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RESEARCH**

APPLICATION NUMBER:

204114Orig1s000

SUMMARY REVIEW

Division Directory Summary Review

Date	May 28, 2013
From	Patricia Keegan
Subject	Division Director Summary Review
NDA #	NDA 204114
Applicant Name	GlaxoSmithKline LLC
Date of Submission	August 2, 2012
PDUFA Goal Date	June 3, 2013
Proprietary Name / Established (USAN) Name	Mekinist trametinib
Dosage Forms / Strength	tablets/ 0.5 mg, 1 mg, and 2 mg
Proposed Indication(s)	MEKINIST™ is indicated for the treatment of patients with unresectable or metastatic melanoma with BRAF (b) (4) mutations as detected by an FDA-approved test. Limitation of use: (b) (4) MEKINIST (b) (4) prior BRAF inhibitor therapy.
Recommended Action for NME:	Approval

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Regulatory Project Manager	Norma Griffin
Medical Officer Review	Marc Theoret
Statistical Review	Huanyu (Jade) Chen
Pharmacology Toxicology Review	Gabriel S. Khasar
CMC Review/	Sue-Ching Lin (DP) & Z. Jean Tang (DS)
Biopharmaceutics Reviewer	Minerva Hughes
Microbiology Review	John Metcalfe
Clinical Pharmacology Review	Ruby Leong
OPDP/DPDP	Tran, Quyn-Van
OSI Reviews	Jean Mulinde
CDTL Review	Suzanne Demko
OSE/DMEPA	James Schlick
OSE/DRISK	Igor Cerny
Ophthalmology Consult	Wiley Chambers

OND=Office of New Drugs
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DSI=Division of Scientific Investigations
 DDRE= Division of Drug Risk Evaluation
 DRISK=Division of Risk Management
 CDTL=Cross-Discipline Team Leader

Division Directory Summary Review

1. Introduction

Trametinib (Mekinist, GlaxoSmithKline), also known as GSK1120212, is a selective, non-competitive inhibitor of MEK1/MEK2 activation and kinase activity. The applicant, GlaxoSmithKline (GSK) states that the clinical development program in melanoma was limited to patients with melanoma containing BRAF V600 mutations based on the intended co-development with GlaxoSmithKline's dabrafenib and the predicted synergism of trametinib and dabrafenib, both of which inhibit proteins in the ERK (extracellular signal-related kinase) transduction signaling pathway. The MEK1 and MEK2 proteins are (b) (4) of the RAF proteins in this signaling pathway and mutations in BRAF which result in constitutive activation (e.g., BRAF V600E) and continuous activation of MEK. However, unlike BRAF inhibitors, MEK inhibition in BRAF wild-type tumors does not result in paradoxical activation of the signaling pathway.

Safety and effectiveness of trametinib is based primarily on the results of a single trial, Protocol MEK114267, entitled "A Phase III randomized, open-label study comparing GSK1120212 to chemotherapy in subjects with advanced or metastatic BRAF V600E/K mutation-positive melanoma." The major efficacy trial was a randomized (2:1), open-label, active-controlled, multinational comparing trametinib to single agent chemotherapy (dacarbazine or paclitaxel). Patients on the chemotherapy arm were allowed to cross-over to trametinib upon progression. Key inclusion criteria were unresectable Stage III or Stage IV melanoma containing either a BRAF V600E or BRAF V600K mutation and no more than one prior systemic treatment regimen (biologic or chemotherapy but not BRAF or MEK inhibitor therapy). The primary endpoint was progression-free survival (PFS) as determined by the clinical investigator and key secondary endpoints were overall survival (OS) and best overall response rate (ORR).

A total of 322 patients were randomized to trametinib (n=214) at a dose of 2 mg orally once daily or one of two chemotherapy regimens (n=108), selected at the discretion of the investigator and consisting of dacarbazine 1000 mg/m² or paclitaxel 175 mg/m² by intravenous infusion every 21 days. Of the 322 patients enrolled and randomized, 87% had melanomas with BRAF V600E mutations, 12% with BRAF V600K, and <1% with both mutations detected, 54% were male, the median age was 54 years, all had baseline ECOG performance status of 0 or 1, and 64% had M1c disease.

The trial demonstrated a statistically significant improvement in the PFS for the trametinib arm compared with chemotherapy [HR 0.47 (95% confidence intervals (CI): 0.34, 0.65)] with an increase in median PFS from 1.5 months in the chemotherapy arm to a median PFS of 4.8 months for the trametinib arm. Analyses of PFS based on review of radiologic information by an independent radiologist or by the combined assessment of an independent radiologist and oncologist, masked to treatment assignment, provided similar results.

Safety evaluation for common adverse reactions was based primarily on the comparative results observed in Protocol MEK114267 (n=211 trametinib-treated patients), with characterization of uncommon and serious adverse reactions supplemented by the results of two additional clinical trials in patients with melanoma treated with trametinib at a dose of 2 mg daily (n=329 trametinib-treated patients). The most serious adverse reactions of trametinib are cardiomyopathy, detected on serial assessment of left ventricular ejection fraction testing, in approximately 7% of patients in MEK114267 based on serial LVEF measurements, retinal pigment epithelial detachment in less than one percent (0.5%) of patients enrolled in MEK114267 and fourteen patients across the entire clinical trial database, retinal vein occlusion in 0.6% of patients (2/329) receiving the recommended dose of trametinib across clinical trials, interstitial lung disease in 2.4% of trametinib treated patients in Protocol MEK114267, and serious skin rash requiring hospitalization in 6% of trametinib treated patients in Protocol MEK114267. The most common ($\geq 10\%$ incidence) adverse reactions were rash, diarrhea, lymphedema, acneiform dermatitis, hypertension, stomatitis, stomach pain, mild-moderate hemorrhage, abdominal pain, dry skin, paronychia, and pruritis.

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

Additional issues included resolution of process validation issues, lack of complete pharmacokinetic characterization resulting in the need for multiple post-marketing requirements, evaluation of the adequacy of objective tumor response data from single-arm trials to support claims [REDACTED] (b) (4) for treatment of BRAF V600K mutation-positive melanoma.

As of the date of this review, agreement on the physician package insert has not been reached.

2. Background

Melanoma

Cutaneous melanoma, arising from malignant transformation of melanocytes in the skin, is the most aggressive malignancy arising from the skin; based on trend analyses, the incidence of melanoma has been increasing over the past several decades. The National Cancer Institute estimates that in 2013 there will be 76,690 new cases of melanoma and 9,480 deaths due to

melanoma in the United States.¹ While 84% of melanoma presents with localized disease which may be cured with surgical excision alone or with adjuvant interferon or investigational agents and has a 5-year survival rate of 98%, for the 4% who present with metastatic disease and receive systemic treatment, the 5-year survival rates is only 15%. Of patients presenting with cutaneous melanoma, approximately 50% will have melanoma bearing BRAF V600 mutations.

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

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

On March 25, 2011, FDA approved ipilimumab (Yervoy, Bristol Myers Squibb) for the treatment of unresectable or metastatic melanoma. The approval of ipilimumab was based on the results of a single, randomized trial which demonstrated a statistically significant improvement in overall survival for patients receiving ipilimumab in combination with a peptide vaccine (gp100 peptides) compared to those receiving peptide vaccine alone [HR 0.66 (95% CI: 0.55, 0.85), p=0.0004] with median survival times of 9.95 months and 6.44 months in the combination and gp100 monotherapy arms, respectively. The application was also supported by the high level results of Protocol CA 184024, which also demonstrated an improvement in overall survival [HR 0.85 (95% CI: 0.76, 0.93)] with a nominal p-value of 0.001, stratified log-rank test.

On August 17, 2011 vemurafenib (ZELBORAF, Genentech Inc.) an inhibitor of some mutated forms of BRAF serine-threonine kinase, including BRAF V600E, was approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test². At the time of approval, labeling for vemurafenib also carried the following limitation of use: "ZELBORAF is not recommended for use in patients with wild-type BRAF melanoma." The approval was based on the results of a single, multicenter, randomized (1:1), open-label, active-controlled (dacarbazine) trial conducted in 675 patients with treatment naive, BRAF V600E mutation-positive unresectable or metastatic melanoma as detected by the cobas 4800 BRAF V600 Mutation Test. The trial demonstrated a statistically significant improvement in overall survival [HR 0.44 (95% CI: 0.33, 0.59);

¹ <http://www.cancer.gov/cancertopics/types/melanoma>

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

$p < 0.0001$] and progression-free survival [HR 0.26 (95% CI: 0.20, 0.33); $p < 0.0001$] for patients in the vemurafenib arm. The median survival time not reached in the vemurafenib arm as compared to 7.9 months in the dacarbazine arm. The median PFS was 5.3 months in the vemurafenib arm compared with 1.6 months in the dacarbazine arm. The confirmed, investigator-assessed best overall response rate was 48.4% (95% CI: 41.6%, 55.2%) in the vemurafenib arm compared to 5.5% (95% CI: 2.8%, 9.3%) in the dacarbazine arm. These data were supported by the results of a single arm trial in 132 patients with previously treated, BRAF V600E mutation-positive, metastatic melanoma. In this trial, the confirmed best overall response rate as assessed by an independent review committee (IRC) was 52% (95% CI: 43%, 61%), with three complete responses. The median duration of response was 6.5 months.

Pre-Submission Regulatory History

April 14, 2008: IND 102175 submitted

July 30, 2010, FDA held a Type B, EOP1/Pre-Phase 3 meeting to discuss the development program for trametinib in the proposed indication treatment of subjects 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 trial MEK114267 to support the proposed indication. The key agreements and comments from this meeting were:

- FDA recommended that GSK enroll patients with BRAF wild type melanoma in MEK114267 to collect more data in this subgroup before concluding a lack of efficacy, but acknowledged that it was GSK's decision whether to include mutation positive subjects only in the proposed trial
- FDA agreed with the proposed comparator arm but stated that whether product labeling will include both treatment-naïve patients and those who have received one prior cytotoxic regimen would be a review issue
- FDA did not agree with the proposed co-primary endpoints of progression-free survival (PFS) and overall survival (OS) and recommended that GSK evaluate OS as the sole primary endpoint. FDA noted that there was insufficient information to determine if an effect on PFS would predict an effect on survival and stated PFS should not be a "stand-alone" primary endpoint.
- FDA 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
- The clinical monitoring plan for cardiac safety was acceptable
- The proposed dose was acceptable
- The proposed plan for development of the companion diagnostic appeared to be acceptable

November 8, 2010: EOP1/preP3 meeting held to discuss the clinical pharmacology development program

November 9, 2010: EOP1/preP3 meeting was held to discuss CMC development.

May 9, 2012: Pre-NDA meeting held. The key agreements and comments from this meeting were:

- The design and the reported results of Study MEK114267 together with the proposed supportive data appear sufficient to support the filing of an NDA from a clinical perspective. The wording of the final indication statement will be determined based on the NDA review.
- FDA agreed to consider labeling the efficacy results on the ITT population, if safety and efficacy in the subgroups (BRAF V600E and BRAF V600K) are adequately supported by clinical study results and mechanism of action of trametinib
- The proposed NDA was incomplete from a Clinical Pharmacology perspective; bioanalytical methods with validation reports and final study reports should be provided to allow assessment of potential drug interactions, potential effects on PK of renal impairment and of hepatic impairment, and the timeline for completion of the QT assessment should be provided. The proposed contents with regard to nonclinical toxicology appeared sufficient for filing
- Safety data should not be integrated unless all data were converted to a uniform grading system because different grading systems (versions of CTCAE) were used to grade toxicity within individual trials across the safety database. GSK stated that recoding of trial data to achieve a uniform grading system “was not warranted or advisable”
- A third party review of all cases of sudden death/cardiac arrest will be conducted; FDA stated that this study report should be submitted to the NDA as soon as available rather than waiting until the 120-day safety update.

December 20, 2010: GlaxoSmithKline received orphan drug designation for (b) (4)

(also referred to as: GSK1 120212) for "treatment of patients with advanced or metastatic melanoma (Stage IIb through IV)."

June 29, 2012: FDA granted Fast Track designation for the development program for the development program the investigation of “trametinib (GSK1120212)” for the treatment of patients with BRAF^{V600K} mutation-positive, unresectable or metastatic melanoma to demonstrate improved progression-free survival. In the same letter, FDA granted a rolling review to be submitted in two portions (July 2, 2012 and August 2, 2012)

NDA Submission History

July 2, 2012: First submission submitted containing a partial submission of Module 1, complete quality information (Modules 2.3 and 3), and partial information from Module 5 (clinical information for planning bioresearch monitoring inspections).

July 13, 2012: Second submission containing partial submission of Modules 1 (draft labeling to facilitate review of the Request For Proprietary Name Review) and 5 (clinical information for planning bioresearch monitoring inspections)

August 2, 2012: Final submission containing the remaining portions of Modules 1, 2, and 5 and the complete submissions of Module 4.

October 14, 2012: The 74-day letter issued, notifying GSK that the NDA had been filed and had been designated as a “standard” review.

The application included more than 60 amendments; the majority of these amendments were submitted in response to information requests and requests for clarification.

3. CMC and Biopharmaceutics/Device

CMC

I concur with the conclusions reached by the chemistry and biopharmaceutics reviewers regarding the acceptability of the manufacturing of the drug product and drug substance for trametinib. Manufacturing site inspections were acceptable. The proposed commercial product was adequately bridged to the product administered in the major efficacy trial using in vitro dissolution. The specifications for genotoxic impurities have been qualified by nonclinical toxicology. Stability testing supports an expiry of 12 months for the 0.5 mg and 2 mg tablets and 9 months for the 1 mg tablets when stored at 2° to 8°C (36°F to 46°F) and protected from moisture and light. There are no outstanding issues that preclude approval; however the following agreed-upon post-marketing commitments will be conducted to further characterize Chemistry, Manufacturing, and Controls:

- To place all future commercial batches on stability to provide concurrent monitoring at 5°C and to notify FDA of any changes to this protocol; modification of this stability protocol will require submission of a prior approval supplement containing data supporting the request.

The commercial drug product is an immediate-release, film-coated tablet for oral administration. Trametinib tablets will be marketed in strengths of 0.5, 1, and 2 mg trametinib (b) (4). Tablet strengths are differentiated by color.

Device

The NDA contained a letter authorizing CDER to refer to bioMerieux’s IDE G120011 for the THxID™ BRAF assay in support of NDA 204114. Concurrent with the review of this NDA, a pre-market application (PMA) was submitted for the companion diagnostic for identification of patients with BRAF V600 mutation-positive melanoma, manufactured by bioMerieux.

4. Nonclinical Pharmacology/Toxicology

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

The NDA contained *in vitro* pharmacology studies demonstrating inhibition of MEK1/MEK2 kinase activity directly as well as that mediated by constitutively activated BRAF in BRAF B600E mutation-positive cells and also demonstrated that trametinib inhibited of BRAF V600 mutation-positive melanoma in tumor xenograft models. The NDA contained evidence of selective MEK inhibition with minimal off-target activity based on *in vitro* studies.

Toxicology studies were conducted in rats and dogs. In rats, target organ toxicity was observed in the skin, the gastrointestinal (GI) tract, lymphoid organs, bone marrow (reversible neutropenia), liver, and adrenal gland at doses of 0.5 to 1 mg/m². In addition, evidence of toxicity with possible impairment of fertility was noted in female rats (decreased corpora lutea). In dogs, target organ toxicity was observed in the skin, GI tract, lymphoid organs, and lungs at doses of 0.6-0.45 mg/m² daily.

In safety pharmacology assessments, inhibition of the hERG channel was observed only at micromolar concentrations (1.5-3.7) and QT prolongation was not observed in dogs, indicating a low potential for QT prolongation in humans. Evidence of cardiomyopathy (decreased left ventricular ejection fraction, increased heart weight) was observed only in mice who were able to tolerate trametinib doses and exposures exceeding those administered in clinical and other non-clinical studies by 3-7-fold.

Trametinib administration resulted in embryofetal lethality in reproductive toxicology studies. In reproductive toxicity studies, administration of trametinib to rats during the period of organogenesis resulted in decreased fetal weights at doses greater than or equal to 0.031 mg/kg/day (approximately 0.3 times the human exposure based on AUC at the recommended dose). In rats, at a dose resulting in exposures 1.8 fold higher than the human exposure at the recommended dose, there was maternal toxicity and an increase in post-implantation loss.

In pregnant rabbits, administration of trametinib during the period of organogenesis resulted in decreased fetal body weight and increased incidence of variations in ossification at doses greater than or equal to 0.039 mg/kg/day (approximately 0.08 times the human exposure at the recommended dose based on AUC). In rabbits administered trametinib at 0.15 mg/kg/day (approximately 0.3 times the human exposure at the recommended dose based on AUC) there was an increase in post-implantation loss, including total loss of pregnancy, compared to control animals.

Carcinogenicity studies with trametinib have not been conducted. Trametinib was not genotoxic in studies evaluating reverse mutations in bacteria, chromosomal aberrations in mammalian cells and micronuclei in the bone marrow of rats.

5. Clinical Pharmacology

I concur with the conclusions reached by the clinical pharmacology, pharmacometrics, and pharmacogenomics reviewers that there are no outstanding clinical pharmacology issues that

preclude approval. As noted by the clinical pharmacologist, evaluation of pharmacokinetics in patients with organ impairment and adequate assessment of effects on QTc were not conducted. Therefore post-marketing trials have been required to assess these effects.

The mean absolute bioavailability of a single 2 mg oral dose of trametinib is 72%, with a median time to achieve peak concentrations (T_{max}) of 1.5 hours and the estimated elimination half-life is 3.9 to 4.8 days. Trametinib is highly protein bound (97.4%). 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. Since the decrease in exposure was considered clinically relevant and given the potential for confusion as to what constitutes a “high fat meal” product labeling recommends taking trametinib in a fasting state.

Trametinib is not significantly metabolized via CYP450. Based on studies with ¹⁴C-trametinib, the major route of elimination is the liver (>80%) with renal elimination responsible for less than 20%. Two major active metabolites are formed through acetylation (M5) or hydroxylation (M7). At steady state, trametinib is the major component (≥ 75%) in plasma, with the remainder equally split between M5 and M7.

The population PK analysis assessed the influence of covariates including age, body weight, height, sex, albumin, total bilirubin, international normalized ratio (INR), mild to moderate renal impairment, tumor types (e.g., melanoma vs. others), BRAF V600 mutation (E vs. K vs. others), study, and mild hepatic impairment. The pharmacometrics review concluded that none of these covariates had a clinically important influence on the CL/F and V/F of trametinib. Effects of race and CYP3A4 inhibitors/inducers were not tested in the model since the majority of patients in the datasets were Caucasian (97%), and did not receive CYP3A4 inhibitors (97%) or inducers (99%).

6. Clinical Microbiology

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

7. Clinical/Statistical-Efficacy

Regulatory History

Efficacy was supported by the results of a single trial, Protocol MEK114267, entitled “A Phase III randomized, open-label study comparing GSK1120212 to chemotherapy in subjects with advanced or metastatic BRAF V600E/K mutation-positive melanoma.” The trial enrolled 322 patients, with first patient accrual on November 23, 2010 and a data cut-off date of October 26, 2011.

There were three IND amendments prior to the data cut-off. The key statistically related amendments were:

October 18, 2010:

- the primary endpoint was changed to PFS only

May 2, 2011 Protocol was amended to require

- documented disease progression on prior chemotherapy in patients who received prior chemotherapy;
- confirmation of absence of CNS metastases or of stable disease in patients with a history of CNS metastases;
- allow patients who discontinued chemotherapy for reasons other than disease progression to crossover if they had not received other anti-cancer treatment and had disease progression confirmed by independent review

October 3, 2011:

- the primary efficacy population changed to patients with a BRAF V600E mutation and no history of CNS metastases, based on results of MEK113583

October 21, 2011

- the primary analysis population was changed from the intent to treatment (ITT) to the primary efficacy (PE) population, defined as patients with a BRAF V600E mutation status without a history of prior brain metastases (a subgroup of ITT population)

December 16, 2011

- The final statistical analysis plan (SAP). As noted by GSK in an email sent Sept. 21, 2012, “Study MEK114267 was never submitted for a Special Protocol Assessment and therefore FDA comments on the statistical analysis plan (SAP) were never requested.”

Trial Design

The trial was a two-arm, open-label, randomized (2:1) trial comparing the safety and efficacy of trametinib to single agent chemotherapy (dacarbazine or paclitaxel). Key eligibility criteria were a diagnosis of Stage IIIc or Stage IV cutaneous melanoma, BRAF V600E/K mutation-positive tumor as determined with the “GSK BRAF mutation assay,” no more than one prior regimen for treatment of unresectable or metastatic disease, no prior treatment with a BRAF or MEK inhibitor.

The primary objective was to demonstrate superior progression-free survival (PFS) as determined by the investigator, with trametinib as compared to chemotherapy in patients with V600E/K locally advanced or metastatic melanoma. The secondary objectives were to further characterize the efficacy, safety, and tolerability of trametinib as a single agent to characterize PFS in the subgroup who received no prior chemotherapy in the advanced or metastatic setting. To characterize PFS in the subgroup who received one prior chemotherapy regimen in the advanced or metastatic setting, to characterize PFS and overall response rate in the subgroup of subjects with BRAF V600 K mutation-positive melanoma, to characterize efficacy (PFS, overall response rate, and duration of response) following crossover from chemotherapy to trametinib. An exploratory objective was to evaluate and compare changes in health related quality of life (HRQOL) between the two study arms. An additional objective was to further validate a BRAF mutation assay.

Patients were randomized (2:1) to receive trametinib 2 mg orally once daily or to receive chemotherapy (either dacarbazine 1000 mg/m² once every 3 weeks or paclitaxel 175 mg/m²

every 3 weeks, at the discretion of the investigator). Treatment continued until disease progression, death or withdrawal. At the time of disease progression, patients randomized to chemotherapy were permitted to receive open-label treatment with trametinib. Randomization was stratified by LDH level (above the upper limit of normal vs. equal to or below the upper limit of normal) and prior chemotherapy for advanced or metastatic disease (yes vs. no).

Results:

A total of 322 patients were enrolled and randomized to trametinib (n=214) or chemotherapy (n=108). Three patients (1%) in the trametinib arm and nine (8%) in the chemotherapy arm never received protocol-specified therapy. Of the 108 patients randomized to chemotherapy, 62 (57%) received dacarbazine, 37 (34%) received paclitaxel, and 9 (8%) did not initiate chemotherapy.

The median age for randomized patients was 54 years, 54% were male, >99% were white, and all patients had baseline ECOG performance status of 0 or 1. Most patients had metastatic disease (94%), were Stage M1c (64%), had elevated LDH (36%), no history of brain metastasis (97%), and received no prior chemotherapy for advanced or metastatic disease (66%). The distribution of BRAF V600 mutations was BRAF V600E (87%), V600K (12%), or both (<1%). The median duration of follow-up was approximately 5 months in both treatment arms (range: 0 to 10 months). Fifty-one (47%) patients crossed over from the chemotherapy arm at the time of disease progression to receive MEKINIST.

The population

The most common reason for treatment discontinuation in both arms was disease progression (54% for those randomized to trametinib and 67% for those randomized to chemotherapy), followed by adverse events (10% and 6%, respectively).

The key efficacy results are summarized in the table below (abstracted from the statistical review). Based on analyses performed by Dr. Chen, the outcomes in the chemotherapy arm were similar in subgroups based on chemotherapy selected (dacarbazine or paclitaxel).

Table 1: Key Efficacy Results from Protocol MEK114267

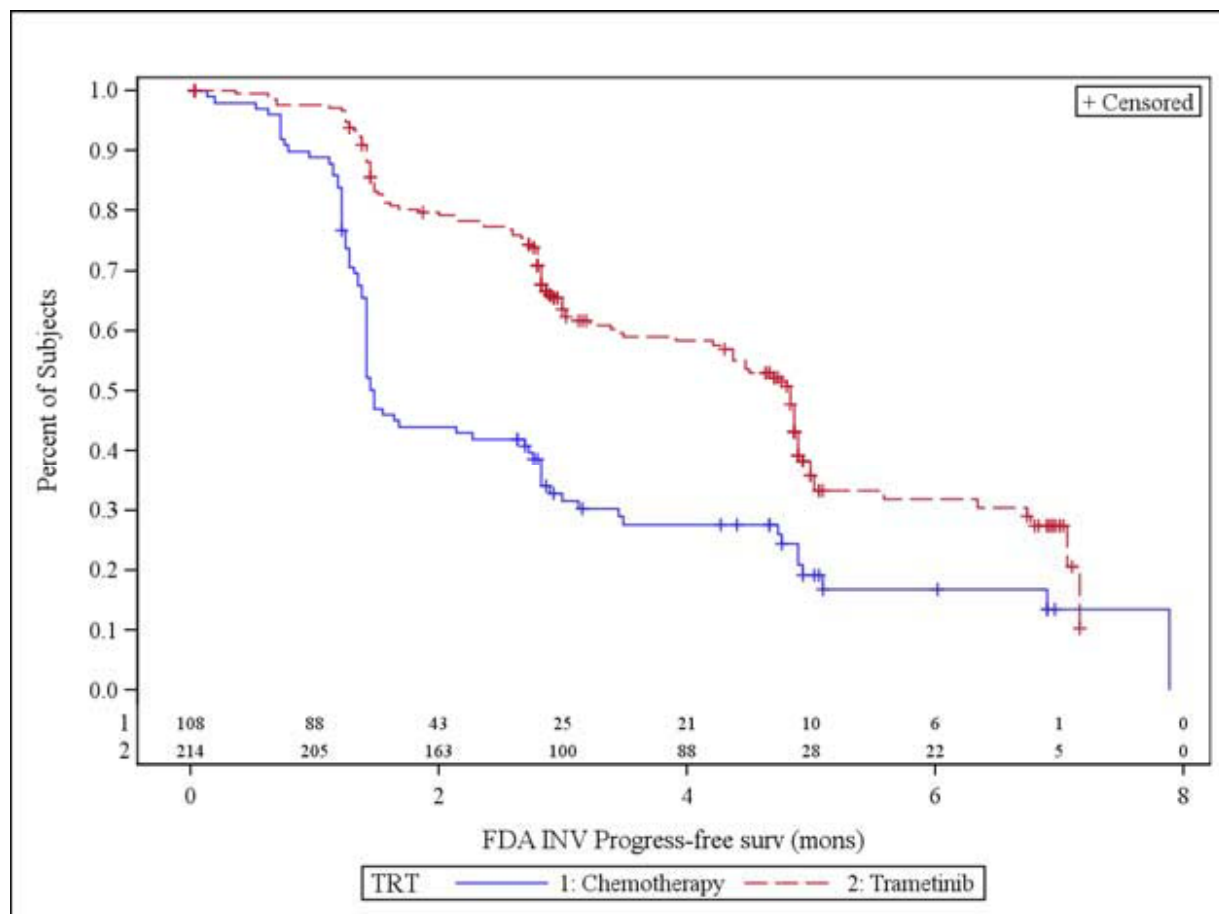
Efficacy Parameter	Trametinib N=214	Chemotherapy N=108
Progression-free survival		
Median PFS in months	4.8	1.5
Hazard ratio ¹ (95% CI)	0.47 (0.34, 0.65)	
p-value	<0.0001	
Overall survival		
Number of deaths	35 (16%)	29 (27%)
Median S in months	NR	NR
Hazard ratio ² (95% CI)	0.54 (0.33, 0.89)	
p-value	Not significant	
Objective Responses		
Overall response rate (95% CI)	22% (17%, 28%)	8% (4%, 15%)
Complete response (rate)	4 (2%)	0
Partial responses (rate)	43 (25%)	9 (8%)
Duration of response		
Median duration in months (95% CI)	5.5 (4.1, 5.9)	NR (3.5, NR)

¹ Pike unstratified

² Cox unstratified

In supportive analyses based on independent radiologic review committee assessment, the PFS results were consistent with those of the primary efficacy analysis. The PFS results were also consistent in exploratory subgroup analyses of patients whose tumors were identified as having BRAF V600E or V600K mutations based on retrospective analysis using the to-be marketed companion diagnostic test (THxID™-^{(b) (4)} assay).

Figure 1: Investigator-Assessed Progression-free Survival



Additional trials informing assessment of efficacy

Protocol MEK113583 was a single arm, two cohort trial which evaluated the anti-tumor activity (objective response rate) of trametinib in patients with unresectable or metastatic, BRAF V600 mutation-positive melanoma. The two cohorts included patients who had not been exposed to prior BRAF inhibitor therapy and a second cohort of patients who had received a BRAF inhibitor. This latter cohort enrolled 40 patients, all of whom were treated with trametinib at a dose of 2 mg orally once daily until disease progression or unacceptable toxicity. The median age was 58 years, 63% were male, all were white, 98% had baseline ECOG PS of 0 or 1, and the majority of patients' tumors had BRAF V600E mutations (83%)

Of note, no patient in this cohort of Protocol MEK113583 achieved a confirmed partial or complete response as determined by the clinical investigators. Based on the unanticipated absence of anti-tumor activity, the results of this cohort are described in the physician package insert and a Limitation of Use has been added to the Indications and Usage section of the package insert.

8. Safety

Size of the database

The safety database of 329 patients with metastatic melanoma, receiving trametinib at the recommended dose and schedule in two open-label single-arm trials (n=118) or in an open-label, randomized, active-controlled trial (n=211), was of adequate size to identify serious adverse reactions occurring at an incidence of 1.0%.

The safety data described in the NDA consists primarily of data obtained in the major efficacy trial (Protocol MEK114267), which provides comparative safety data from 211 trametinib-treated patients and 99 chemotherapy-treated patients. This is supplemented by an integrated safety database on 329 patients with metastatic melanoma receiving the recommended dose of trametinib 2 mg orally once daily (n=329).

Major safety concerns related to labeling

There were no specific contraindications to treatment identified and no patient population at increased risk. The following paragraphs serious adverse reactions described in the Warnings and Precautions of the physician package insert and in patient labeling.

Cardiomyopathy:

(b) (4)
trial, cardiomyopathy (defined as cardiac failure, left ventricular dysfunction, or decrease in LVEF (b) (4) in 7% (14/211) of patients treated with trametinib (b) (4) chemotherapy-treated patients. The median time to onset of cardiomyopathy in patients treated with MEKINIST was 63 days (range 16 to 156 days); cardiomyopathy was identified within the first month of trametinib (b) (4) in 5 of these 14 patients. Four percent of patients in (b) (4) required discontinuation (4/211) and/or dose reduction (7/211) of trametinib. Cardiomyopathy resolved in 10 of these 14 (71%) patients (b) (4)

Across clinical trials (n=329), 11% (b) (4) patients developed (b) (4) evidence of cardiomyopathy (decrease in LVEF below institutional limits of normal with an absolute decrease in LVEF \geq 10% below baseline) and 5% demonstrated a decrease in LVEF below institutional limits of normal with an absolute decrease in LVEF of \geq 20% below baseline.

Retinal Pigment Epithelial Detachment (RPED) (b) (4)
ophthalmologic (b) (4) including retinal evaluation were performed pretreatment and at regular intervals during treatment, (b) (4) one patient (0.5%) receiving trametinib developed RPED (b) (4) cases of RPED were identified in chemotherapy-treated patients. Across all clinical trials of trametinib, the incidence of RPED was 0.8% (14/1749).

Retinal detachments were often bilateral and multifocal, occurring in the macular region of the retina. RPED led to reduction in visual acuity that resolved after a median of 11.5 days (range

3 to 71 days) following the interruption (b) (4) trametinib dosing, although Ocular Coherence Tomography (OCT) abnormalities persisted beyond a month in at least several cases.

For most of the adverse reactions, there was no evidence of an exposure-toxicity relationship. However, as noted by Dr. Leong, there were 3 cases of chorioretinopathy among patients receiving loading doses of trametinib (6/6/2 mg [n=6] and 10/10/3 mg [n=4]) or trametinib 4 mg QD [n=3] in Study MEK111054, which suggest that the risks of ocular toxicity are dose-related.

Retinal Vein Occlusion:

(b) (4)
Across clinical trials (b) (4)
of RVO was 0.2% (4/1749). (b) (4) RVO may lead to macular edema, decreased visual function, neovascularization, and glaucoma.

Interstitial Lung Disease

In clinical trials (n=329), interstitial lung disease (ILD) or pneumonitis occurred in 1.8% of patients. In (b) (4), 2.4% (5/211) of patients treated with trametinib developed ILD or pneumonitis; all five patients required hospitalization. The median time to first presentation of ILD or pneumonitis was 160 days (range 60 to 172 days).

Serious (b) (4) toxicity:

(b) (4)
hospitalization (b) (4)
secondary infections of the skin
requiring intravenous antibiotics or severe (b) (4) without secondary infection. No (b) (4)
patients treated with chemotherapy (b) (4) required hospitalization for severe rash or infections of the skin. The median time to onset of rash in patients treated with MEKINIST was 15 days (range 1 to 221 days) and median time to resolution of rash was 48 days (range 1 to 282 days). Reductions in the dose of MEKINIST were required in 12% and permanent discontinuation of MEKINIST was required in 1% of patients with rash.

Table 2: Selected Adverse Reactions Occurring in $\geq 10\%$ of Patients Receiving MEKINIST and at a Higher Incidence than in the Control Arm^f

Adverse Reaction Term	Trametinib (n=211)		Chemotherapy (n=99)	
	All Grades ^a	Grade 3-4	All Grades ^a	Grade 3-4
Skin and subcutaneous tissue disorders				
Rash	57	8	10	0
Dermatitis acneiform	19	<1	1	0
Dry skin	11	0	0	0
Paronychia	10	0	1	0
Pruritis	10	2	1	0
Gastrointestinal disorders				
Diarrhea	43	0	16	2
Stomatitis ^b	15	2	2	0
Abdominal pain ^c	13	1	5	1
Vascular disorders				
Lymphedema ^d	32	1	4	0
Hypertension	15	12	7	3
Hemorrhage ^e	13	<1	0	0

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

^b Includes the following terms: stomatitis, aphthous stomatitis, mouth ulceration, and mucosal inflammation

^c Includes the following terms: abdominal pain, abdominal pain lower, abdominal pain upper, and abdominal tenderness

^d Includes the following terms: lymphedema, edema, and peripheral edema

^e Includes the following terms: epistaxis, gingival bleeding, hematochezia, rectal hemorrhage, melena, vaginal hemorrhage, hemorrhoidal hemorrhage, hematuria, conjunctival hemorrhage.

^f Overall incidence $\geq 5\%$ or Grade 3-4 adverse reactions $\geq 2\%$ higher in trametinib arm compared to chemotherapy

REMS

GSK did not propose a REMS. The clinical review team and DRISK consultant agree that a REMS is not needed to ensure safe use of trametinib and that risk communication and mitigation can be addressed through product labeling.

9. Advisory Committee Meeting

Trametinib is a new molecular entity and the first drug approved in this class (MEK inhibitor). It was not referred for review to the Oncologic Drugs Advisory Committee (ODAC) because the safety profile is acceptable for the indication of metastatic or unresectable melanoma, the clinical study design for the major efficacy trial is acceptable and similar to that used for previously approved products for this indication, the application did not raise significant public health questions on the role of trametinib in the treatment of metastatic melanoma, and outside expertise was not necessary as there were no controversial issues that would benefit from advisory committee discussion.

10. Pediatrics

Trametinib, which was identified as [REDACTED] (b) (4) [REDACTED] (also referred to as GSK1 120212) in the orphan drug designation request, was granted orphan drug designation for the "treatment of patients with advanced or metastatic melanoma (Stage IIB through IV). Therefore trametinib is exempt from the requirements of the Pediatric Research Equity Act (PREA) for the approved indication.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name: The proposed proprietary name, Mekinist, has been deemed acceptable by the clinical review division (DOP2) and the Division of Medication Error Prevention and Analysis (DMEPA).
- Physician labeling
 - Indications and Usage: Indication modified for greater specificity (from BRAF V600 mutations to BRAF V600E or V600K mutations. The limitation of use stating [REDACTED] (b) (4) [REDACTED] Finally, the limitation of use for patients who had received prior BRAF inhibitors was strengthened from "[REDACTED] (b) (4) [REDACTED]" to "Mekinist is not indicated for the treatment of...").
 - Dosage and Administration: new Section 2.1 (Patient Selection) added. Other sections edited for brevity, essential information, and consistency with FDA Guidance for Industry on this section of product labeling. Recommended dose

modifications added for interstitial lung disease, RPED, and RVO. Modified based on change in storage conditions to 2-8°C as product is not stable at room temperatures.

- Dosage Forms/strengths: No modifications
- Contraindications: No modifications
- Warnings and Precautions: Warnings subsections on “Visual Impairment” broken up into two subsections on RPED and RVO. In addition, subsection on the serious risk of interstitial lung disease was added. Titles modified to specific serious risk in greater detail and each subsection was modified to include detailed information on the per-patient incidence of risks, time-to-event (if available) and outcomes (if available). The subsection on BRAF testing deleted, as information is conveyed in new subsection 2.1 on Patient Selection and because there is no evidence suggesting potential harmful effects for patients with BRAF wild-type melanoma (in contrast to BRAF inhibitors).
- Adverse Reactions: [REDACTED] (b) (4)
- Drug Interactions: Information on metabolic pathway removed (described in section 12). Noted that formal drug interaction studies have not been conducted.
- Use in Specific Populations: Assignment of Pregnancy Category D based on the mechanism of action. Reformatted section 8.1 and added new subsection 8.6 (Females and Males of Reproductive Potential) based on current labeling policy developed by Maternal Health team (pending formal Guidance). Provided data on Trial 1 enrollment for elderly patients for context and removed regulatory language consistent with OHOP practices to avoid potential for delivery of ineffective doses in elderly subjects. Edited sections on renal and hepatic impairment for brevity, to include dosing information where supported and to identify lack of recommended dosing information for patients with severe impairment.
- Overdosage: Edited to describe potential risk of [REDACTED] (b) (4) based on limited clinical information at highest doses as there is no information on unintentional overdose.
- Description: Reduced information on mechanism of action to pharmacologic class
- Clinical Pharmacology: Removed promotional terms [REDACTED] (b) (4) and edited for brevity, essential information, and data relevant to clinical use in subsections 12.1 and 12.2. Pharmacokinetic data edited for brevity (lack of effect on PK summarized) in specific populations or in those with organ impairment. Information on drug interactions edited for brevity. [REDACTED] (b) (4)

- Nonclinical Toxicology: [REDACTED] (b) (4)
 - Clinical Studies Created two subsections, 14.1 to describe the major efficacy trial supporting approval and 14.2 to describe the clinical trial in which activity was not established (patients with prior BRAF inhibitor therapy), with inclusion of a more description of the trial, study population, and results observed. [REDACTED] (b) (4)
[REDACTED] summarized results with retrospective evaluation with the to-be-approved companion diagnostic. Limited description of efficacy to the primary efficacy population (those without CNS metastases), provided additional details on study design (stratification). [REDACTED] (b) (4)
[REDACTED] Results expanded to include PFS events (disease progression or death) and median response duration.
 - How Supplied: Modified based on change in storage conditions to 2-8°C as product is not stable at room temperatures.
 - Patient Counseling: Edited for brevity, inclusion of essential information, such as when to contact healthcare providers
- Carton and immediate container labels: All revisions to carton and container labeling, as requested by the DMEPA reviewer have been incorporated.
 - Patient labeling/Medication guide: GSK submitted patient labeling for communication of important safety and dosing information. Revisions were incorporated by FDA reviewers for consistency with modifications to the physician package insert and based on the review of the NDA. In addition, modifications to format were made as recommended by the Patient Labeling Team consultant.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval
- Risk Benefit Assessment
Metastatic melanoma is a serious and life-threatening disease, with a 5-year survival rate of only 15%. While the recent approvals of ipilimumab and vemurafenib have demonstrated improvement in overall survival, such patients are not cured and additional effective treatments are needed for palliation and control of disease.

The single trial supporting efficacy in this application demonstrated a statistically significant improvement in the PFS for the trametinib arm compared with chemotherapy [HR 0.47 (95% confidence intervals (CI): 0.34, 0.65); p <0.001] with an increase in median PFS from 1.5 months in the chemotherapy arm to a median PFS of 4.8 months for the trametinib arm. In addition, the overall response rate was superior for the trametinib arm compared to chemotherapy (22% vs. 8%) with a median duration of response of 5.5 months for responders in the trametinib arm. An immature

analysis of overall survival did not suggest potentially harmful effects. The most serious adverse reactions of trametinib are cardiomyopathy (7% per-patient incidence), retinal pigment epithelial detachment (0.5%), retinal vein occlusion (0.6%), interstitial lung disease (2.4%), and serious skin rash requiring hospitalization in 6% of trametinib treated patients in Protocol MEK114267. The most common ($\geq 10\%$ incidence) adverse reactions were rash, diarrhea, lymphedema, acneiform dermatitis, hypertension, stomatitis, stomach pain, mild-moderate hemorrhage, abdominal pain, dry skin, paronychia, and pruritis.

The major efficacy trial for trametinib demonstrated a clinically meaningful and statistically robust improvement in progression-free survival and a significant improvement in overall response rate. Although FDA expressed a preference for assessment of overall survival as the primary endpoint, in discussions of the trial design, FDA stated a willingness to discuss the results of Protocol 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. The toxicity profile of trametinib is acceptable given the seriousness of the disease and, with the exception of unique ocular toxicities in less than one percent of patients, is similar to toxicities considered acceptable with anti-neoplastic therapy for metastatic solid tumors with poor prognoses.

The magnitude of the effect on progression-free survival observed with trametinib is similar to that with BRAF inhibitors. It is further noted that vemurafenib, which has a similar magnitude of effect on progression-free survival also demonstrated an increase in overall survival, suggesting that improvements in progression-free survival for agents inhibiting the ERK pathway may predict effects on survival. As compared to BRAF inhibitors, trametinib has a different toxicity profile which may offer advantages to individual patients. In addition, as compared to ipilimumab, trametinib offers the potential for tumor reduction and tumor control with an alternative toxicity profile. Based on the totality of the data provided, the application contains substantial evidence of effectiveness, an acceptable risk: benefit ratio, and while not superior to recently approved drugs for the treatment of metastatic melanoma, offers a different toxicity profile which may be of importance in treatment selection for individuals with specific co-morbid conditions.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
I concur with the recommendations of the clinical reviewer, CDTL, and DRISK reviewer that a REMS is not required to ensure safe and effective use of trametinib and that the risks can be conveyed through physician package insert and patient labeling.
- Recommendation for other Postmarketing Requirements and Commitments
 - Complete a clinical trial to evaluate the potential for trametinib to prolong the QT/QTc interval in an adequate number of patients administered repeat doses of trametinib in accordance with the principles of the FDA Guidance for Industry entitled “*E14 Clinical Evaluation of QT/QTc Interval Prolongation*.” Submit the

final report that includes central tendency, categorical and concentration-QT analyses, along with a thorough review of cardiac safety data.

Rationale: Adequate evaluation of the potential effects on QTc prolongation has not been conducted in human subjects

- Conduct a pharmacokinetic trial to determine the appropriate dose of trametinib in patients with hepatic impairment in accordance with the FDA Guidance for Industry entitled “*Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.*”

Rationale: The hepatic pathway is the major route of elimination and insufficient numbers of patients with impaired hepatic function were enrolled and evaluated pharmacokinetically to assess whether dose modifications would be appropriate in patients with hepatic impairment.

- 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 cardiomyopathy and subsequent sequelae, including safety evaluations adequate to inform labeling of patient populations at 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.

Rationale: There is insufficient experience to characterize the subacute and chronic toxicities of trametinib with regard to both cardiomyopathy and secondary malignancies. Such data will further inform the risk: benefit assessment for trametinib.

- Submit integrated safety analyses from an adequate number of randomized controlled clinical trial(s) using Mekinist (trametinib) 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.

Rationale: Controlled data are needed to further assess this unique and uncommon toxicity of trametinib and will inform the risk: benefit assessment for this drug.

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

/s/

PATRICIA KEEGAN
05/28/2013