy in post-study follow-up period. In the sixth case, the contribution of the treatment-related, serious cardiopulmonary toxicity experienced by patient MEK114267.0400263 to the fatal SAE of "death" is undetermined based on the improvement in these toxicities observed approximately two to three weeks prior to the death event.

The Applicant reported that one fatal AE occurred in the trametinib cross-over population in the 120-day safety update. Patient MEK114267.0404286, a 60 year old women with melanoma metastases involving the lymph nodes and skin and a PMH otherwise significant for diabetes, hypertension, obesity, and prior trophic ulcer, developed a trophic ulcer (Grade 1) while on the paclitaxel treatment arm (administered on Study Days 1, 22, 44, and 63) and subsequently developed and succumbed to (Study Day 251) an infection of the ulcer after crossing over to receive trametinib (administered Study Days 161-245). The investigator reported that the patient died of an SAE unrelated to study treatment.

7.3.2 Nonfatal Serious Adverse Events

The Applicant defined SAE as any untoward medical occurrence that:

- Resulted in death
- Was life-threatening
- Required hospitalization or prolongation of existing hospitalization
- Resulted in disability/incapacity
- Was a congenital anomaly/birth defect
- Were otherwise considered important medical events, that might not be immediately life-threatening or resulting in death or hospitalization, but might have jeopardized the patient or might have required medical or surgical intervention to prevent one of the other outcomes in the bulleted list above
- Were Hy's Law events, i.e., possible drug-induced liver injury events with hyperbilirubinemia defined as ALT $\geq$ 3x ULN and bilirubin $\geq$ 2x ULN (>35% direct) (or ALT $\geq$3x ULN and INR >1.5, if INR measured)
- Was a new primary cancer
- Was a laboratory abnormalities or other safety assessments (e.g. ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, felt to be clinically significant in the medical and scientific judgment of the investigator

Non-fatal SAEs occurred in 17.5% (19/211) of trametinib-treated patients and 19.2% (19/99) of chemotherapy-treated patients in the MEK114267 trial. The most frequent non-fatal SAEs in the trametinib treatment group compared to the chemotherapy treatment group were cellulitis (4 patients vs. 0 patients), anemia (3 vs. 2), and pulmonary embolism (3 vs. 0). Table 32

summarizes the non-fatal SAEs that occurred in one or more patients the trametinib treatment group.

Table 32: Incidence of Non-Fatal Serious Adverse Events (Occurring in at Least One Trametinib-Treated Patient) by Treatment Group. Safety Population. MEK114267 Trial.

	Trametinib N=211 n (%)	Chemotherapy N=99 n (%)
INFECTIONS AND INFESTATIONS	13 (6)	1 (1)
Cellulitis	4 (2)	0
Infection[1]	3 (1)	0
Erysipelas	2 (1)	0
Bronchopneumonia	1 (<1)	0
Eye infection	1 (<1)	0
Klebsiella infection	1 (<1)	0
Lymphangitis	1 (<1)	0
Rash pustular	1 (<1)	0
Sepsis	1 (<1)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	6 (3)	0
Pulmonary embolism	3 (1)	0
Dyspnea	2 (1)	0
Pleural effusion	2 (1)	0
Pneumonitis	2 (1)	0
Interstitial lung disease	1 (<1)	0
INVESTIGATIONS	5 (2)	3 (3)
Ejection fraction decreased	2 (1)	0
Alanine aminotransferase increased	1 (<1)	0
Blood bilirubin increased	1 (<1)	1 (1)
Blood creatine phosphokinase increased	1 (<1)	0
Hemoglobin decreased	1 (<1)	1 (1)
CARDIAC DISORDERS	4 (2)	1 (1)
Cardiac failure	1 (<1)	0
Conduction disorder	1 (<1)	0
Left ventricular dysfunction	1 (<1)	0
Acute coronary syndrome[2]	1 (<1)	1 (1)
GASTROINTESTINAL DISORDERS	4 (2)	3 (3)
Vomiting	2 (1)	1 (1)
Dysphagia	1 (<1)	0
Gastric hemorrhage	1 (<1)	0
Nausea	1 (<1)	1 (1)

	Trametinib N=211 n (%)	Chemotherapy N=99 n (%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	4 (2)	6 (6)
General physical health deterioration	1 (<1)	0
Local swelling	1 (<1)	0
Edema	1 (<1)	0
Pyrexia	1 (<1)	4 (4)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	3 (1)	4 (4)
Anemia	3 (1)	2 (2)
NERVOUS SYSTEM DISORDERS	3 (1)	0
Epilepsy	1 (<1)	0
Ischemic stroke	1 (<1)	0
Syncope	1 (<1)	0
HEPATOBILIARY DISORDERS	2 (1)	2 (2)
Gallbladder obstruction	1 (<1)	0
Jaundice	1 (<1)	0
IMMUNE SYSTEM DISORDERS	2 (1)	1 (1)
Corneal graft rejection	1 (<1)	0
Hypersensitivity	1 (<1)	0
METABOLISM AND NUTRITION DISORDERS	2 (1)	1 (1)
Decreased appetite	1 (<1)	0
Dehydration	1 (<1)	1 (1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	2 (1)	0
Back pain	1 (<1)	0
Rhabdomyolysis	1 (<1)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (1)	0
Rash	2 (1)	0
VASCULAR DISORDERS	2 (1)	0
Deep vein thrombosis	1 (<1)	0
Orthostatic hypotension	1 (<1)	0
PSYCHIATRIC DISORDERS	1 (<1)	0
Anxiety	1 (<1)	0

Source: RAE.xpt, AE.xpt (09/24/2012 version)
[1] composite of infection and localized infection.
[2] composite of acute coronary syndrome, myocardial infarction.

The review of safety included further analyses of the following SAEs to identify adverse reactions of trametinib:

- Cardiac events
- Pneumonitis
- Skin-related toxicity
- Rhabdomyolysis
- Hypersensitivity

Cardiac Events Related to Ventricular Dysfunction

Eighteen cardiac events related to ventricular dysfunction, as defined by the Applicant based on a composite of preferred terms (see Appendix 9.5), occurred in 14 patients treated with trametinib: decreased ejection fraction (n=13), left ventricular dysfunction (n=4), and cardiac failure (n=1). No patient treated with chemotherapy experienced a cardiac-related event based on these composite terms. The median time to onset was 9 weeks (minimum 2.3 weeks, maximum 22.3 weeks).

Of the 14 trametinib-treated patients with cardiac-related events, three patients (1.4%) experienced a total of four SAEs.

- Patient MEK114267.0400263, a 78 year old man with melanoma metastatic to the lymph nodes, liver, spleen, and lung and a PMH otherwise significant for hyperlipidemia, Grade 1 emphysema, and syncope--no prior history of coronary artery disease, congestive heart failure, arrhythmia, valvular disease, pulmonary embolism, COPD—required hospitalization on Day 108 for pneumonitis (Grade 3), decreased LVEF (Grade 3), and heart failure (Grade 3). Echocardiogram performed at the time of heart failure showed an EF that decreased from 60% at baseline to 35% on Study Day 108. The patient's clinical condition improved following BIPAP with oxygen supplementation, loop diuretics, and subsequent initiation of beta-blockers and ACE inhibitors. The decreased LVEF was reported as resolved on Day 120 (nuclear myocardial perfusion test results) and the heart failure was reported as ongoing.
- Patient MEK114267.0401271, a 58 year old women with melanoma metastatic to the liver and lymph nodes with a PMH otherwise significant for Grade 1 hypertension and hypothyroidism, experienced left ventricular dysfunction (Grade 3) on Day 34—her LVEF decreased from 80% at baseline to 30% on Day 34 in association with Grade 1 fatigue—which recovered on Day 59 following trametinib discontinuation (total duration of event was 17 days). The event was considered serious based on it being an important medical event.
- Patient MEK114267.0402820, a 56 year old woman with melanoma metastatic to the lung, liver, bone, and lymph nodes and no other significant PMH, on Day 88 experienced a Grade 2 decrease in her ejection fraction in association with Grade 1 dyspnea on exertion. The echocardiogram results demonstrated a decreased in the baseline LVEF from 65% to 54% on Day 88. The events were considered serious by the investigator based on it being an important medical event. The patient recovered from the event on Day 98 and she restarted trametinib at a reduced dose on Day 99.

Of all 18 cardiac events related to ventricular dysfunction, dose reduction was the most common treatment modification (n=8) followed by investigational product withdrawal (n=5), dose interruption (n=4), and dose not changed (n=1). There were three recurrences of the decreased ejection fraction in two patients following rechallenge with dose-reduced trametinib. The cardiac related events were recovered/resolved in nine patients, recovering/resolving in one patient, recovered with sequelae in one patient, or not recovered/not resolved in 3 patients at the time of the data cutoff. The median duration of the cardiac AE in patients in whom the event recovered was 2.1 weeks (minimum 1.1 weeks, maximum 10.1 weeks).

Investigators withheld trametinib treatment in 12 patients with an absolute decrease in LVEF of 10% that was <LLN. Per protocol defined treatment modification criteria, the LVEF had to recover to normal and within 10% of the baseline LVEF to restart trametinib. Trametinib was restarted in 9 of the 12 patients. As summarized in Table 33, four of nine patients who were re-treated with trametinib experienced a positive rechallenge.

Table 33: All Cases of Decreased Left Ventricular Ejection Fraction Resulting in Withholding Trametinib. MEK 114267 Trial.

Subject	Age / Sex	Cardiac History	LVEF ECHO/MUGA						AEs temporally Associated with Worst Case LVEF decrease	Withhold (Day) / Rechallenged (Day) / Outcome
			LVEF LLN (%)	Screen LVEF (%)	Worst Case LVEF		Recovery LVEF			
					(%)	Day	(%)	Day		
MEK114267.0400259	51/M	+	50%	61%	49%	148	55%	155	Sinus bradycardia	D148-154 / Yes (D155[†]) / Negative
MEK114267.0400263 [a]	78/M	+	50%	60%	35%	108	64%	119	Heart failure, tachycardia, pneumonitis	D108 / No / NA
MEK114267.0400379 [b]	77/M	+	50%	65%	25%	61	-	-	Myocardial infarction, coronary artery disease	D12-25; 64 / Yes (D26[†]) / Positive
MEK114267.0401271 [c]	58/F	+	60%	80%	30%	34	59%	50	-	Day 35 / No / NA
MEK114267.0402009	54/M	-	55%	50%	25%	36	-	-	Peripheral edema	D23 / No / NA
MEK114267.0402226	42/M	-	55-60%	80%	50%	148	60%	166	-	D153-169/ Yes (D170[‡]) / Negative

Subject	Age / Sex	Cardiac History	LVEF ECHO/MUGA						AEs temporally Associated with Worst Case LVEF decrease	Withhold (Day) / Rechallenged (Day) / Outcome
			LVEF LLN (%)	Screen LVEF (%)	Worst Case LVEF		Recovery LVEF			
					(%)	Day	(%)	Day		
MEK114267.0402395 [d]	65/F	-	50%	56%	23%	70	-	-	T wave inversion anteriorly and QRS complexes	D20-55 / Yes (D56[‡]) / Positive
MEK114267.0402820	56/F	-	55%	65%	54%	88	65%	98	Dyspnea	D89-98 / Yes (D99[¦]) / Negative
MEK114267.0402953	72/F	+	50%	58%	47%	29	51%	39	Right ventricular dysfunction, hypertension	D27-42 / Yes (D43 [‡]) / Negative
MEK114267.0402956 [e]	73/M	+	50%	60%	42%	169	62%	212	Fatigue, hypertension, dyspnea, chest pain	D44-49, 65-72/ Yes (D50[‡],73[¦]) / Positive (twice)
MEK114267.0403893	28/F	-	55%	62%	30%	83	55%	111	-	D85-112 / Yes (D113[‡]) / Negative
MEK114267.0404641 [f]	53/M	-	55%	70%	45%	141	-	-	-	D85-112, 141-154 / Yes (D113[†], 155) / Positive

Source: MEK 114267 Clinical Study Report(Table 55) and case narratives. Verified and supplemented information from CRDSCN.xpt

Abbreviations in Table: AE, adverse events; D, day; Echo, echocardiogram; F, female; LVEF, left ventricular ejection fraction; NA, not applicable; M, male; MUGA, multi-gated acquisition.

Reviewer Notes:

[a] *Patient had two LVEF assessments on same day, LVEF of 48% by echocardiogram and a LVEF of 64% based on an undocumented assessment method.*

[b] *Patient first met criteria for stopping on Day 16 (LVEF of 45%), one day after diagnosis with MI. The patient restarted at the same trametinib dose (2 mg).*

[c] *Patient first met criteria for stopping on Day 22 with an LVEF of 35%.*

[d] *Patient first met stopping criteria on Day 18 with an LVEF of 27%. Subsequent LVEF assessments were:47% on Day 32, 44% on Day 46, 53% on Day 53, and 23% on Day 70.*

[e] *Patient first met criteria with LVEF of 45% on Day 43. Subsequent LVEF assessments were 50% on Day 50, 45% on Day 64, 50% on Day 73, 45% on Day 155, 53% on Day 157, and 42% on Day 169.*

[f] *Patient first met criteria for stopping on Day 85 with an LVEF of 51%. Subsequent LVEF assessments were: 53% on Day 99; 51% on Day 113, 53% on Day 127; and 45% on Day 141.*

[†] *Rechallenge with trametinib 2 mg dose (same dose)*

[‡] *Rechallenge with trametinib1.5 mg dose (reduced dose)*

[¦] *Rechallenge with trametinib 1.0 mg dose (reduced dose)*

Routine echocardiogram monitoring in the MEK114267 trial demonstrated an increased risk of impaired left ventricular function in the trametinib treatment group compared to the chemotherapy treatment group. Left ventricular ejection fraction was assessed by echocardiogram or MUGA at baseline, Cycles 2, 5, 8, 11, and every 4 cycles thereafter until treatment discontinuation. In addition to investigator assessment of LVEF, a central reviewer—blinded to the sequence of imaging and time point designation— assessed LVEF based on echocardiograms or MUGA scans. Of the patients with a baseline- and at least one post-baseline LVEF assessment available (updated data using the data cutoff date for the 120-Day safety update), reductions in LVEF > 10% and below the lower limit of normal (LLN), based on investigator and blinded independent review determinations, occurred in 10 to 14% of patients treated with trametinib compared to 3% of patients treated with chemotherapy as summarized in Table 34.

Table 34: Worst-Case Change From Baseline in Left Ventricular Ejection Fraction. Investigator and Independent Review Assessments. 120-Day Safety Update. MEK114267 Trial.

	Trametinib[1]		Chemotherapy[1]	
	INV	IR	INV	IR
Number Evaluable	**200**	**150**	**86**	**68**
	n (%)	**n (%)**	**n (%)**	**n (%)**
No change or any increase	47 (24)	31 (21)	39 (45)	30 (44)
Any decrease	153 (77)	119 (79)	47 (55)	38 (56)
0 to <10 decrease	99 (50)	72 (48)	36 (42)	30 (44)
10 to 19 decrease	43 (22)	37 (25)	11 (13)	8 (12)
≥20 decrease	11 (6)	10 (7)	0	0
≥10 decrease and ≥LLN	35 (18)	26 (17)	8 (9)	6 (9)
≥10 decrease and below LLN[2]	19 (10)	21 (14)	3 (3)	2 (3)
≥20 decrease and ≥ LLN	2 (1)	1 (1)	0	0
≥20 decrease and below LLN	9 (5)	9 (6)	0	0

Source: Verified with CRDSCN.xpt; CRDSCEX1.xpt (120-Day Update)
Abbreviations in Table: INV, investigator determined; IR, independent reviewer assessed; LLN, lower limit of normal
[1] Subjects with a baseline assessment and at least one post-baseline assessment are included in this table.
[2] Pre-defined treatment modification criteria to temporarily interrupt treatment (>10% LVEF compared to baseline and LVEF below the LLN)

The review of safety included analyses of the MEK114267 trial to evaluate potential complications of left ventricular dysfunction including arrhythmias, syncope, and sudden death. The incidence of cardiac arrhythmias was 3% in the trametinib treatment group and 1% in the chemotherapy treatment group in a search of narrow-based standardized MedDRA query (SMQ) for cardiac arrhythmias (Table 35). There was one serious cardiac arrhythmia event, a Grade 4 conduction disorder. The remainder of cardiac arrhythmia AEs were Grade 1 or 2.

Table 35: Incidence of Cardiac Arrhythmias (Narrow Based Standardized MedDRA Query) by Treatment Group. Safety Population. MEK114267 Trial.

	Trametinib N=211 n (%)	Chemotherapy N=99 n (%)
ANY	7 (3)	1 (1)
Sinus bradycardia	2 (1)	0
Ventricular arrhythmia	2 (1)	0
Atrial fibrillation	1 (<1)	1 (1)
Atrioventricular block	1 (<1)	0
Conduction disorder	1 (<1)	0
Electrocardiogram QT prolonged	1 (<1)	0
Ventricular extrasystoles	1 (<1)	0

There were five patients with syncope in the MEK114267 trial, all cases occurred in the trametinib treatment group. Two of the five cases were Grade 3 in severity; one serious case occurred which required hospitalization. Four of the five cases occurred within the first three weeks of trametinib treatment (range 10 to 47 days). Trametinib was withheld in one patient and continued uninterrupted in the remaining patients. All patients recovered within 1 to 3 days. There were no cases of sudden cardiac death or sudden death reported in the MEK114267 trial or in the ISS database.

REVIEWER COMMENT:
The Applicant commissioned an independent panel of experts to review and adjudicate all fatal SAEs that the Applicant identified across all studies of trametinib as of May 31, 2012 (n=65) based on report of five cases of sudden death across all trials in the trametinib development program (see Section 7.4.5).

Pneumonitis

Four pneumonitis events (including one interstitial lung disease AE) occurred in two patients treated with trametinib compared to no events of pneumonitis in patients treated with chemotherapy:

- Patient MEK 114267.0400263, a 78 year old man, former tobacco user, with metastatic melanoma to the lymph nodes, liver, spleen, lung and PMH otherwise significant for emphysema (Grade 1), experienced the AE pneumonitis requiring hospitalization on Study Day 60. At an undefined time, the patient began supplemental oxygen which was noted at the time of the interstitial pneumonitis. Pulmonary function tests performed on Day 48 demonstrated a DLCO of 30% predicted. On Study Day 60, the patient presented with fever, chills, and fatigue; he was noted to be tachycardic and to have an oxygen saturation of 52% on 2L supplemental oxygen. A CT scan demonstrated interval development of bilateral ground glass and interstitial opacities in both lungs in the setting

of stable lung metastases. A workup, including bronchoscopy and secretion cultures, was negative. Trametinib was interrupted on Study Day 61. The patient received treatment with IV and oral steroids. A CT scan performed Study Day 83 was noted to have improvement in the ground glass changes in the lungs, and the symptoms resolved by Day 87 thus he restarted dose reduced trametinib (1 mg daily) on Day 88. On Study Day 102, repeat PFTs demonstrated a DLCO of 38% and a pulmonologist recommended decreasing supplemental oxygen and a 4 week tapering off of corticosteroids. The patient subsequently was hospitalized on Study Day 108 for recurrent Grade 3 pneumonitis, Grade 3 decreased LVEF, and Grade 3 heart failure. The oxygen saturation was reported to be 45% on 5L supplemental oxygen. Imaging studies including a chest x-ray and a CT scan demonstrated interval progression of diffuse interstitial ground glass changes through both lungs. In addition to intravenous corticosteroids, the patient received treatment for heart failure including loop diuretics. Pneumonitis improved to Grade 2 by Day 114.

- Patient MEK114267.0403826, a 63 year old man with metastatic melanoma to the subcutaneous tissue and bone, and PMH otherwise significant for hypertension, hyperlipidemia, and MI, experienced Grade 2 pneumonitis requiring hospitalization on Study Day 79 and treatment interruption on Study Day 80. Evaluation included imaging, bronchoscopy, and lung biopsy. Bronchial washings showed leukocytes, gram positive cocci, and occasional gram positive bacilli. Lung biopsy showed non-specific changes. The clinical diagnosis was drug-induced pneumonitis. The patient received treatment with antibiotics and dexamethasone with resolution of pneumonitis with sequelae on Study Day 84. The patient declined rechallenge with trametinib.

In the ISS database, three additional trametinib-treated patients in the MEK114267 trial experienced five pneumonitis events [pneumonitis (n=4) and interstitial lung disease (n=1)]. All five additional events were Grade 3 and were serious (required hospitalization). There were no cases of pneumonitis/interstitial lung disease in the chemotherapy treatment group at the time of the 120-Day safety cutoff.

Table 36 summarizes the clinical characteristics of the five (2.4%) trametinib-treated patients who experienced pneumonitis or interstitial lung disease. The mean and median time to onset of the first occurrence of pneumonitis was 128 and 160 days, respectively (minimum 60 days, maximum 172 days). Trametinib was withdrawn in all five patients and the outcome of pneumonitis was not recovered/not resolved (n=1), recovering/resolving (n=1), recovered/resolved with sequelae (n=2), and recovering/resolving (n=1).

Table 36: All Cases of Pneumonitis or Interstitial Lung Disease in Trametinib-Treated Patients. 120-Day Safety Update. MEK114267 Trial.

Patient ID	Age/ Sex	Pulm History	Confounding Meds	Study Day	Intervention	Outcome	Dur (days)	Dose Modification/ Interruption
MEK114267.0400263	78/M	+	-	60 108	IV and oral steroids; IV corticosteroids, diuretics	R NR	28 n/a	Dose reduced Investigational product withdrawn
MEK114267.0402779	70/F	-	-	172	IV and oral corticosteroids	R	25	Investigational product withdrawn
MEK114267.0402832	47/M	+	+	168	IV and oral corticosteroids	RR	n/a	Investigational product withdrawn
MEK114267.0403642	58/M	+	-	160 345 359	Corticosteroids and bronchodilators	R RR RS	37 n/a 4	Dose reduction Investigational Product withdrawn n/a
MEK114267.0403826	63/M	-	-	79	Corticosteroids and antibiotics	RS	6	Investigational Product withdrawn

Source: MEK114267 Clinical Study Report; ISS 120-Safety Update Report; RAE.xpt
Abbreviations in Table; Dur, duration; M, male; F, female; IV, intravenous; n/a, not applicable; R, recovered; NR, not recovered/not resolved; RR, recovering/resolving; RS, recovered/resolved with sequelae; Pulm, pulmonary

The Applicant reported one additional case of pneumonitis in the ISS database. Patient MEK113583.0210001, a 41 year old female with melanoma metastatic to the lungs and lymph node and no other significant PMH, developed Grade 1 pneumonitis on Day 53. The patient withheld trametinib on Days 53 to 70 and restarted dose-reduced trametinib at 1.5 mg once daily on Day 71. Pneumonitis resolved after 67 days.

Skin-related toxicity

Fourteen cases of serious adverse reactions related to skin-toxicities or infectious sequelae thereof, all requiring hospitalization, occurred in 12 (6%) trametinib-treated patients compared to none in the chemotherapy treatment group. The most frequent SAEs related to skin-toxicity in trametinib-treated patients were cellulitis (1.9%), infection (1.4%) erysipelas (0.9%), and rash (0.9%). The two cases of serious rash (Grade 3) required dose-reduction of trametinib. Rash was

reported to be recovering/resolving in one patient and not recovered/not resolved in the other patient.

The time to onset of serious infection cases related to skin was a mean of 56 days and median of 41 days (range 8 to 126 days). Dosing with trametinib was withheld and then reduced in one patient, withheld in two additional patients, and not changed in the remaining patients. The Applicant reported that all cases of infection (n=12) resolved.

Overall, skin related toxicity, as defined by the Applicant based on a composite of preferred terms (see Appendix 9.5), comprised 253 events in 184 patients (87%) treated with trametinib and 17 events in 13 patients (13.1%) treated with chemotherapy, most frequently rash (57% of trametinib-treated patients vs. 10% of chemotherapy-treated patients), acneiform dermatitis (19% vs. 1%), and pustular rash (5% vs. 0) as summarized in Table 37.

Table 37: Incidence of Skin-Related Toxicities by Treatment Group. Safety Population. MEK114267 Trial.

	Trametinib N=211		Chemotherapy N=99	
	All n (%)	Grade 3-4 n (%)	All n (%)	Grade 3-4 n (%)
Any skin-related AESI	184 (87)	26 (12)	13 (13)	0
Rash	121 (57)	17 (8)	10 (10)	0
Dermatitis acneiform	40 (19)	2 (1)	1 (1)	0
Rash pustular	10 (5)	2 (1)	0	0
PPES	9 (4)	0	0	0
Erythema	8 (4)	1 (<1)	0	0
Photosensitivity reaction	3 (1)	1 (<1)	2 (2)	0
Rash maculo-papular	5 (2)	1 (<1)	0	0
Acne	4 (2)	1 (<1)	0	0
Dermatitis	4 (2)	1 (<1)	0	0
Rash macular	4 (2)	0	0	0
Seborrheic dermatitis	3 (1)	0	0	0
Rash generalized	1 (<1)	1 (<1)	0	0
Rash pruritic	1 (<1)	0	0	0
Skin exfoliation	1 (<1)	0	0	0

Source: RAE.xpt dataset
Abbreviations in Table: AESI, adverse event of special interest; G, Grade; PPES, Palmar-plantar erythrodysesthesia syndrome

The median time to onset of any skin-related adverse event of special interest (AESI) was 2.1 weeks (minimum 0.1 weeks, maximum 31.6 weeks) in the trametinib treatment group compared to 6.3 weeks (minimum 0.1 weeks, maximum 21.1 weeks) in the chemotherapy treatment group.

In the trametinib treatment group, dose reduction was the most common treatment modification for these events (n=30) followed by dose interruption (n=13) and investigational product withdrawal (n=2). In 82% (208/253) of the events, the trametinib dose was not changed. Skin-related AESIs were recovered/resolved in 43% of the events (109/253 events), recovering/resolving in 9% (23/253), recovered with sequelae in 7% (17/253), or not recovered/not resolved in 41% (104/253) at the time of the data cutoff. The median duration of the skin-related AESI in which the event had recovered was 6.9 weeks (minimum 0.1 weeks, maximum 40.4 weeks).

Table 38 summarizes the characteristics of the four most common skin-related AESIs occurring in the trametinib group: rash, acneiform dermatitis, pustular rash, and palmar-plantar erythrodysesthesia syndrome (PPES). The time to onset of rash was earlier in the trametinib treatment group compared to the chemotherapy treatment group (median 13 vs. 32 days) and the duration of rash (first occurrence) was longer (median of 54.5 vs. 18 days). Of the nine cases of PPES encountered in the trametinib treatment group, none were Grade 3 or 4 in severity and none required treatment modification.

Table 38: Characteristics of Most Common Skin-Related Adverse Events in Trametinib Treatment Group. Safety Population. MEK114267 Trial.

	Rash		Acneiform dermatitis[1]	Pustular rash[1]	PPES[1]
	Trametinib N=211	Chemo N=99	Trametinib	Trametinib	Trametinib
Any	121 (57.3)	10 (10)	40 (19)	10 (5)	9 (4)
Event Characteristics, n (%)					
Serious	2 (1)	0	0	1 (<1)	0
Grade 4	1 (<1)	0	0	0	0
Grade 3	16 (8)	0	2 (1)	2 (1)	0
Grade 2	40 (19)	3 (3)	20 (9)	2 (1)	3 (1)
Grade 1	64 (30)	7 (7)	18 (9)	6 (3)	6 (3)
Number of Occurrences, n (%)					
One	99 (47)	8 (8)	37 (18)	10 (5)	9 (4)
Two	17 (8)	2 (2)	3 (1)	0	0
Three	2 (1)	0	0	0	0
Four	3 (1)	0	0	0	0
Outcome, n (%)[2]					
Recovered/Resolved	52 (25)	6 (6)	17 (8)	3 (1)	5 (2)
Recovering/Resolving	10 (5)	0	7 (3)	2 (1)	0
Not recovered/Not resolved	61 (29)	4 (4)	17 (8)	5 (2)	3 (1)
Recovered/Resolved with sequelae	11 (5)	1 (1)	1 (<1)	0	1 (<1)

	Rash		Acneiform dermatitis[1]	Pustular rash[1]	PPES[1]
	Trametinib N=211	Chemo N=99	Trametinib	Trametinib	Trametinib
Action(s) Taken, n (%)[2]					
Investigational Product Withdrawn	2 (1)	0	0	0	0
Dose Reduced	19 (9)	0	2 (1)	2 (1)	0
Dose not changed	102 (48)	10 (10)	39 (18)	8 (4)	9 (4)
Dose interrupted/delayed	7 (3)	0	1 (<1)	0	0
Time to onset of first occurrence, days					
Median (min-Max)	13 (1-137)	32 (2-77)	14 (7-44)	9 (7-54)	55 (22-113)
Duration of first occurrence[3], days					
Median (min-Max)	54.5 (1-227)	18 (3-42)	67 (29-155)	128 (106-183)	45 (3-93)

Source: AE.XPT (MEK114267 dataset, 09/24/2012 submission)
Abbreviations in Table: Chemo, chemotherapy treatment group; PPES, palmar-plantar erythrodysesthesia syndrome
[1] Chemotherapy treatment group not included in analysis based on few events, acneiform dermatitis (n=1), pustular rash (n=0), PPES (n=0).
[2] Patients may be counted in more than one category.
[3] patients with adverse event that recovered/resolved.

The Applicant performed a retrospective analysis to evaluate the benefit of the protocol defined primary prophylaxis as a treatment for patients who encountered dermatologic adverse reactions (Table 39). Of the 211 trametinib-treated patients, 28 (13%) received supportive therapy for dermatologic AE with prophylactic intent while 183 (87%) did not receive prophylactic therapy. Within these non-randomized subgroups, the proportion of patients who experienced a dermatologic AE was similar in both subgroups, 93% (26/28) in patients who received primary prophylactic therapy and 86% (158/183) in patients who did not receive primary prophylactic therapy for dermatologic AEs.

Table 39: Applicant Analysis of Incidence of Dermatologic Adverse Events in Trametinib-Treated Patients. Prior or No Prior Use of Primary Prophylaxis for Dermatologic Toxicity Subgroups. MEK114267 Trial.

	Primary Prophylaxis Administered for Dermatologic AE	
	Yes N=28	No N=183
Number of dermatologic AEs	37	216
Number of patients with AE	26	158
Grade 1, n (%)	15 (58)	78 (49)
Grade 2, n (%)	6 (23)	60 (38)
Grade 3, n (%)	5 (19)	19 (12)
Grade 4, n (%)	0	1 (1)
Dermatologic AEs characteristics		
Serious Adverse Reaction	0	3 (2)
Led to Trametinib Dose Reduction, n (%)	4 (15)	21 (13)
Led to Trametinib Withdrawal, n (%)	1 (4)	1 (1)

Rhabdomyolysis

Overall, there were four cases of rhabdomyolysis, including one case of rhabdomyolysis requiring hospitalization, experienced by three patients (1.4%) in the trametinib treatment group compared to no cases in the chemotherapy treatment group. All three patients developed rhabdomyolysis within the first month of beginning trametinib (Range 21 to 22 days). Two of the three patients required trametinib dose-reduction for rhabdomyolysis. The status of rhabdomyolysis was recovered/resolved or resolving in three cases and not recovered/not resolved in one case. The serious case of rhabdomyolysis occurred in Patient MEK114267.0404741, a 76 year old man with melanoma metastases involving the lung, liver, bone, and lymph nodes and a concomitant medication history significant for atorvastatin. On Day 21, the patient required hospitalization for fever and Grade 3 rhabdomyolysis in association with possible erysipelas. Laboratory evaluation demonstrated an increased creatine phosphokinase (5.7 times the upper limit of normal). The patient withheld trametinib on Days 22-28 and the AE rhabdomyolysis resolved. There was no recurrence of rhabdomyolysis following rechallenge of trametinib at a reduced dose (1.5 mg orally once daily).

REVIEWER COMMENT:
The review of rhabdomyolysis as an adverse reaction of trametinib in the three patients was confounded by use of concomitant medications at baseline which are associated with rhabdomyolysis. The Applicant did not collect CK values in the laboratory testing panel in the MEK114267, MEK113583, and MEK111054 trials at baseline or while on-treatment. CK elevations and muscular weakness appears to be an emerging class effect of MEK inhibitors based on review of the side effect profile of other MEK inhibitors in development. Although causality cannot be definitively established for the three patients described above, the totality of

the evidence supports inclusion of rhabdomyolysis as a clinically important AE occurring in < 10% of patients in the trametinib label. The severity of rhabdomyolysis events should be assessed in post-marketing surveillance to determine if this risk of rhabdomyolysis will need to be communicated in a different section of the label based on the severity of events.

Hypersensitivity

Overall, the incidence of hypersensitivity reactions was similar between treatment groups. Hypersensitivity or anaphylactic reactions occurred in 4 (1.9%) trametinib-treated patients and 2 (2%) chemotherapy-treated patients. The two cases of drug hypersensitivity in the trametinib treatment group were allergic reactions to concomitant antibiotics. Table 40 summarizes the incidence of hypersensitivity reactions by treatment group.

Table 40: Incidence of Hypersensitivity Reactions by Treatment Group. Safety Population. MEK114267 Trial.

	Trametinib N=211 n (%)		**Chemotherapy N=99 n (%)**	
	Grade 1-4	**Grade 3-4**	**Grade 1-4**	**Grade 3-4**
ANY	4 (2)	1 (<1)	2 (2)	1 (1)
Drug hypersensitivity	2 (1)	0	1 (1)	0
Hypersensitivity	2 (1)	1 (<1)	1 (1)	1 (1)
Anaphylactic reaction	0	0	1 (1)	1 (1)

Patient MEK114267.0402816—a 65 year old women with malignant melanoma with metastases to the abdomen, colon, and peritoneum/omentum and no other significant PMH or use of concomitant medications at baseline or at the time of hypersensitivity—developed fever, asthenia, joint pain, muscular pain, vomiting and visual disturbance with bilateral serous detachment of the retina on Day 8 requiring hospitalization. On Day 10, the patient developed a non-infectious cough, lower limb edema, hand edema, and erythema nodosum, cytolysis, and hepatitis and trametinib was discontinued. An infectious work-up for hepatitis as well as a transabdominal ultrasound were unremarkable. The patient received amoxicillin/clavulanic acid, antipyretics, and NSAIDS for the event. Maximum elevation in transaminases was on Study Day 17 with an ALT of 7.3 times ULN, AST of 67.5 times ULN and alkaline phosphatase of 3.8 times ULN and normal total bilirubin. Biopsy of nodular skin lesions demonstrated non-malignant hypodermatitis. The patient received hydroxyzine and desloratadine on Day 20 and the hypersensitivity reaction resolved on Day 22. Erythema nodosum and hepatitis resolved on Day 24. The retinal detachment was resolving on Day 24.

REVIEWER COMMENT:
Considering the absence of confounding medications in this case and chronology of the event in relation to trametinib dosing, this reviewer agrees with the Applicant's inclusion of

(b) (4) *in the label under the clinically relevant adverse reactions reported in <10% of patients treated with MEKINIST.*

In the ISS database, there were two additional cases of hypersensitivity:

- Patient MEK113583.0209026 developed an environmental allergy (verbatim term) on Day 588 which was ongoing at the time of data cutoff.
- Patient MEK113583.0211003 developed swelling of the lips and eyes on Day 10 of dosing with trametinib which resolved after 5 days. Both cases were Grade 1 reactions and neither required a change in trametinib dosing.

7.3.3 Dropouts and/or Discontinuations

Sixty-nine percent (146/211) and 87% (86/99) of patients treated with trametinib and chemotherapy, respectively, had treatment discontinued at the time of data cutoff for the MEK114267 trial as summarized (Table 41). The most common reason for discontinuing treatment was progressive disease which occurred in 55% of trametinib-treated patients and 73% of chemotherapy-treated patients. The incidence of treatment discontinuations for AE was 10% in the trametinib treatment group and 6% in the chemotherapy treatment group.

Table 41: Incidence of Treatment Discontinuations. Safety Population. MEK114267 Trial.

	Trametinib N=211	**Chemotherapy N=99**
Total Discontinued	146 (69)	86 (87)
Disease Progression	116 (55)	72 (73)
Adverse Event	21 (10)	6 (6)
Investigator Discretion	5 (2)	4 (4)
Decision by patient or proxy	4 (2)	4 (4)

Source: MEK114267 Clinical Study Report, Table 6. Verified with RIPDISC.xpt dataset

Table 42 summarizes the rate of treatment modifications (i.e., discontinuations, delays, and dose reductions) because of AEs in the MEK114267 trial. Treatment modifications as a result of AEs occurred more frequently in the trametinib treatment group than in the chemotherapy treatment group, 44% vs. 30%, respectively.

Table 42: Incidence of Treatment Modifications for Adverse Events by Treatment Group. Safety Population. MEK114267 Trial

	Trametinib N=211 n (%)	Chemotherapy N=99 n (%)
ANY TREATMENT MODIFICATION	93 (44.1)	30 (30.3)
Investigational product withdrawn	20 (9.5)	9 (9.1)
Reduction of any study treatment	56 (26.5)	10 (10.1)
Delay of any study treatment	42 (19.9)	16 (16.2)

Source: AE.xpt dataset (MEK114267)

Treatment discontinuations due to AEs occurred with similar frequency in the trametinib treatment group (9.5%) as in the chemotherapy group (9.1%). Overlap in AEs leading to treatment discontinuation was nearly absent between treatment groups and uncommon within each treatment group (Table 43). Adverse events leading to trametinib discontinuation that occurred in two or more patients were decreased cardiac function (four patients) and pneumonitis, rash, and renal failure (each occurring in two patients).

Table 43: Adverse Events Leading to Treatment Discontinuation by Treatment Group. Safety Population. MEK114267 Trial

	Trametinib N=211 n (%)	Chemotherapy N=99 n (%)
ANY	20 (10)	9 (9)
CARDIAC DISORDERS		
Left ventricular dysfunction	2 (1)	0
Cardiac failure	1 (<1)	0
Myocardial infarction	1 (<1)	0
Tachycardia	1 (<1)	0
INVESTIGATIONS		
Ejection fraction decreased	2 (1)	0
Increased alanine aminotransferase	1 (<1)	0
Increased blood bilirubin	1 (<1)	0
Increased gamma-glutamyltransferase	1 (<1)	0
Increased blood creatine phosphokinase	1 (<1)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Pneumonitis	2 (1)	0
RENAL AND URINARY DISORDERS		
Renal failure	2 (1)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Rash	2 (1)	0
Erythema nodosum	1 (<1)	0

	Trametinib N=211 n (%)	Chemotherapy N=99 n (%)
EYE DISORDERS		
Chorioretinopathy	1 (<1)	0
Retinal detachment	1 (<1)	0
HEPATOBILIARY DISORDERS		
Hepatic failure	1 (<1)	0
Hepatitis	1 (<1)	0
Hepatobiliary disease	1 (<1)	0
GASTROINTESTINAL DISORDERS		
Duodenal perforation	1 (<1)	0
Esophagitis	1 (<1)	0
Vomiting	1 (<1)	0
Diarrhea	1 (<1)	1 (1)
Abdominal pain upper	1 (<1)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Face edema	1 (<1)	0
Edema peripheral	1 (<1)	0
Fatigue	1 (<1)	0
Pyrexia	1 (<1)	0
METABOLISM AND NUTRITION DISORDERS		
Decreased appetite	1 (<1)	0
Hyponatremia	1 (<1)	0
Cell death	1 (<1)	0
IMMUNE SYSTEM DISORDERS		
Hypersensitivity	1 (<1)	0
Corneal graft rejection	1 (<1)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia	1 (<1)	0

REVIEWER COMMENT:
Please see Section 7.2.1, Deaths, for the review of the two patients who discontinued due to renal failure (Patient MEK114267.0402007 and MEK114267.0402229).

Overall, 10 percent of patients in the ISS database discontinued trametinib due to AEs. The most common AEs leading to trametinib discontinuation were pneumonitis (1.2%), increased ALT (0.9%), decreased ejection fraction (0.9%), left ventricular dysfunction (0.6%), diarrhea (0.6%), rash (0.6%), renal failure (0.6%), and retinal vein occlusion (0.6%).

The review of AEs leading to trametinib discontinuation included further analyses of the following:

- Ocular events
- Hepatotoxicity

Ocular Events

Overall, ocular related AEs occurred more frequently in trametinib-treated patients (9%) compared to chemotherapy-treated patients (3%). Two trametinib-treated patients experienced AEs related to retinal disorders which led to treatment discontinuation—one case of retinal detachment and one case of chorioretinopathy (central serous retinopathy). One Grade 3 ocular-related event, central serous retinopathy (CSR), occurred in the trametinib treatment group compared to none in the chemotherapy treatment group as summarized in Table 44.

Table 44: Incidence of Ocular Related Adverse Events By Treatment Group. Safety Population. MEK114267 Trial.

	Trametinib N=211		Chemotherapy N=99	
	All (%)	Grade 3-4[a] (%)	All (%)	Grade 3-4[a] (%)
ANY OCULAR EVENT	18 (9)	1 (<1)	3 (3)	0
Vision blurred	8 (4)	0	1 (1)	0
Dry eye	6 (3)	0	0	0
Central serous retinopathy	1 (<1)	1 (<1)	0	0
Papilledema	1 (<1)	0	0	0
Photophobia	1 (<1)	0	0	0
Visual acuity reduced	1 (<1)	0	0	0
Visual impairment	1 (<1)	0	0	0
Vitreous floaters	0	0	1 (1)	0
Diplopia	0	0	1 (1)	0

Source: MEK114267 Clinical Study Report; table verified using RAE.xpt.
[a] There were no Grade 4 ocular-related adverse events.

In the ISS database, 42 patients (13%) experienced ocular events. The most frequent ocular events were blurred vision (6%), dry eye (3%), and visual impairment (2%). The most significant ocular events were RVO and CSR.

- RVO occurred in two patients (<1%) treated with trametinib compared no patients treated with chemotherapy. RVO was serious and led to treatment discontinuation in both cases
- CSR occurred in three trametinib-treated patients (<1%), two patients with Grade 3 CSR and one patient with Grade 1 CSR. No chemotherapy-treated patients experienced CSR.

Ocular toxicities, including RVO and CSR, are emerging as a class effect of MEK inhibitors in development. Considering the rarity of the events in the ISS database, the Applicant provided further analysis of these ocular events entire trametinib development program.

Across the trametinib development program, there were four cases of RVO reported (out of >1800 patients). All four cases were unilateral. The Applicant reports that in all cases, the patients received trametinib for at least 12 weeks on study and in one case the patient was treated for 50 weeks prior to development of RVO. RVO was associated with substantial decreases in visual acuity in two of the four patients—the two patients diagnosed with central retinal vein occlusion—and with minor decrements in visual acuity (20/20 to 20/25) in the other two patients.

- Patient MEK114267.0402315, a 52 year old man with melanoma metastases to the spleen, lungs, and lymph nodes and a PMH significant for hypertension (Grade 2), experienced blurry vision on Day 85 to 106 without an associated decrease in visual acuity followed by a recurrence in blurry vision in the left eye on Day 191. On Day 203, ophthalmological examination of the left eye demonstrated Grade 4 central retinal vascular disorder (mixed retinal vein and artery occlusion) and macular edema. In addition, the examiner suspected wide angle glaucoma of the left eye. Visual acuity of the left eye decreased from 20/20 at baseline to 20/400 in the left eye, the acuity of the right eye remained unchanged. Intraocular pressures at baseline were 21 mm Hg in the left eye and 18 mm Hg in the right eye and at Day 203 were 23 mm Hg bilaterally. The patient required hospitalization for treatment which included intravenous corticosteroids, intravenous hemorrheologics, low molecular weight heparin, and carbonic anhydrase/beta-blocker eye drops. The patient subsequently received intravitreal vascular endothelial growth factor inhibitor therapy every 4 weeks starting on Day 217. By Day 308, the patient's visual acuity was recovering with an improvement to 20/25 in the left eye and the macular edema had resolved.
- Patient MEK111054.0002404, a 58 year old man with non-small cell lung cancer with metastases involving the lymph nodes and a right pleural effusion and a PMH significant for vitreous floaters, developed Grade 3 retinal hemorrhages in the left eye on Day 217. Grade 1 blurred vision presented on Day 15 which worsened to Grade 2 on Day 211. Ophthalmoscopy demonstrated new retinal hemorrhages in the left eye which resulted in decreased visual acuity to 20/60 from the baseline examination of 20/20. Patient was referred to a retinal specialist who diagnosed a central retinal vein occlusion in the left eye. Other retinal findings included macular edema and ischemia. The patient discontinued trametinib on Day 212. The patient received the following treatments: NSAIDS, corticosteroids, antibiotics, and intravitreal injections of anti-VEGF monoclonal antibody. Decreased visual acuity and macular edema was ongoing at the time of the 120-Day safety update—the treatment plan included additional intravitreal injections of anti-VEGF mAb.

Of the four patients with RVO, three had predisposing factors at baseline including glaucoma and hypertension (n=1), hypertension and elevated hematocrit (n=1), and chronic non-ischemic vein occlusion. The patients discontinued trametinib due to RVO in each case. Treatment for both cases of RVO associated with marked decreases in visual acuity included intravitreal anti-VEGF monoclonal antibodies within two weeks of diagnosis; visual acuity resolved in one case and improved to near baseline in the other case.

In the trametinib development program, CSR was reported in 14 patients receiving trametinib in daily doses ranging from 1.5 mg to 4 mg, including two patients who received loading doses of 6 or 10 mg, administered either as monotherapy or in combination with other products. The Applicant reported that none of the patients with CSR had potential risk factors including precipitating medications. CSR was bilateral in all cases. The most frequently reported symptom was blurry vision or altered light perception. Visual acuity was decreased in five patients, unchanged in six patients, and not reported in three patients. The onset of CSR was a mean of 27 days and a median of 15 days (range 1 to 90 days) from start of trametinib treatment. The initial occurrence of CSR resolved in all patients. The duration of the initial occurrence of CSR was a mean of 13 days and a median of 19.5 days (range 4-72 days). Seven patients discontinued treatment due to CSR and seven patients restarted trametinib at a reduced dose. Of the seven patients with CSR who restarted trametinib at a reduced dose, three required further dose reduction, two discontinued trametinib, and two continued without further modification. Two of the seven patients experienced a positive rechallenge with trametinib with recurrent central serous retinopathy; two additional patients developed visual symptoms following rechallenge. None of the patients required therapeutic intervention.

REVIEWER COMMENT:
DOP2 consulted the Division of Transplant and Ophthalmology Products (DTOP) to provide recommendations concerning the risk of ocular disorders, including RVO and CSR, with trametinib. FDA requested the available images for patients reported to experience CSR for review by the consulting ophthalmologist. The FDA ophthalmological review of these cases determined that CSR did not accurately describe the findings associated with this ocular toxicity of trametinib. In addition, the ocular events described throughout the NDA as CSR did not follow a typical clinical course for CSR. The recommended description for these ocular events is retinal pigment epithelial detachments (RPED). This reviewer agrees with the FDA ophthalmology consultant's recommendation to provide descriptive language in labeling to identify the adverse reaction based on the retinal findings rather than as CSR. Please see Dr. Chamber's ophthalmology consult review for additional details.

Hepatic adverse events

In MEK114267, the incidence of hepatic-related events, as defined by the Applicant based on a composite of preferred terms (see Appendix 9.5), in the trametinib treatment group (12%) was higher than in the incidence in the chemotherapy treatment group (6%). The most frequent hepatic-related AEs in the trametinib treatment group were increased AST (9%) and increased ALT (7%) as summarized in Table 45.

Table 45: Incidence of Hepatic-Related Adverse Events by Treatment Group. Safety Population. MEK114267 Trial.

	Trametinib N=211 n (%)	Chemotherapy N=99 n (%)
ANY HEPATIC-RELATED AE	25 (12)	6 (6)
Aspartate aminotransferase increased	18 (9)	1 (1)
Alanine aminotransferase increased	14 (7)	2 (2)
Blood bilirubin increased	2 (1)	1 (1)
Cytolytic hepatitis	1 (<1)	1 (1)
Hepatic failure	1 (<1)	0
Hepatic pain	1 (<1)	1 (1)
Hepatitis	1 (<1)	1 (1)
Hepatobiliary disease	1 (<1)	0
Hepatomegaly	1 (<1)	0
Jaundice	1 (<1)	0
Hepatic enzyme increased	0	1 (1)

Source: RAE.xpt.
Abbreviation in Table: AE, adverse event

The median time to onset of first hepatic-related event in the trametinib treatment group was 41 days (range 1 to 147 days). The median duration of all hepatic AEs in trametinib-treated patients in whom the event recovered was 43 days (range 4 to 169 days).

The incidence of Grade 3-5 hepatic events was higher in the trametinib compared to the chemotherapy treatment group (3.8% vs. 3.0%). Hepatic-related SAEs occurred in two patients in each treatment group. There was one fatal hepatic event (Subject MEK114267.0402229). Patient MEK114267.0402229, a 23-year-old man with nodular melanoma and a PMH significant for cholecystolithiasis, received trametinib and was diagnosed with new liver metastases on Day 105. He subsequently began treatment with paclitaxel and carboplatin on Study Day 111 for progression of disease on trametinib. Following initiation of new anticancer therapy, the patient subsequently died on Study Day 119 due to Grade 5 liver failure and Grade 5 renal failure which was reported to be related to the disease under study (see patient narrative of this case in Section 7.3.1).

Overall, treatment was not modified in either treatment group in most cases of hepatic-related events [trametinib, 36/50 (72%) of the events; chemotherapy, 6/8 (75%) of the events). Of the 50 hepatic-related events occurring in the trametinib treatment group, trametinib dosing was modified for 14 events: withdrawn (n=5 events), dose reduced (n=4 events), or withheld (n=5 events). Two patients discontinued treatment for four AEs potentially related to hepatic toxicities:

- Patient 402423, a 34-year-old male with melanoma metastases to the liver, prior left tri-sectionectomy and caudate lobe resection, required hospitalization on Day 10 for Grade

2 jaundice, Grade 3 ALT increased, and Grade 4 blood bilirubin leading to trametinib discontinuation on Day 11. The patient narrative reported evidence of biliary obstruction on multiple imaging modalities indicative of progression of disease.

- Patient MEK114267.0402816, a 65 year old women with melanoma metastatic to the abdomen/abdominal wall, colon, and peritoneum/omentum and no significant alcohol consumption reported during the trial, required hospitalization on Day 10 for a Grade 3 hypersensitivity reaction. Initial symptoms included fever, asthenia, joint pain, muscular pain, vomiting, and CSR; these symptoms progressed while continuing on trametinib treatment to cough, lower limb edema, hand edema, and erythema nodosum which led to trametinib discontinuation on Day 10. The patient received the following supportive care medications: antibiotics (Day 11), anti-pyretics/analgesic (Day 15), and anti-inflammatory/analgesics (Day 15). On Day 17, the patient developed Grade 3 elevations in ALT and AST without concomitant increases in total bilirubin. The elevations in ALT/AST recovered to Grade 2 by Day 21 and resolved by Day 48.

In addition, elevations in ALT or AST led to dose reductions of trametinib in two patients (MEK114267.0402682, MEK114267.0401006) and dose interruptions in another three patients (MEK114267.0401087, MEK114267.0404514, MEK114267.0402681). The outcomes of hepatic-related events in trametinib-treated patients were recovered/resolved in 14 patients, recovering/resolving in two patients, not recovered/not resolved in eight patients, and fatal in one patient at the time of the data cutoff.

One patient treated with chemotherapy (MEK114267.0403647) experienced the AE "hepatic enzyme increased" in Cycle 1 of dacarbazine leading to a dose reduction. Patient MEK114267.0403647 was listed in the laboratory dataset as having a Grade 3 elevation which occurred on the start day of the hepatic enzyme increased AE. No patients treated with chemotherapy underwent treatment discontinuation due to a hepatic-related event.

Laboratory abnormalities related to liver enzyme elevations occurred more frequently in the trametinib treatment group than in the chemotherapy treatment group as summarized in Table 46. Review of the laboratory data in the trametinib treatment group did not identify any Hy's Law cases.

Table 46: Incidence of Liver Enzyme Elevations (All Grades and Grade 3-4) By Treatment Group. MEK114267 Trial.

	Trametinib N=211		Chemotherapy N=99	
	Grade 1-4 n (%)	Grade 3-4 n (%)	Grade 1-4 n (%)	Grade 3-4 n (%)
Aspartate Amino Transferase	142 (67)	5 (2)	24 (24)	1 (1)
Alanine Amino Transferase	102 (48)	6 (3)	31 (31)	3 (3)
Alkaline Phosphatase	76 (36)	5 (2)	27 (27)	3 (3)
Total Bilirubin	8 (4)	1 (<1)	4 (4)	1 (1)

7.3.4 Significant Adverse Events

Grade 3 or 4 Adverse Events

Overall, a higher incidence of trametinib-treated patients experienced any Grade 3 or 4 TEAE than in the chemotherapy group (Table 47). The most common Grade 3 or 4 TEAEs in the trametinib treatment group were hypertension (13% in the trametinib treatment group vs. 4% in the chemotherapy treatment group) and rash (8% vs. 0). In general, most TEAEs occurring in the trametinib treatment group were Grade 3 in severity.

Table 47: Incidence of Grade 3 and 4 Treatment-Emergent Adverse Events (>1% Trametinib Group) by Treatment Group. Safety Population. MEK114267 Trial.

	Trametinib N=211 n (%)			Chemotherapy N=99 n (%)		
	Grade 3	Grade 4	Grade 3-4	Grade 3	Grade 4	Grade 3-4
ALL	93 (44)	8 (4)	101 (48)	29 (29)	6 (6)	35 (35)
Hypertension	27 (13)	0	27 (13)	4 (4)	0	4 (4)
Rash	16 (8)	1 (<1)	17 (8)	0	0	0
Fatigue	8 (4)	0	8 (4)	3 (3)	0	3 (3)
Anemia	4 (2)	0	4 (2)	2 (2)	0	2 (2)
Dehydration	3 (1)	1 (<1)	4 (2)	0	1 (1)	1 (1)
Increased alanine aminotransferase	4 (2)	0	4 (2)	0	0	0
Dyspnea	2 (1)	1 (<1)	3 (1)	1 (1)	0	1 (1)
Hypoalbuminemia	3 (1)	0	3 (1)	1 (1)	0	1 (1)
Pruritus	4 (2)	0	4 (2)	0	0	0
Vomiting	2 (1)	0	2 (1)	2 (2)	0	2 (2)
Blood creatine phosphokinase increased	3 (1)	0	3 (1)	0	0	0
Cellulitis	3 (1)	0	3 (1)	0	0	0
Infection	3 (1)	0	3 (1)	0	0	0

Source: RAE.xpt.

Adverse Events Leading to Dose Reductions

Adverse events led to dose reductions more frequently in the treatment group (27%) than in the chemotherapy treatment group (10%). The most frequent cause of dose reductions of trametinib was rash (9%) and decreased ejection fraction (3%). Table 48 summarizes the AEs leading to dose reduction in ≥ 1 patient in the trametinib treatment group.

Table 48: Incidence of Adverse Events Leading to Trametinib Dose Reductions. Safety Population. MEK114267 Trial.

	Trametinib N=211		Chemotherapy N=99	
	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Rash	19 (9)	14 (7)	0	0
Acne	2 (1)	1 (<1)	0	0
Dermatitis acneiform	2 (1)	0	0	0
Pruritus	2 (1)	2 (1)	0	0
Erythema	1 (<1)	0	0	0
Rash maculo-papular	1 (<1)	0	0	0
Rash papular	1 (<1)	1 (<1)	0	0
Skin ulcer	1 (<1)	0	0	0
Toxic skin eruption	1 (<1)	0	0	0
INVESTIGATIONS				
Decreased ejection fraction	6 (3)	0	0	0
Increased alanine aminotransferase	2 (1)	2 (1)	0	0
Increased aspartate aminotransferase	2 (1)	0	0	0
Increased blood creatine phosphokinase	2 (1)	1 (<1)	0	0
Increased blood alkaline phosphatase	1 (<1)	0	0	0
Electrocardiogram abnormal	1 (<1)	0	0	0
Decreased hemoglobin	1 (<1)	1 (<1)	0	0
GASTROINTESTINAL DISORDERS				
Stomatitis	2 (1)	1 (<1)	0	0
Abdominal pain	1 (<1)	1 (<1)	0	0
Anal ulcer	1 (<1)	0	0	0
Diarrhea	1 (<1)	0	0	0
Lip ulceration	1 (<1)	1 (<1)	0	0
Oral pain	1 (<1)	1 (<1)	0	0
INFECTIONS AND INFESTATIONS				
Rash pustular	2 (1)	1 (<1)	0	0
Folliculitis	1 (<1)	1 (<1)	0	0
Klebsiella infection	1 (<1)	1 (<1)	0	0
Nail infection	1 (<1)	0	0	0
Pulpitis dental	1 (<1)	0	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
Fatigue	2 (1)	2 (1)	1 (1)	1 (1)
Mucosal inflammation	2 (1)	2 (1)	0	0
Pyrexia	1 (<1)	0	0	0

	Trametinib N=211		Chemotherapy N=99	
	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
Rhabdomyolysis	2 (1)	2 (1)	0	0
Neck pain	1 (<1)	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
Exertional dyspnea	1 (<1)	1 (<1)	0	0
Interstitial lung disease	1 (<1)	1 (<1)	0	0
Nasal ulcer	1 (<1)	0	0	0
CARDIAC DISORDERS				
Conduction disorder	1 (<1)	1 (<1)	0	0
Left ventricular dysfunction	1 (<1)	0	0	0
VASCULAR DISORDERS				
Hypertension	2 (1)	2 (1)	0	0
EYE DISORDERS				
Central serous retinopathy	1 (<1)	0	0	0
METABOLISM AND NUTRITION DISORDERS				
Hypertriglyceridemia	1 (<1)	1 (<1)	0	0

In analyses based on MedDRA HLTs, the most common AEs (n ≥2 patients) leading to dose reductions were:

- Rashes, eruptions, and exanthems NEC (9.5% with trametinib vs. 0 with chemotherapy)
- Cardiac function diagnostic procedures (2.8% vs. 0)
- Acnes (1.9% vs. 0)
- Skin structures and soft tissue infections (1.4% vs. 0)
- Asthenic conditions (0.9 vs. 1)
- Liver function analyses (0.9 vs. 1.1)
- Mucosal findings abnormal (0.9% vs. 0)
- Myopathies (0.9% vs. 0)
- Pruritis nec (0.9% vs. 0)
- Skeletal and cardiac muscle analyses (0.9% vs. 0)
- Stomatitis and ulcerations (0.9% vs. 0)
- Vascular hypertensive disorders NEC (0.9% vs. 0)

In analyses of the ISS database, 26% of patients experienced AEs leading to dose reductions. The most common AEs resulting in trametinib dose reductions were rash (8%), decreased ejection fraction (2.4%), acneiform dermatitis (1.5%), increased ALT (1.2%), mucosal inflammation (1.2%), increased AST (0.9%), increased blood creatinine phosphokinase (0.9%), and fatigue (0.9%).

Adverse Events Leading to Treatment Interruptions/Delays

Adverse events leading to treatment interruptions/delays occurred in 20% of trametinib-treated patients and 16% of chemotherapy-treated patients. Adverse events leading to withholding treatment in more than 1% of the trametinib-treated patients were rash (4.3% in the trametinib treatment group vs. 0 in the chemotherapy treatment group), diarrhea (2.4% vs. 0), peripheral edema (1.9% vs. 0), ALT/AST increase (1.4% vs. 0), and ejection fraction decreased (1.4% vs. 0). Table 49 summarizes AEs leading to dose delays in ≥2 trametinib-treated patients.

Table 49: Adverse Events Leading to Treatment Interruption/Delay (≥2 Trametinib-Treated Patients) by Treatment Group. Safety Population. MEK114267 Trial.

	Trametinib N=211 n (%)	Chemotherapy N=99 n (%)
Rash [a]	9 (4)	0
Diarrhea	5 (2)	0
Peripheral edema	4 (2)	0
Ejection fraction decreased	3 (1)	0
Increased ALT or AST	3 (1)	0
Cardiac disorder	2 (1)	0
Cellulitis	2 (1)	0
Nausea	2 (1)	0
Pyrexia	2 (1)	1 (1)

[a] Composite term including rash, rash maculo-papular, rash generalized
[b] The investigator reported that both patients had an ejection fraction decreased AE and these patients are also included in this Table with the patients with ejection fraction decreased AEs.

In analyses of the ISS database, AEs leading to withholding of trametinib dosing but not resulting in trametinib discontinuation occurred in 36% of patients. The most common AEs leading to an interruption in trametinib administration were rash (8.5%), diarrhea (4.6%), decreased ejection fraction (3.3%), peripheral edema (2.4%), increased ALT (2.1%), left ventricular dysfunction (2.1%), fatigue (1.8%), pyrexia (1.8%), cellulitis (1.5%), dehydration (1.5%), nausea (1.5%), vomiting (1.5%), increased AST (1.2%), increased blood creatine phosphokinase (1.2.%), acneiform dermatitis (1.2%), and mucosal inflammation (1.2%).

REVIEWER COMMENT:
Adverse events leading to treatment modifications in the ISS database are consistent with those based on the analysis of the MEK114267 trial.

The review of significant AEs included additional analyses of the following:

- Hypertension
- Diarrhea

Hypertension

In MEK114267, 47% of trametinib-treated patients and 43% of chemotherapy-treated patients had hypertension at baseline. Overall, 16% of trametinib-treated patients and 7% of chemotherapy-treated patients experienced hypertension (any Grade) on-treatment. Grade 3-4 hypertension occurred in 13% of trametinib-treated patients and 4% of chemotherapy-treated patients. In both treatment groups, the median time to onset of new or worsening hypertension was within the first month of treatment (22 days in the trametinib treatment group vs. 23 days in the chemotherapy treatment group); the mean time to onset was 35 days (range 1 to 126 days) in the trametinib treatment group and 43 days (range 22 to 85 days) in the chemotherapy treatment group.

Most hypertension AEs occurred in patients with hypertension at baseline: 26/33 (79%) of cases in the trametinib treatment group and 6/7 (86%) of cases in the chemotherapy treatment group. Eight patients of the 26 trametinib-treated patients with pre-existing hypertension experienced a two Grade increase (i.e., increase from Grade 1 at baseline to Grade 3 on treatment). Of the cases of hypertension in patients with no prior history of hypertension at baseline, the severity of hypertension reported at onset was Grade 3 in six of the seven trametinib-treated patients and was Grade 1 in the chemotherapy-treated patient.

There were no serious cases of hypertension reported in either treatment group. Most cases of hypertension in trametinib-treated patients and all cases of hypertension in chemotherapy-treated patients did not require treatment modifications; hypertension leading to dose reduction occurred in only two of 33 patients with a hypertension AE in the trametinib treatment group. The outcome of hypertension was not recovered/not resolved (5% in the trametinib treatment group vs. 2% in the chemotherapy–treatment group), recovered/resolved with sequelae (<1% vs. 0), recovering/resolving (1% vs. 0), and recovered/resolved (9% vs. 5%).

Analyses of worst case increases from baseline in systolic and diastolic blood pressure demonstrated a higher incidence of Grade 2 and Grade 3 treatment-emergent hypertension in the trametinib treatment group compared to the chemotherapy treatment group (Table 50).

Table 50: Worst Case Increase from Baseline in Systolic and Diastolic Blood Pressure. MEK114267 Trial.

	Trametinib n (%)	**Chemotherapy n (%)**
Number of patients in evaluation	207 (100)	93 (100)
Systolic blood pressure		
Any Grade increase	112 (54)	31 (33)
Grade 2 (increase to 140-159 mm Hg)	47 (23)	15 (16)
Grade 3 (increase to ≥160 mm Hg)	41 (20)	7 (8)

	Trametinib n (%)	Chemotherapy n (%)
Diastolic blood pressure		
Any Grade increase	125 (60)	32 (34)
Grade 2 (increase to 90-99 mm Hg)	54 (26)	15 (16)
Grade 3 (increase to ≥100 mm Hg)	44 (21)	7 (8)

Source: MEK114267 Clinical Study Report.

Table 51 summarizes an analysis evaluating the worst case on-treatment systolic or diastolic blood pressure (NCI CTCAE toxicity grade) stratified by the baseline toxicity grade for systolic or diastolic blood pressure.

Table 51: Worst-Case Increase From Baseline in Systolic and Diastolic Blood Pressure by Baseline Toxicity Grade. MEK114267 Trial.

Baseline Grade	N	Worst-case On-Treatment Toxicity Grade					Any Increase from Baseline n/n (%)
		Missing	0	1	2	3	
SYSTOLIC BLOOD PRESSURE							
Trametinib (N=211)							
Missing	1	0	0	0	1	0	-
Grade 0	40	1	9	23	5	2	30/40 (75)
Grade 1	107	2	3	47	40	15	55/107 (51)
Grade 2	53	1	0	3	25	24	24/53 (45)
Grade 3	10	0	0	0	2	8	-
Chemotherapy (N=99)							
Missing	2	1	0	1	0	0	-
Grade 0	13	1	5	7	0	0	7/13 (54)
Grade 1	48	4	3	25	14	2	16/48 (33)
Grade 2	27	1	0	5	16	5	5/27 (19)
Grade 3	9	0	0	1	2	6	
DIASTOLIC BLOOD PRESSURE							
Trametinib (N=211)							
Missing	1	0	0	0	0	1	-
Grade 0	71	1	20	26	16	8	50/71 (70)
Grade 1	87	1	6	23	38	19	57/87 (66)
Grade 2	46	1	0	9	20	16	16/46 (35)
Grade 3	6	1	0	1	0	4	-
Chemotherapy (N=99)							
Missing	2	1	1	0	0	0	-
Grade 0	36	3	17	8	7	1	16/36 (44)
Grade 1	43	3	7	22	8	3	11/43 (26)
Grade 2	13	0	0	3	7	3	3/13 (23)
Grade 3	5	0	0	2	2	1	-

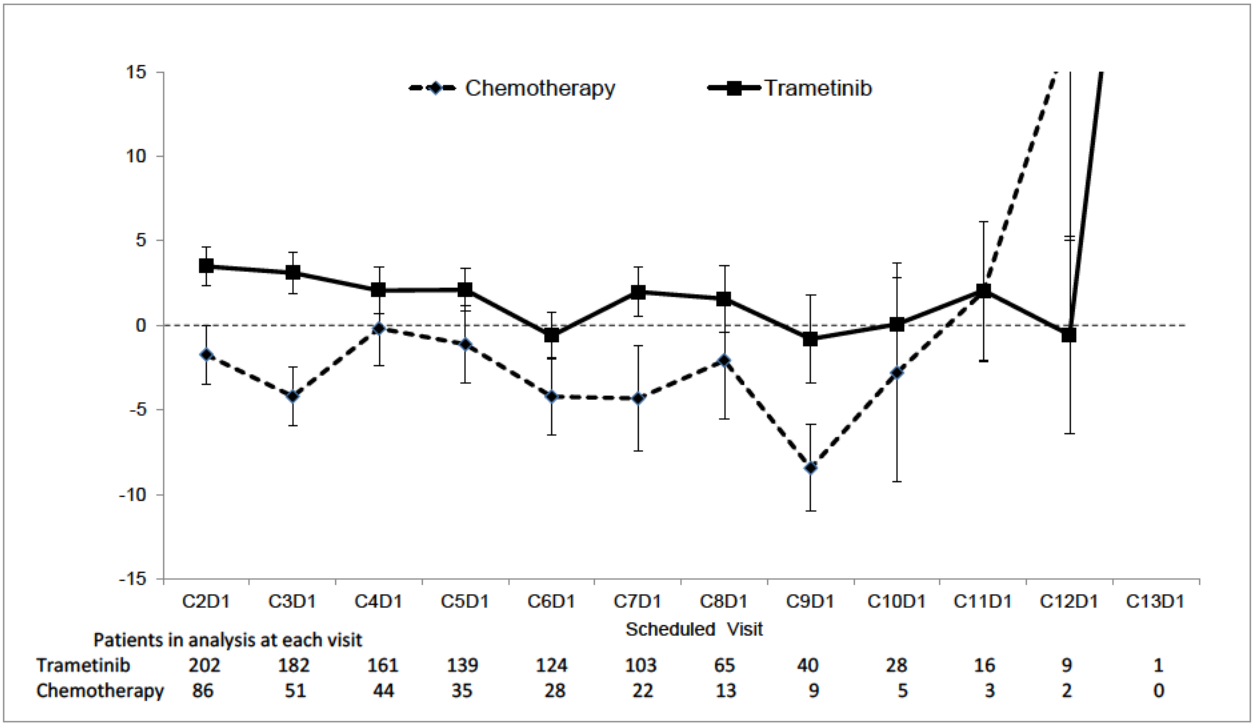
Source: RVITALS.xpt
Values shaded in gray represent increases from baseline in toxicity grade.

REVIEWER COMMENT: Minor differences exist in the worst-case increase from baseline in systolic and diastolic blood pressure based on differences in the method of analysis used in the

Applicant's analysis (Table 50) and that used in reviewer's analysis based on rvitals.xpt raw dataset (Table 51). These differences do not affect the interpretation of this analysis. A higher proportion of patients treated with trametinib demonstrated an increase from baseline in systolic or diastolic blood pressure when compared to those treated with chemotherapy, a finding which was irrespective of the severity of hypertension present at baseline.

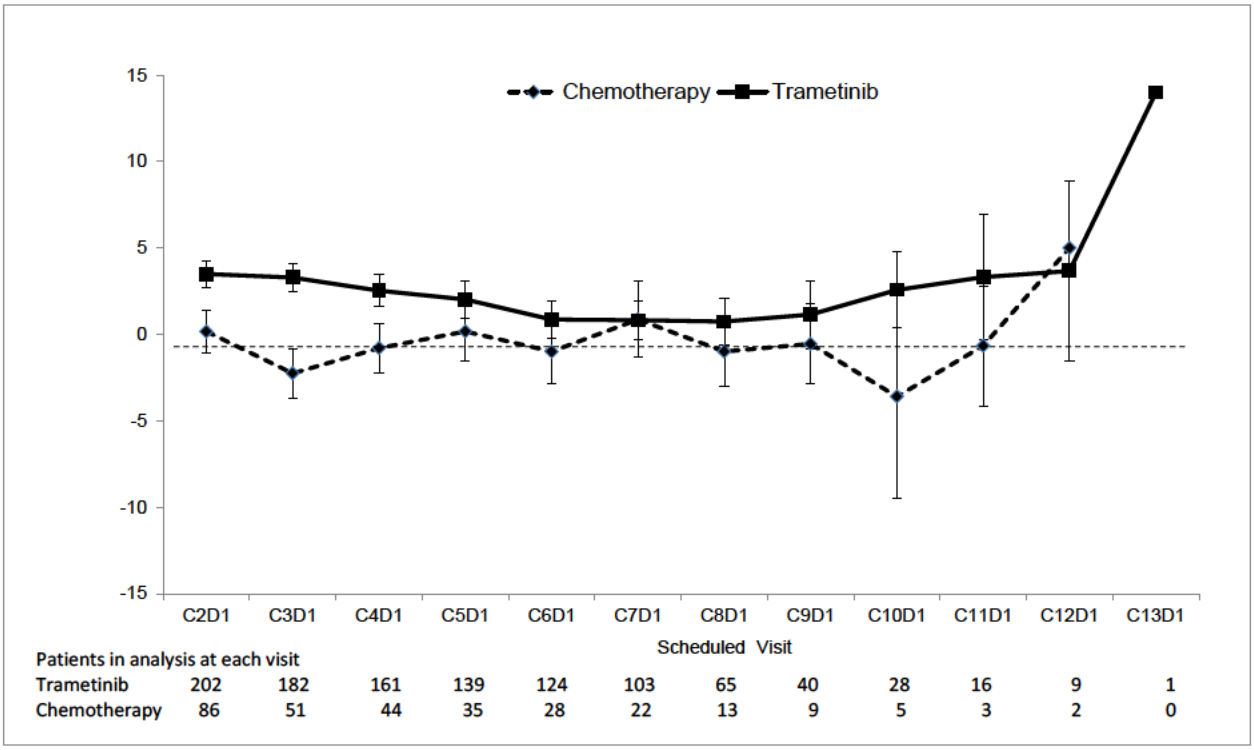
The clinical review included an analysis of increases from baseline in systolic and diastolic blood pressure by time. This demonstrated an initial increase in both systolic and diastolic blood pressure in the trametinib treatment group, an effect which normalized (systolic blood pressure) or improved (diastolic blood pressure) over time as presented in Figure 8 and Figure 9.

Figure 8: Mean Change from Baseline in Systolic Blood Pressure by Treatment Cycle. MEK114267 Trial.



Source: VITALS.xpt
Error bars, standard error

Figure 9: Mean Change from Baseline in Diastolic Blood Pressure by Cycle. MEK114267 Trial.



Source: VITALS.xpt
Error bars, standard error

The Applicant evaluated trametinib effects on systolic and diastolic blood pressure using mixed model repeated measure analyses for changes in systolic and diastolic blood pressure. The Applicant reported that there were statistically significant differences between the trametinib arm and the chemotherapy arm in change from baseline adjusted systolic blood pressures at Cycle 2 and Cycle 3 and in change from baseline adjusted diastolic blood pressures at Cycle 2, Cycle 3, and Cycle 4 (see Section 7.4.3).

Diarrhea

A higher incidence of diarrhea occurred in the trametinib treatment group (43.1%) compared to the chemotherapy treatment group (16.2). The median time to onset of diarrhea was 5.1 weeks (minimum 0.3 weeks, maximum 35 weeks) and the median duration of diarrhea was 0.4 weeks (minimum 0.1 weeks, maximum 27 weeks) in the trametinib treatment group. All cases of diarrhea encountered in the trametinib treatment group were Grade 1 or Grade 2 in severity. Six patients required treatment interruption, one patient required trametinib dose reduction, and one patient discontinued trametinib because of diarrhea.

7.3.5 Submission Specific Primary Safety Concerns

None.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most frequent affected MedDRA System Organ Classes (SOCs) in either treatment group in the MEK114267 trial were:

- Skin and subcutaneous disorders (92% in the trametinib group vs. 36% in the chemotherapy group)
- Gastrointestinal disorders (69% vs. 64%)
- General disorders and administration site conditions (59% vs. 53%)
- Infections and Infestations (39% vs. 18%)
- Investigations (29% vs. 17%)
- Nervous system disorders (27% vs. 37%)
- Musculoskeletal and connective tissue disorders (26% vs. 33%)
- Respiratory, thoracic and mediastinal disorders (25% vs. 18%)
- Vascular disorders (24% vs. 16%)
- Eye disorders (18% vs. 5%)
- Metabolism and nutrition disorders (17% vs. 14%)
- Psychiatric disorders (11% vs. 14%)
- Cardiac disorders (9% vs. 8%)
- Blood and lymphatic system disorders (9% vs. 22%)

The most common AEs (≥10%) occurring more frequently (>5%) in the trametinib treatment group compared to the chemotherapy group were rash (57% vs. 10%), diarrhea (43% vs. 16%), peripheral edema (26% vs. 3%), acneiform dermatitis (19% vs. 1%), hypertension (15% vs. 7%), dry skin (11% vs. 0), paronychia (10% vs. 1%), and pruritis (10% vs. 1%). Nausea, vomiting, constipation, and anemia occurred less frequently in the trametinib group. Table 52 lists TEAEs occurring in ≥5% of trametinib-treated patients.

Table 52: Incidence of Treatment-Emergent Adverse Events (≥5% of Trametinib-Treated Patients) by Treatment Group. Safety Population. MEK 114267 Trial.

	Trametinib N=211		Chemotherapy N=99	
	All Grades n (%)	Grades 3-4 n (%)	All Grades n (%)	Grades 3-4 n (%)
Rash	121 (57)	17 (8)	10 (10)	0
Diarrhea	91 (43)	0 (0)	16 (16)	2 (2)
Fatigue	54 (26)	8 (4)	27 (27)	3 (3)
Edema peripheral	54 (26)	2 (1)	3 (3)	0
Dermatitis acneiform	40 (19)	2 (1)	1 (1)	0
Nausea	38 (18)	2 (1)	37 (37)	1 (1)
Alopecia	36 (17)	2 (1)	19 (19)	0
Hypertension[a]	33 (16)	27 (13)	7 (7)	4 (4)
Constipation	30 (14)	0	23 (23)	1 (1)
Vomiting	27 (13)	2 (1)	19 (19)	2 (2)
Headache	25 (12)	2 (1)	13 (13)	0
Dry skin	24 (11)	0	0	0
Paronychia	21 (10)	0	1 (1)	0
Pruritus	21 (10)	4 (2)	1 (1)	0
Folliculitis	20 (9)	2 (1)	2 (2)	0
AST increased	18 (9)	2 (1)	1 (1)	0
Cough	18 (9)	0	3 (3)	0
Dry mouth	17 (8)	0	2 (2)	0
Abdominal pain	16 (8)	2 (1)	1 (1)	1 (1)
Arthralgia	15 (7)	0	9 (9)	0
Abdominal pain upper	14 (7)	0	3 (3)	0
Mucosal inflammation	14 (7)	2 (1)	0	0
ALT increased	14 (7)	4 (2)	2 (2)	0
Decreased appetite	14 (7)	1 (<1)	10 (10)	0
Insomnia	14 (7)	0	7 (7)	0
Stomatitis	13 (6)	2 (1)	1 (1)	0
Epistaxis	13 (6)	0	0	0
Anemia	12 (6)	4 (2)	11 (11)	2 (2)
Asthenia	12 (6)	1 (<1)	10 (10)	1 (1)
Pyrexia	12 (6)	1 (<1)	10 (10)	1 (1)
Dyspnea	12 (6)	3 (1)	6 (6)	1 (1)
Alkaline phosphatase increased	11 (5)	2 (1)	1 (1)	0
Ejection fraction decreased	11 (5)	1 (<1)	0	0
Lymphedema	11 (5)	1 (<1)	0	0

Source: RAE.xpt, REXPOSUR.xpt, AE.xpt

[a] Composite term of the following: hypertension and increased blood pressure.

The review of safety evaluated additional potential toxicities of trametinib through analyses of the incidence of AEs based on hierarchical composite of MedDRA preferred terms (i.e., high level terms) and a hierarchical composite of MedDRA high-level terms (i.e., high-level group terms) in each treatment group as summarized in Table 53 and Table 54, respectively. These analyses identified the following additional potential toxicities of trametinib: soft tissue infections, bacterial infections, liver function analyses, and ocular disorders.

Table 53: Incidence of Treatment-Emergent Adverse Events (≥ 10% of Trametinib-Treated Patients or ≥5% Higher in Trametinib Treatment Group) by High Level Term. Safety Population. MEK114267 Trial.

	Trametinib N=211 n (%)	**Chemotherapy N=99** n (%)
Rashes, eruptions and exanthems NEC	126 (60)	10 (10)
Diarrhea (excl infective)	91 (43)	16 (16)
Asthenic conditions	67 (32)	37 (37)
Edema NEC	61 (29)	4 (4)
Nausea and vomiting symptoms	47 (22)	44 (44)
Acnes	43 (20)	1 (1)
Alopecias	36 (17)	19 (19)
Dermal and epidermal conditions NEC	36 (17)	3 (3)
Skin structures and soft tissue infections	33 (16)	2 (2)
Vascular hypertensive disorders NEC	32 (15)	7 (7)
Gastrointestinal atonic and hypomotility disorders NEC	31 (15)	24 (24)
Gastrointestinal and abdominal pains (excl oral and throat)	29 (14)	5 (5)
Bacterial infections NEC	26 (12)	2 (2)
Headaches NEC	25 (12)	13 (13)
Musculoskeletal and connective tissue pain and discomfort	23 (11)	18 (18)
Pruritus NEC	23 (11)	1 (1)
Liver function analyses	22 (10)	4 (4)
Coughing and associated symptoms	18 (9)	3 (3)
Oral dryness and saliva altered	18 (9)	2 (2)
Stomatitis and ulceration	18 (9)	2 (2)
Tissue enzyme analyses NEC	18 (9)	1 (1)
Dermatitis and eczema	15 (7)	1 (1)
Nasal disorders NEC	15 (7)	0
Mucosal findings abnormal	14 (7)	0
Cardiac function diagnostic procedures	11 (5)	0
Lymphedemas	11 (5)	0

Table 54: Incidence of Treatment-Emergent Adverse Events (≥ 10% of Trametinib-Treated Patients or ≥5% Higher in Trametinib Treatment Group) by High Level Group Term. Safety Population. MEK 114267 Trial.

	Trametinib N=211 n (%)	Chemotherapy N=99 n (%)
Epidermal and dermal conditions	164 (78)	17 (17)
General system disorders NEC	118 (56)	47 (47)
Gastrointestinal motility and defecation conditions	107 (51)	33 (33)
Skin appendage conditions	80 (38)	23 (23)
Gastrointestinal signs and symptoms	73 (34)	45 (45)
Infections - pathogen unspecified	59 (28)	11 (11)
Respiratory disorders NEC	38 (18)	15 (15)
Vascular hypertensive disorders	32 (15)	7 (7)
Bacterial infectious disorders	31 (15)	2 (2)
Neurological disorders NEC	31 (15)	15 (15)
Oral soft tissue conditions	29 (14)	3 (3)
Headaches	26 (12)	13 (13)
Musculoskeletal and connective tissue disorders NEC	23 (11)	18 (18)
Hepatobiliary investigations	22 (10)	4 (4)
Enzyme investigations NEC	22 (10)	1 (1)
Salivary gland conditions	18 (9)	2 (2)
Upper respiratory tract disorders (excl infections)	18 (9)	0
Eye disorders NEC	17 (8)	0
Cardiac and vascular investigations (excl enzyme tests)	14 (7)	0
Lymphatic vessel disorders	12 (6)	0
Skin and subcutaneous tissue disorders NEC	12 (6)	0

The clinical review also included safety analyses of the MEK114267 trial using a narrow-based Standardized MedDRA Queries (SMQ). SMQs with a relative risk (RR) of 5 or greater in the trametinib treatment group compared to the chemotherapy group were hemorrhages (RR= 16), cardiac failure (RR=6), cardiomyopathy (RR=6), and angioedema (RR=6). Table 55 summarizes the incidence of narrow based SMQ terms with a relative risk ≥ 2.

Table 55: Analysis of Narrow Based Standardized MedDRA Queries by Treatment Group. Safety Population. MEK114267 Trial.

	Trametinib N=211 n (%)	Chemotherapy N=99 n (%)	RR
Hemorrhages	35 (17)	1 (1)	16.4
Cardiac failure	11 (5)	0	5.7
Cardiomyopathy	11 (5)	0	5.7
Angioedema	23 (11)	2 (2)	5.4
Gastrointestinal perforation, ulceration, hemorrhage or obstruction	10 (5)	1 (1)	4.7
Periorbital and eyelid disorders	10 (5)	1 (1)	4.7
Hemodynamic edema, effusions and fluid overload	74 (35)	8 (8)	4.3
Taste and smell disorders	9 (4)	1 (1)	4.2
Conjunctival disorders	9 (4)	1 (1)	4.2
Lacrimal disorders	7 (3)	0	3.8
Cardiac arrhythmias	7 (3)	1 (1)	3.3
Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias)[1]	7 (3)	1 (1)	3.3
Bradyarrhythmias (incl conduction defects and disorders of sinus node function)[2]	5 (2)	0	2.8
Oropharyngeal lesions, non-neoplastic, non-infectious and non-allergic[1]	39 (18)	7 (7)	2.6
Accidents and injuries	11 (5)	2 (2)	2.6
Rhabdomyolysis/myopathy	4 (2)	0	2.4
Ocular infections	5 (2)	1 (1)	2.3
Hypertension	33 (16)	7 (7)	2.2
Oropharyngeal disorders	45 (21)	10 (10)	2.1

Source: Analysis of RAE.xpt dataset
Abbreviation in Table: RR, relative risk.
[1] Second SMQ level.
[2] Third SMQ level.

The clinical review included additional analyses of the following narrow-based SMQs:

- Hemorrhage
- Cardiac arrhythmias (see Table 35)
- Oropharyngeal disorders

Hemorrhage

The incidence of the SMQ hemorrhage was 17% in the trametinib treatment group and 1% in the chemotherapy treatment group. Grade 3 hemorrhage occurred in three (1%) patients treated with trametinib. One patient in each treatment group experienced a SAE of hemorrhage, both for AEs of decreased hemoglobin requiring hospitalization. As summarized in Table 56, the most

common AEs (preferred term) within the SMQ of hemorrhage were epistaxis (6%), gingival bleeding (2%), and contusion (2%).

Table 56: Incidence of Hemorrhage (Narrow Based SMQ) by Treatment Group. Safety Population. MEK114267 Trial.

	Trametinib N=211 n (%)	Chemotherapy N=99 n (%)
ANY	35 (17)	4 (4)
Epistaxis	13 (6)	0
Gingival bleeding	4 (2)	0
Contusion	3 (1)	1 (1)
Hematochezia	3 (1)	0
Rectal hemorrhage	3 (1)	0
Hemoglobin decreased	2 (1)	1 (1)
Vaginal hemorrhage	3 (1)	0
Petechiae	2 (1)	0
Conjunctival hemorrhage	1 (<1)	0
Hemorrhoidal hemorrhage	1 (<1)	0
Melena	1 (<1)	0
Periorbital hematoma	1 (<1)	0
Post procedural hemorrhage	1 (<1)	0
Hematuria	1 (<1)	0
Purpura	1 (<1)	0
Bloody discharge	1 (<1)	0
Intra-abdominal hematoma	1 (<1)	0
International normalized ratio increased	0	1 (1)
Red blood cell count decreased	0	1 (1)

REVIEWER COMMENT:
In the trametinib treatment group, many of the observed AEs under the SMQ of hemorrhage appear to be consistent with mucocutaneous bleeding which suggests a common underlying pathophysiology. Hemorrhage was Grade 1 or 2 in severity in the majority of cases—two patients experienced a severe, albeit non-serious hemorrhage, one patient with a Grade 3 intra-abdominal hematoma and another patient with Grade 3 melena.

Oropharyngeal Disorders

The incidence of the SMQ oropharyngeal disorders was 21% in the trametinib treatment group and 10% in the chemotherapy treatment group. There were no SAEs of oropharyngeal disorders. Two patients with Grade 2 or 3 stomatitis required dose reductions The incidence of Grade 3 oropharyngeal disorders was 2% in trametinib-treated patients—three cases of stomatitis and one

case of oral pain—and was nil in the chemotherapy-treated patients. As summarized in Table 57, the most common AEs (preferred term) within the SMQ of oropharyngeal disorders were dry mouth (8%), stomatitis (6%), aphthous stomatitis (2%), and gingival bleeding (2%).

Table 57: Incidence of Oropharyngeal Disorders (Narrow Based SMQ) by Treatment Group. Safety Population. MEK114267 Trial.

	Trametinib N=211 n (%)	Chemotherapy N=99 n (%)
ANY	45 (21)	10 (10)
Dry mouth	17 (8)	2 (2)
Stomatitis	13 (6)	1 (1)
Aphthous stomatitis	5 (2)	0
Gingival bleeding	4 (2)	0
Oral pain	3 (1)	0
Tongue ulceration	2 (1)	0
Oropharyngeal pain	2 (1)	3 (3)
Oral discomfort	2 (1)	0
Oral herpes	2 (1)	0
Mouth ulceration	1 (<1)	1 (1)
Oral candidiasis	1 (<1)	2 (2)
Lip infection	1 (<1)	0
Oral dysesthesia	1 (<1)	0
Paresthesia oral	1 (<1)	0
Pharyngeal ulceration	1 (<1)	0
Pharyngitis	1 (<1)	1 (1)
Gingival erythema	0	1 (1)
Glossodynia	0	1 (1)

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 58, the most common (≥20%) laboratory abnormalities (all Grades) in the trametinib treatment group were increased glucose (82% in the trametinib treatment group vs. 80% in the chemotherapy treatment group), increased AST (67% vs. 24%), decreased albumin (49% vs. 30%), increased ALT (48% vs. 31%), decreased hemoglobin (48% vs. 40%), and increased alkaline phosphatase (36% vs. 27%). Grade 3 or 4 elevation of AST occurred in 2.4% of trametinib-treated patients and 1% of chemotherapy-treated patients.

Table 58: Incidence of Treatment-Emergent Grade 1-4 Laboratory Abnormalities (≥10% of Trametinib-Treated Patients) by Treatment Group. Safety Population. MEK114267 Trial.

	Trametinib N=211		Chemotherapy N=99	
	All Grades	**Grades 3-4**	**All Grades**	**Grades 3-4**
Hyperglycemia	172 (82)	3 (1)	79 (80)	2 (2)
Increased AST	142 (67)	5 (2)	24 (24)	1 (1)
Decreased albumin	103 (49)	6 (3)	30 (30)	2 (2)
Increased ALT	102 (48)	6 (3)	31 (31)	3 (3)
Anemia	101 (48)	5 (2)	39 (39)	3 (3)
Increased alkaline phosphatase	76 (36)	5 (2)	27 (27)	3 (3)
Thrombocytopenia	33 (16)	0	21 (21)	2 (2)
Lymphopenia	33 (16)	5 (2)	38 (38)	5 (5)
Leukopenia	31 (15)	0	29 (29)	6 (6)
Neutropenia	28 (13)	0	23 (23)	8 (8)
Hyponatremia	22 (10)	6 (3)	10 (10)	3 (3)

Source: RLAB.xpt

7.4.3 Vital Signs

The following vital signs were recorded at the beginning of each treatment cycle: blood pressure, pulse rate, and body weight. There were no major differences in body weight changes from baseline between patients treated with trametinib compared to those treated with chemotherapy. However, trametinib-treated patients experienced more frequent elevations in systolic and diastolic blood pressure than chemotherapy-treated patients early in the treatment course (see Section 7.3.4).

The Applicant performed a mixed model repeated measure analysis for changes in systolic (Table 59) and diastolic blood pressure (Table 60). The analysis method was analysis of covariance adjusted for baseline measurement using mixed-model repeated measures with time (i.e., Cycle), treatment, and treatment by time interaction as fixed effects. Time was treated as the repeated variable within subject.

Table 59: Systolic Blood Pressure Changes from Baseline. Mixed Model Repeated Measures Analysis. Intent-to-Treat Population. MEK114267 Trial.

Time	Trametinib (N=211)			Chemotherapy (N=99)			Difference[2]	95% CI[3]	P-value
	n	Mean[1]	SE	n	Mean[1]	SE			
Cycle 2	195	2.55	1.044	84	-2.52	1.595	5.073	1.314, 8.833	0.008
Cycle 3	176	2.05	1.096	49	-3.66	1.989	5.704	1.229, 10.180	0.013
Cycle 4	155	0.92	1.216	42	-0.76	2.269	1.687	-3.389, 6.763	0.513
Cycle 5	134	1.20	1.161	33	-0.78	2.290	1.979	-3.086, 7.045	0.442
Cycle 6	120	-1.02	1.206	26	-3.29	2.457	2.266	-3.137, 7.669	0.409
Cycle 7	99	-0.05	1.334	20	-6.77	2.849	6.717	0.497, 12.937	0.034

Abbreviations in Table: CI, confidence interval; SE, standard error of the mean.
n=number of patients assessed
[1] mean systolic blood pressure change in mm Hg adjusted for baseline.
[2] Difference for Mean (trametinib – chemotherapy) in mm Hg.
[3] Confidence interval for treatment difference.

Table 60: Diastolic Blood Pressure Changes from Baseline. Mixed Model Repeated Measures Analysis. Intent-to-Treat Population. MEK114267 Trial.

Time	Trametinib (N=211)			Chemotherapy (n=99)			Difference[2]	95% CI[3]	P-value
	n	Mean[1]	SE	n	Mean[1]	SE			
Cycle 2	195	2.51	0.672	84	-0.93	1.026	3.434	1.019, 5.849	0.005
Cycle 3	176	2.54	0.717	49	-2.13	1.290	4.672	1.765, 7.579	0.002
Cycle 4	155	1.88	0.803	42	-1.99	1.496	3.871	0.525, 7.218	0.024
Cycle 5	134	1.10	0.935	33	-1.89	1.826	2.992	-1.054, 7.038	0.146
Cycle 6	120	0.62	0.892	26	-1.82	1.812	2.438	-1.547, 6.423	0.229
Cycle 7	99	0.63	0.861	20	-1.67	1.850	2.301	-1.731, 6.333	0.261

Abbreviations in Table: CI, confidence interval; SE, standard error of the mean.
n=number of patients assessed
[1] mean systolic blood pressure change in mm Hg adjusted for baseline.
[2] Difference for Mean (trametinib – chemotherapy) in mm Hg.
[3] Confidence interval for treatment difference.

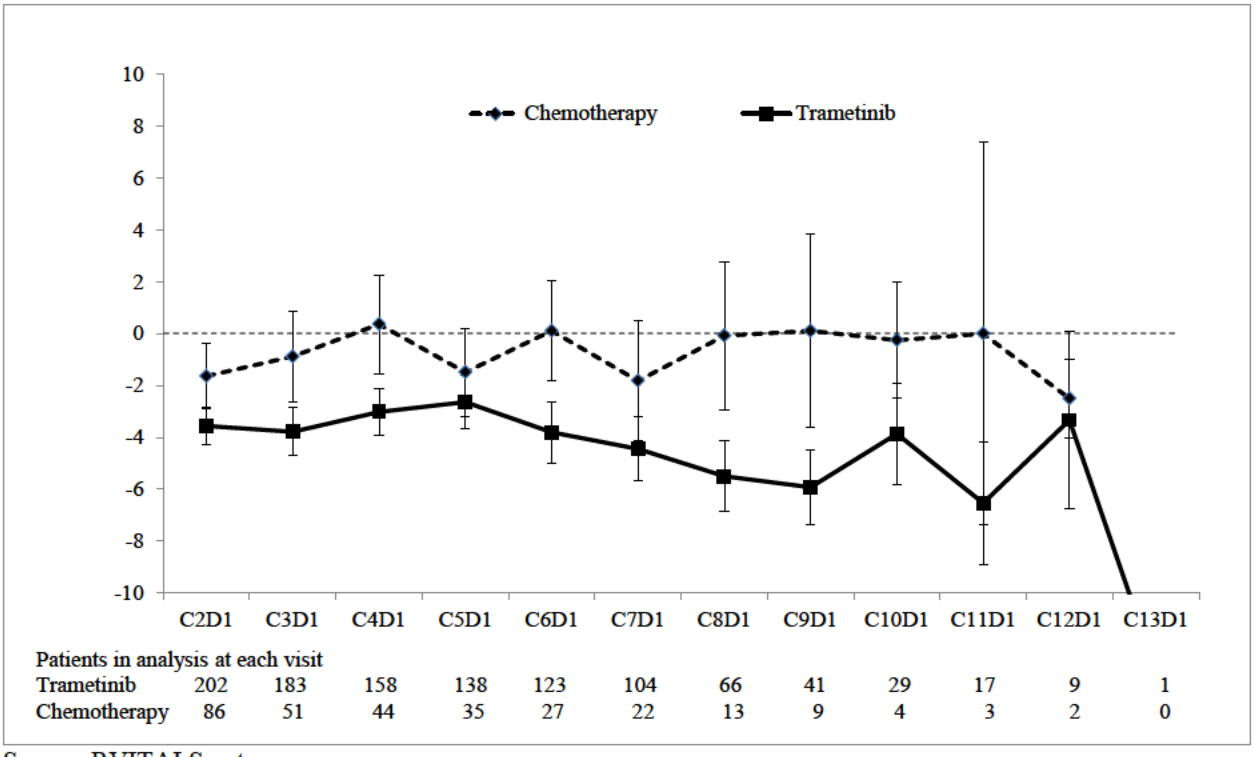
Within the safety population, 207/211 (98%) of trametinib-treated patients and 92/99 (93%) of chemotherapy-treated patients had a baseline and on-treatment assessment of heart rate (HR). Categorical changes from baseline in HR to < 60 beats per minute (bpm) occurred more frequently in the trametinib treatment group (16%) than in the chemotherapy treatment group (4%). As summarized in Table 61, categorical changes from baseline in HR to ≥100 bpm occurred less frequently in the trametinib treatment group (11%) than in the chemotherapy treatment group (17%). Worst case increases from baseline in HR were similar in both treatment groups, i.e., a mean increase of 7 bpm. The trametinib treatment group experienced a worst-case mean decrease from baseline in HR of 11 bpm whereas the chemotherapy treatment group experienced a worst-case mean decrease in HR of 6 bpm.

Table 61: Changes in Heart Rate by Treatment Group. MEK114267 Trial.

	Trametinib	Chemotherapy
N, n (%)	207 (100)	92 (100)
Categorical Changes		
<60, n (%)	33 (16)	4 (4)
>100, n (%)	22 (11)	16 (17)
Central tendency		
Worse-case increase in heart rate		
Mean	7.1	7.2
Median	6	6
Standard error	0.9	1.4
Worst-case decrease in heart rate		
Mean	11.1	6.2
Median	10	5
Standard error	0.8	1.3

In a time dependency analysis of mean changes from baseline in HR by treatment cycle (Figure 10), the trametinib treatment group demonstrated with each treatment cycle an increasing mean decrease in HR from baseline. In comparison, the chemotherapy treatment group demonstrated minimal to no change from baseline in HR with each treatment cycle.

Figure 10: Plots of Mean Change From Baseline in Heart Rate by Treatment Cycle (Scheduled Visits) by Treatment Group. MEK114267 Trial.



Source: RVITALS.xpt
Error bars, standard error

7.4.4 Electrocardiograms (ECGs)

The MEK114267 trial collected serial ECGs using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT (QTc) intervals at baseline, Cycle 2 Day 1, Cycle 5 Day 1, Cycle 8 Day 1, Cycle 11 Day 1, every four Cycles thereafter, and at treatment discontinuation. The protocol specified use of triplicate ECGs if the initial ECG demonstrated a prolonged QT interval.

Of the 211 patients treated with trametinib and the 99 patients treated with chemotherapy, 196 (93%) and 85 (86%), respectively, had a corrected QT interval assessed based on Bazett's formula (QTcB). Four patients (2%) in the trametinib treatment group and no chemotherapy-treated patients developed a worst-case increase from baseline in QTc to ≥501 msec. One patient (0.5%) in the trametinib treatment group and two patients (2%) in the chemotherapy treatment group developed a QTcB value greater than 480 msec and less than 500 msec.

Of the 187 patients with a QTcB measured at baseline and on-treatment in the trametinib treatment group, four patients (2%) developed a post-baseline increase in QTcB of > 60 msec. Of the 80 patients with a QTcB measured at baseline and on-treatment in the chemotherapy treatment group, one patient (1%) developed a post-baseline increase in QTcB of > 60 msec.

REVIEWER COMMENTS:
According to review of the submitted data, the effect of trametinib on the QT interval is inconclusive. The Applicant is performing a dedicated, placebo-controlled, blinded trial, trial MEK114655, to evaluate the effect of trametinib on cardiac repolarization. Completion of trial MEK114655 and submission of the final study report with the primary data is recommended as a post-marketing requirement.

7.4.5 Special Safety Studies/Clinical Trials

On January 9, 2012, the Applicant sent a Dear Investigator Letter to inform investigators on trials MEK111054, MEK111759, MEK112110, MEK112111, MEK113177, MEK113486, MEK113487, MEK113583, MEK114267, MEK114375, MEK114653, MEK114784, MEK115064, BRF113220, TAC113886, TAC115829, P3K113794 of changes in the informed consent document in regard to cases of potential sudden death/cardiac arrest (n=5) in the safety database of > 1200 patients who have received trametinib as a single agent or in combination.

The Applicant commissioned an independent panel of experts to review and adjudicate all fatal SAEs that the Applicant identified across all studies of trametinib as of May 31, 2012 (n=65). The clinical events classification charter required that the panel determine whether or not it was a cardiovascular death and whether there were any confounding factors that could contribute to death (i.e., cardiovascular co-morbidities or concomitant medications). The panel signed a confidentiality agreement with the Applicant which required that all information provided to the panel and reports, meeting discussions, minutes, and recommendation of the panel be treated as confidential information. Members of the panel were to declare any financial or other interests in

the Applicant or its products, or in a competitor company or its products prior to appointment to the panel as well as during their tenureship.

The charter specified that all death events were assigned to one to three oncologists and two to three cardiologists for pre-review. Following pre-review, the Phase II review comprised three reviewers, including the reviewers which pre-reviewed the death events, which by consensus adjudicated the events. The charter specified that all deaths be considered cardiovascular unless an unequivocal non-cardiovascular cause of death could be established.

The expert panel provided the following summary of its analysis:

> Overall 65 deaths were reported from 13 clinical studies evaluating GSK1120212 in multiple disease states. All 65 patients were initially assigned to be treated with GSK1120212. Of the 65 deaths, 12 (18.5%) patients died of cardiovascular cause, 38 (58.5%) of non-cardiovascular causes and 15 (23%) had an undetermined cause of death. Of the cardiovascular deaths, 42% were sudden cardiac death and one-third were deaths due to stroke. In addition, confounding factors (defined as CV risk factors and/or concomitant medications) were present in 66.7% of the cardiovascular deaths and in 23.7% of the non-cardiovascular. Infection was reason for non-cardiovascular death accounting for over two-thirds of all non-cardiovascular deaths. The number of deaths is too few to make any observations about cause of death in different disease states or study drug dosing.
>
> Three suggestions are provided for further consideration:
>
> 1. Adjudicate the cause of death in patients included in these studies not randomized to GSK1120212 or did not receive GSK1120212 and perform appropriate comparative analyses recognizing the limitation of non-randomized comparisons as well as the competing risks involved on these analyses (for example, if the compound was effective in reducing the risk of cancer death, there could be a higher risk of CV deaths in GSK1220212).
> 2. Compare the pattern of cause of death in historical datasets with similar patients' populations and diseases states with these data.
> 3. Include a strategy in future trials of GSK1120212 for standardized and systematic data collection and adjudication of cause of death to minimize the proportion of deaths that are due to undetermined causes.

REVIEWER COMMENT:
These cases include one cardiac death (Patient BRF113220/072211-1601) in a patient documented with dilated cardiomyopathy and no coronary artery disease—the etiology of the dilated cardiomyopathy was uncertain. The reviewer agrees with the concerns of the review committee about the reliability of this data for assignment of causality. However, the Applicant submitted additional information in response to an FDA information request for additional

details of these cases—this is currently under review. A clinical review addendum will be generated if there are any substantive changes based on review of this data.

7.4.6 Immunogenicity

See Section 7.3.2.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

According to the Clinical Pharmacology NDA review, population pharmacokinetic (PK) and exposure-response (E-R) analyses using PK data across clinical studies did not identify significant covariates influencing trametinib PK or evident E-R relationships for effectiveness and safety.

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

7.5.2 Time Dependency for Adverse Events

Please see sections 7.3.2 (cardiac events and skin-related toxicity), 7.3.3 (hepatic events), and 7.3.4 (hypertension and diarrhea) for analyses of time dependency for AEs.

7.5.3 Drug-Demographic Interactions

In the MEK114267 trial, patients age 65 years or older represented 22% and 21% of the trametinib and chemotherapy treatment groups, respectively, whereas female patients represented 44% and 52% of the trametinib and chemotherapy treatment groups, respectively. The incidence of any AE (all grades) was similar across these demographic subgroups within each treatment arm. The incidence of Grade 3 or 4 AEs was similar in male and female patients in the trametinib treatment group, 52% and 42%, respectively. In addition, patients age 65 years or older in the trametinib treatment group experienced a higher incidence of Grade 3 or 4 AEs compared to those younger than 65 years. In contrast, the incidence of Grade 3 or 4 AEs in the chemotherapy treatment group was similar in patients 65 years of age or older compared to younger than 65 years. The incidence of SAEs was higher in patients age 65 years or older compared to patients younger than 65 years, a finding which was similar in both treatment groups. Table 62 summarizes the incidence of AEs by toxicity grade as well as serious AEs by age and gender subgroups.

Table 62: Summary of Safety Analyses by Age (< 65 vs. ≥65) and Gender Subgroups. MEK114267 Trial.

	Age Subgroup				Gender Subgroup			
	Trametinib		Chemotherapy		Trametinib		Chemotherapy	
	<65 N=164 n (%)	≥65 N=47 n (%)	<65 N=78 n (%)	≥65 N=21 n (%)	Female N=93 n (%)	Male N=118 n (%)	Female N=51 n (%)	Male N=48 n (%)
All Grade AE	163 (99.4)	46 (97.9)	71 (91.0)	20 (95.2)	93 (100)	116 (98.3)	47 (92.2)	44 (91.7)
Grade 3-4	68 (41.5)	30 (63.8)	27 (34.6)	7 (33.3)	48 (51.6)	50 (42.4)	23 (45.1)	11 (22.9)
Grade 4	6 (3.7)	2 (4.3)	4 (5.1)	1 (4.8)	3 (3.2)	5 (4.2)	4 (7.8)	1 (2.1)
Any SAE	26 (15.9)	12 (25.5)	12 (15.4)	7 (33.3)	17 (18.3)	21 (17.8)	12 (23.5)	7 (14.6)
AE leading to withdrawal	10 (6.1)	10 (21.3)	6 (7.7)	3 (14.3)	8 (8.6)	12 (10.2)	5 (9.8)	4 (8.3)

As summarized in Table 63, there were few Grade 3 or 4 AEs with an inter-subgroup (i.e., age or gender) difference of ≥5% within either treatment group (trametinib or chemotherapy).

Table 63: Incidence of Grade 3 or 4 Treatment-Emergent Adverse Events (≥ 5% Difference Within Either Subgroup). Age (<65 or ≥ 65) and Gender Subgroups. MEK114267 Trial.

	Trametinib		Chemotherapy		Trametinib		Chemotherapy	
	%		%		%		%	
	<65	≥65	<65	≥65	Female	Male	Female	Male
	N=164	N=47	N=78	N=21	N=93	N=118	N=51	N=48
Rash	6	21	0	0	12	5	0	0
Fatigue	2	9	1	10	6	2	6	0
Hypertension	12	43	5	0	13	13	6	2

REVIEWER COMMENTS:

1. *The safety review included analyses of Grade 3 or 4 TEAEs at the level of MedDRA preferred terms within age and gender subgroups. Several exploratory analysis methods, including analyses of attributable and relative risk, suggest that patients age ≥65 are at an increased risk for Grade 3 or 4 hypertension with trametinib when compared to the risk of this AE in trametinib-treated patients less than 65 years of age or in chemotherapy-treated patients age ≥65 years. The strength of these exploratory analyses was limited by the small numbers in the comparator chemotherapy subgroups enrolled in the MEK114267 trial as well as the ISS database which consisted of trials that used different versions of NCI CTCAE to grade toxicities. For example, the grading of hypertension underwent substantial revisions between version 3 (*MEK111054 and MEK113583*) and version 4 (MEK114267) of the NCI CTCAE.*
2. *The FDA Clinical Pharmacology NDA Review concluded that age and gender did not have a clinically important influence on the clearance or volume of distribution of trametinib based*

on a population pharmacokinetic analysis. Please see the FDA Clinical Pharmacology NDA Review for details.

3. *The safety population consisted of >99% white patients which precluded safety analyses based on racial subgroups.*

7.5.4 Drug-Disease Interactions

Please refer to Section 4.4.3 and to the FDA Clinical Pharmacology NDA review for details. The FDA Clinical Pharmacology NDA review recommends that the Applicant perform a trial in patients with impaired hepatic function as a post-marketing requirement.

7.5.5 Drug-Drug Interactions

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

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The Applicant did not submit carcinogenicity studies to the NDA. The following is excerpted from the FDA Pharmacology/Toxicology NDA Review:

> No carcinogenicity studies with trametinib were submitted. For justification, the Applicant cited ICH S1A: The Need for Long-term Rodent Carcinogenicity Studies of Pharmaceuticals (1996), and ICH S9: Nonclinical Evaluation for Anticancer Pharmaceuticals (2009), which state that carcinogenicity studies are not considered necessary to support the use of therapeutics (trametinib) intended to treat patients with advanced cancer (metastatic melanoma), where the life expectancy of the patients is short (i.e. less than 2 to 3 years).

7.6.2 Human Reproduction and Pregnancy Data

There are no data available on the use of trametinib in pregnant or lactating women. The FDA Pharmacology/Toxicology reviewers recommend classification of trametinib as Pregnancy Category D based on the nonclinical reproductive toxicology data. See the FDA Pharmacology/Toxicology NDA Review for details.

7.6.3 Pediatrics and Assessment of Effects on Growth

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

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Applicant states that there have been no reports of overdose with trametinib. Patients have received daily doses of up to 4 mg as well as loading dose regimens of up to 10 mg once daily for two consecutive days. There are no studies on the potential for trametinib to cause dependence. However, the Applicant states that there is no evidence from the available data that treatment with trametinib can result in dependence—there were no reports of withdrawal or rebound effects associated with trametinib.

7.7 Additional Submissions / Safety Issues

None.

8 Postmarket Experience

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

9 Appendices

9.1 Literature Review/References

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9.2 Labeling Recommendations

Please refer to the package insert of Mekinist.

9.3 Advisory Committee Meeting

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

9.4 Treatment Modification Plan for Toxicity, MEK114267 Trial

GSK1120212 (Trametinib) Modification Guidelines:

- Rash (Table A)
- Ejection fraction changes (Table B)
- Visual changes (Table C)
- Pneumonitis (Table D)
- Diarrhea (Table E)

Table A: Rash, GSK1120212 Dose Modification and Management Guidelines. MEK114267 Protocol.

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[a] if not already started. 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 steroids.[a,b] Reassess after 2 weeks; if rash worsens or does not improve, proceed to step 3	Reduce dose by one 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.	Temporarily 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.

[a] Protocol recommended prophylactic measures or rash:

- Avoidance of unnecessary exposure to sunlight
- Broad-spectrum sunscreen (containing titanium dioxide or zinc oxide) with a skin protection factor (SPF) ≥15
- Thick, alcohol-free emollient cream (e.g. glycerine and cetomacrogol cream) on dry areas of the body
- Mild strength topical steroid (e.g. hydrocortisone 1% cream) with escalation to higher strength and/or oral steroid as detailed below
- Offer doxycycline 100mg bid or minocycline 100mg bid for the first 2-3 weeks of study drug administration.

- Topical agents should be applied on a daily basis starting on Day 1 of study treatment, and more often as needed. Oral antibiotics should also be started on Day 1; consider topical antibiotics if the patient cannot tolerate oral doxycycline or minocycline.

[b] Protocol specified concomitant medications for management of rash:

- For pruritic lesions, the use of cool compresses and oral antihistamine agents may be helpful.
- For fissuring, the use of Monsel's solution, silver nitrate, or zinc oxide cream is advised.
- For desquamation, thick emollients and mild soap are recommended.
- For paronychia, antiseptic bath and local potent corticosteroids in addition to oral antibiotics are recommended and, if no improvement is seen, a dermatology or surgery consultation is recommended.
- For infected lesions, bacterial and fungal culturing followed by the appropriate culture-driven systemic or topical antibiotics is indicated.

Table B: LVEF, GSK1120212 Dose Modification and Management Guidelines. MEK114267 Protocol.

Description	Management	Dose Adjustment of GSK1120212
Asymptomatic, absolute decrease of >10% in LVEF compared to baseline and the EF is < the institution's lower limit of normal (LLN)	Interrupt GSK1120212 LVEF recovers (≥LLN and absolute decrease <10% of baseline) within 4 weeks LVEF does not recover within 4 weeks	 Restart on reduced dose and repeat LVEF after 2, 4, 8, 12, 16 weeks then per protocol Permanently discontinue and consider evaluation by a cardiologist. Monitor LVEF after 2, 4, 8, 12, 16, and 20 weeks or until resolution
Grade 3 or 4 left ventricular cardiac dysfunction	Consider evaluation by cardiologist	Permanently discontinue and consider evaluation by a cardiologist. Monitor LVEF after 2, 4, 8, 12, 16, and 20 weeks or until resolution.

Table C: Visual Changes, GSK1120212 Dose Modification and Management Guidelines. MEK114267 Protocol.

Grade	Description	Management	Dose Adjustment of GSK1120212
1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Immediately refer the patient for ophthalmic exam; if an ophthalmic exam cannot be performed within 7 days, withhold treatment with GSK1120212 until exam can be performed. If a retinal abnormality is noted, withhold GSK1120212 immediately and consider referral to a retinal specialist for further evaluation.	RVO, permanently discontinue CSR, temporarily interrupt until signs and symptoms have resolved, then resume by reducing one dose level No RVO or CSR, continue GSK1120212 at same dose level
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Immediately withhold GSK1120212 and refer the patient for ophthalmic exam. For all patients with findings consistent with RVO or CSR based on the ophthalmic exam, referral to a retinal specialist for further evaluation should be considered.	RVO, permanently discontinue CSR, temporarily interrupt until signs and symptoms have resolved, then resume by reducing one dose level No RVO or CSR, resume GSK1120212by reducing one dose level
3	Severe or medically significant but not immediately sight-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self-care ADL		
4	Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye		Permanently discontinue treatment with GSK1120212

Table D: Pneumonitis, GSK1120212 Dose Modification and Management Guidelines. MEK114267 Protocol.

Grade	Required Investigations	Management of Pneumonitis	Dose Adjustment for GSK1120212
1	CT scans with lung windows (high resolution CT recommended). Consider evaluation by pulmonologist. Consider room air O2 saturation at rest via pulse oximetry reading (X 2, 5 minutes apart). Repeat every 8-12 weeks until return to within normal limits	No specific therapy is required	Administer 100% of study treatment dose.
2	CT scan with lung windows (high resolution CT recommended). Consider evaluation by pulmonologist. Consider pulmonary function tests including: spirometry, DLCO, and room air O2 saturation at rest via pulse oximetry reading (X 2, 5 mins apart). Repeat every 8-12 weeks until return to wnl. Consider a bronchoscopy with biopsy and/or BAL.	Symptomatic only. Consider corticosteroids if symptoms are troublesome and infective origin is ruled out. Taper as medically indicated.	Temporarily interrupt treatment until recovery to≤ Grade 1, then reduce by one dose level. Permanently discontinue treatment if no recovery to ≤ Grade 1 within 4 weeks. May consider escalation to pre- event dose after discussion with GSK Medical Monitor.
3	CT scan with lung windows (high resolution CT recommended). Evaluation by pulmonologist. Required pulmonary function tests including: spirometry, DLCO, and room air O2 saturation at rest via pulse oximetry reading (X 2, 5 mins apart). Repeat at least every 8 weeks until return to wnl. Bronchoscopy with biopsy and/or BAL is recommended.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Temporarily hold treatment until recovery to ≤ Grade 1. Permanently discontinue treatment if no recovery to ≤ Grade 1 within 4 weeks. May consider restarting study treatment at a reduced dose after discussion with GSK Medical Monitor if there is clinical benefit.
4	CT scan with lung windows (high resolution CT recommended). Evaluation by pulmonologist. Required pulmonary function tests including: spirometry, DLCO, and room air O2 saturation at rest via pulse oximetry reading (X 2, 5 mins apart). Repeat at least every 8 weeks until return to wnl. Bronchoscopy with biopsy and/or BAL is recommended if possible.	Consider corticosteroids if infective origin is ruled out. Taper as medically indicated.	Permanently discontinue treatment.

Considerations for diarrhea management included ruling out concomitant causes including medications (eg, stool softeners, laxatives, antacids, etc.), infection by C. difficile or Candida species, partial bowel obstruction, malabsorption/lactose intolerance, fecal impaction, diets high in fiber or lactose. Table E: summarizes recommended supportive care and dose modification guidelines for diarrhea based on toxicity severity grade.

Table E: Diarrhea, GSK1120212 Dose Modification and Management Guidelines. MEK114267 Protocol.

Grade	Management of Diarrhea	GSK1120212 Dose Adjustment
Uncomplicated, Grade 1 & 2	Dietary modifications (stop all lactose containing products and eat small meals, BRAT (banana, rice apples, toast) diet • Hydration: drink 8-10 large glasses of clear liquids per day (e.g., Gatorade or broth) • Loperamide (consider) initial dose of 4 mg followed by 2 mg every four hours or after every unformed stool; maximum 16mg/day. Continuation of loperamide is suggested until diarrhea free for 12 hours If mild to moderate diarrhea persists for more than 24 hours, administer: • Loperamide 2 mg every two hours; maximum 16mg/day. Consider adding oral antibiotics. If mild to moderate diarrhea persists after 48 hours total treatment with loperamide, start second-line agents: • Octreotide, or • Budesonide, or • Tincture of opium • Consider adding oral antibiotics.	Consider a temporary GSK1120212 dose interruption until symptoms have resolved to baseline or Grade 1. Re-treatment with GSK1120212 may then be resumed at 100%.
Grade 3 or 4 or complicated Grade 1 or 2 (i.e., cramping, nausea/vomiting, ≥ Grade 2, decreased ECOG PS, fever, sepsis, Grade 3 or 4 neutropenia, frank bleeding, dehydration	• Loperamide initial dose of 4 mg followed by 2 mg every four hours or after every unformed stool; maximum 16mg/day. • For dehydration, use intravenous fluids as appropriate; if severe dehydration, administer octreotide. • Administer antibiotics as needed (e.g., fluoroquinolones), especially if diarrhea is persistent beyond 24 hours or there is fever or Grade 3 to 4 neutropenia. • Intervention should be continued until the patient is diarrhea free for at least 24 hours.	Temporarily interrupt GSK1120212 treatment and hold until symptoms resolve to ≤Grade 1 or baseline. Re-start therapy at a reduced dose level.

9.5 Definitions of Adverse Events of Special Interest

AE of Special Interest	Preferred AE Terms Comprising Category
Skin-related toxicities	Acne, dermatitis, dermatitis acneiform, dermatitis psoriasiform, drug eruption, erythema, exfoliative rash, genital rash, palmar-plantar erythrodysesthesia syndrome, photosensitivity reaction, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculo-papular, rash pruritic, rash pustular, rash vesicular, seborrheic dermatitis, skin exfoliation, urticaria
Diarrhea	Diarrhea
Ocular events	Chorioretinopathy, cyclitis, diplopia, dry eye, eye naevus, glaucoma, halo vision, intraocular pressure increased, iritis, keratoconjunctivitis sicca, papilledema, photophobia, photopsia, retinal haemorrhage, retinal edema, retinal vein occlusion, retinal vein thrombosis, uveitis, vision blurred, visual acuity reduced, visual impairment, vitreous floaters
Cardiac-related events	Acute left ventricular failure, acute pulmonary edema, acute right ventricular failure, cardiac asthma, cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, cardiac failure high output, cardiogenic shock, cardiopulmonary failure, cardiorenal syndrome, chronic left ventricular failure, chronic right ventricular failure, cor pulmonale, cor pulmonale acute, cor pulmonale chronic, dilatation ventricular, ejection fraction decreased, hepatic congestion, hepatojugular reflux, left ventricular dysfunction, left ventricular failure, low cardiac output syndrome, neonatal cardiac failure, pulmonary edema, pulmonary edema neonatal, right ventricular failure, ventricular failure
Hepatic events	Alanine aminotransferase increased, ammonia increased, aspartate aminotransferase increased, blood bilirubin increased, hepatic enzyme increased, hyperbilirubinemia, transaminases
Pneumonitis	Pneumonitis, interstitial lung disease

Abbreviation in Table: AE, adverse event

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

/s/

MARC R THEORET
05/23/2013

SUZANNE G DEMKO
05/24/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 204,114 **Applicant: GlaxoSmithKline** **Stamp Date: 08/03/2012**

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

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

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:	X			The applicant's attempt to determine an appropriate dose and schedule in the phase 1 trial, MEK111054 (Module 5.3.5.2), is appropriate based on the serious and life-threatening indication.
EFFICACY					

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? **Pivotal Study #1**: MEK114267 **Indication**: for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutations as detected by an FDA-approved test. Pivotal Study #2 Indication:	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.			X	There were no previous agreements regarding primary/secondary endpoints for trial MEK114267. In a Type B, EOP1/2 meeting held on July 30, 2010, FDA recommended that GSK conduct the trial MEK114267 using the primary endpoint of OS.
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	MEK114267, conducted under IND 102175, was a multicenter, international study, which included U.S. study sites.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			The assessment of the arrhythmogenic potential is adequate based on the serious and life-threatening indication. (b) (4) [redacted]
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	A requisite number of patients was not provided to the applicant. The safety population for trametinib is based on 329 melanoma patients administered trametinib at 2 mg QD; 68 patients received trametinib for > 6 months.
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			MedDRA v14.1 for MEK114267 and v14.0 for MEK113583 and MEK111054
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			

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

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

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			On 9/24/2012, GSK submitted the requested narratives for on-study patient deaths which were attributed to disease progression.
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			GSK is requesting waiver of pediatric studies for NDA 204114, MEKINIST for the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation as detected by an FDA approved test. Trametinib received orphan designation on December 20, 2010, for treatment of BRAF V600 mutation positive Stage IIb through IV melanoma.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

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

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE?
__YES_____

ADDITIONAL COMMENT:

Reviewing Medical Officer Date

Clinical Team Leader Date

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

/s/

MARC R THEORET
09/27/2012

SUZANNE G DEMKO
09/27/2012