

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204114Orig1s000

STATISTICAL REVIEW(S)



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

Memorandum

Date: May 6, 2013

From: Norma Griffin, Regulatory Health Project Manager DOP2/OHOP

Subject: NDA 204114: Biostatistics Secondary/Tertiary Reviews

Drs. Kun He and Rajeshwari Sridhara signed off on Dr. Huanyu Chen's April 8, 2013, review as a complete review on April 9, 2013.



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES – ADDENDUM 1

NDA #: 204,114

Drug Name: Mekinist ® (trametinib)

Indication(s): Unresectable or Metastatic Melanoma

Applicant: The GlaxoSmithKline Group of Companies

Date(s): Submission: 8/3/2012
PDUFA: 6/2/2012

Review Priority: Standard

Biometrics Division: Division of Biometrics V

Statistical Reviewer: Huanyu (Jade) Chen

Concurring Reviewers: Kun He, Team Leader
Rajeshwari Sridhara, Division Director

Medical Division: Division of Oncology Products 2

Clinical Team: Marc Theoret, Medical Reviewer
Suzanne Demko, Team Leader
Patricia Keegen, Division Director

Project Manager: Norma Griffin

Keywords: log-rank test, K-M curve, Pike Estimate

ADDENDUM 1

Statistical Review and Evaluation of the MEK114267 Trial

This addendum summarizes PFS, OS, DOR, and ORR subgroup exploratory analysis results by actual chemotherapy regimens (paclitaxel vs. dacarbazine). Of note, the applicant did not report the chemotherapy regimen at the randomization in the entire NDA submission.

Table 1 presents the patient population by chemotherapy regimens.

Table 1 Patient Population by Chemotherapy Regimens (ITT)

	Trametinib	Chemotherapy	
		Dacarbazine	Paclitaxel
ITT population, N	214	108	
Never treated, n (%)	3 (1)	9 (8)	
Actual Chemotherapy Regimen (%)	211 (99)	62 (57)	37 (34)

1 PFS Subgroup Analyses by Chemotherapy Regimens

Table 2 summarizes FDA's PFS subgroup analysis results per investigator (INV) assessment by chemotherapy regimens.

Table 2 Subgroup PFS Analysis Results Based on the INV Measurements by Chemotherapy Regimens

Treatment	Event/ Censored	Median PFS (95%CI, Months)	Unstratified HR (95%CI)	
			Pike	Cox
Dacarbazine	47/ 15	1.5 (1.4, 2.8)	0.50 (0.33 , 0.75)	0.48 (0.34, 0.68)
Trametinib	116/ 95	4.8 (4.3, 4.9)		
Paclitaxel	28/ 9	2.3 (1.3, 2.8)	0.41 (0.23 , 0.73)	0.40 (0.27, 0.61)
Trametinib	116/ 95	4.8 (4.3, 4.9)		

Table 3 summarizes FDA's PFS subgroup analysis results per blinded independent review committee (IRC) Independent Radiology (IR) assessment by chemotherapy regimens.

Table 3 Subgroup PFS Analysis Results Based on the IRC IR Measurements by Chemotherapy Regimens

Treatment	Event/ Censored	Median PFS (95%CI, Months)	Unstratified HR (95%CI)	
			Pike	Cox
Dacarbazine	45/ 17	2.2 (1.4, 2.9)	0.47 (0.30 , 0.72)	0.45 (0.32, 0.65)
Trametinib	97/114	4.9 (4.7, 5.0)		
Paclitaxel	26/ 11	1.4 (1.3, 4.8)	0.37 (0.20 , 0.68)	0.36 (0.23, 0.55)
Trametinib	97/114	4.9 (4.7, 5.0)		

Table 4 summarizes FDA’s PFS subgroup analysis results per IRC independent radiology and independent oncology (IRIO) assessment by chemotherapy regimens.

Table 4 Subgroup PFS Analysis Results Based on the IRC IRIO Measurements by Chemotherapy Regimens

Treatment	Event/ Censored	Median PFS (95%CI, Months)	Unstratified HR (95%CI)	
			Pike	Cox
Dacarbazine	46/ 16	2.2 (1.4, 2.9)	0.47 (0.31 , 0.71)	0.45 (0.32, 0.65)
Trametinib	99/112	4.9 (4.5, 5.0)		
Paclitaxel	28/ 9	1.4 (1.3, 3.1)	0.35 (0.19 , 0.65)	0.34 (0.22, 0.52)
Trametinib	99/112	4.9 (4.5, 5.0)		

2 OS Subgroup Analyses by Chemotherapy Regimens

Table 5 summarizes OS subgroup analysis results by chemotherapy regimens.

Table 5 Subgroup OS Analysis Results by Chemotherapy Regimens

Treatment	Event/ Censored	Median PFS (95%CI, Months)	Unstratified HR (95%CI)	
			Pike	Cox
Dacarbazine	16/ 46	N/A (6.1, N/A)	0.64 (0.33 , 1.24)	0.64 (0.35, 1.16)
Trametinib	34/177	N/A (N/A, N/A)		
Paclitaxel	11/ 26	N/A (5.3, N/A)	0.50 (0.21 , 1.16)	0.50 (0.25, 0.98)
Trametinib	34/177	N/A (N/A, N/A)		

N/A: Not available

3 ORR Subgroup Analyses by Chemotherapy Regimens

Table 6 summarizes FDA’s ORR subgroup analysis results per INV assessment by chemotherapy regimens.

Table 6 Subgroup ORR Analysis Results Based on the INV Measurements by Chemotherapy Regimens

	Trametinib (N=211)	Dacarbazine (N=62)	Paclitaxel (N=37)
Overall Response	47(22.3%)	9 (14.5%)	0
Complete Response	4(1.9%)	0	0
Partial Response	38 (18.0%)	9 (14.5%)	0
95% CI	(16.8%, 28.5%)	(6.9%, 25.8%)	N/A

N/A: Not available

Table 7 summarizes FDA’s ORR subgroup analysis results per IRC IR assessment by chemotherapy regimens.

Table 7 Subgroup ORR Analysis Results Based on the IRC IR Measurements by Chemotherapy Regimens

	Trametinib (N=211)	Dacarbazine (N=62)	Paclitaxel (N=37)
Overall Response	41 (19.4%)	6 (9.7%)	0
Complete Response	0	1 (1.6%)	0
Partial Response	41 (19.4%)	5 (8.1%)	0
95% CI	(14.3%, 25.4%)	(3.6%, 19.9%)	N/A

N/A: Not available

Table 8 summarizes FDA’s ORR subgroup analysis results per IRC IRIO assessment by chemotherapy regimens.

Table 8 Subgroup ORR Analysis Results Based on the IRC IRIO Measurements by Chemotherapy Regimens

	Trametinib (N=211)	Dacarbazine (N=62)	Paclitaxel (N=37)
Overall Response	41 (19.4%)	5 (8.1%)	0
Complete Response	0	1 (1.6%)	0
Partial Response	41 (19.4%)	4 (6.5%)	0
95% CI	(14.3%, 25.4%)	(2.7%, 17.8%)	N/A

N/A: Not available

4 DoR Subgroup Analyses by Chemotherapy Regimens

Table 9 presents the FDA’s DoR analysis results based on the INV measurements by chemotherapy regimens.

Table 9 DoR Analyses Based on the INV Measurements by Chemotherapy Regimens

	Trametinib (N=47)	Dacarbazine (N=9)	Paclitaxel (N=0)
Events	12	2	0
Median in months (95% CI)	5.5 (4.1, 5.9)	N/A (3.5, N/A)	N/A

N/A: Not available

Table 10 presents the FDA’s DoR analysis results based on the INV measurements by chemotherapy regimens.

Table 10 DoR Analyses Based on the IRC IR Measurements by Chemotherapy Regimens

	Trametinib (N= 41)	Dacarbazine (N=6)	Paclitaxel (N= 0)
Events	8	1	0
Median in months (95% CI)	5.6 (3.8, 5.9)	N/A (3.5, N/A)	N/A

N/A: Not available

Table 11 presents the FDA’s DoR analysis results based on the INV measurements by chemotherapy regimens.

Table 11 DoR Analyses Based on the IRC IRIO Measurements by Chemotherapy Regimens

	Trametinib (N= 41)	Dacarbazine (N=5)	Paclitaxel (N= 0)
Events	8	1	0
Median in months (95% CI)	5.6 (3.8, 5.9)	N/A (3.5, N/A)	N/A

N/A: Not available

5 Corrections to Typographical Error

The correct Tables 23 and 24 in the Section 4.1 ***PFS Subgroup Analysis*** of the earlier Statistical Review and Evaluation (April 9, 2013) are:

Table 23 summarizes PFS subgroup analysis results based on IRC IR measurements.

Table 12 PFS (Months) Subgroup Analysis Based on IRC IR Measurements

	Diff in Median PFS	Event/Censor (TRT: KMO)	HR (95% CI)*	HR (95% CI)**
Male	3.3	55/65: 33/ 20	0.48 (0.29 , 0.79)	0.47 (0.30, 0.73)
Female	2.6	43/51:40/15	0.38 (0.23 , 0.62)	0.36 (0.23, 0.56)
Age <65	3.4	74/91: 60/26	0.39 (0.26 , 0.57)	0.37 (0.26, 0.52)
≥ 65	2.0	24/ 25: 13/9	0.67 (0.32 , 1.39)	0.66 (0.33, 1.31)
East Europe	2.7	16/15: 8/9	0.45 (0.16 , 1.27)	0.42 (0.17, 1.04)
North America	0.5	12/10: 8/5	0.77 (0.31 , 1.95)	0.75 (0.29, 1.92)
Oceania	3.7	6/13: 11/2	0.21 (0.07 , 0.60)	0.19 (0.07, 0.52)
West Europe	2.8	63/78: 45/18	0.43 (0.27 , 0.67)	0.42 (0.28, 0.61)

* HRs were estimated using unstratified Pike Estimate; ** HRs were estimated using unstratified Cox Estimate the; TRT: Trametinib; KMO: chemotherapy; Oceania: Australia and New Zealand

Table 24 summarizes PFS subgroup analysis results based on IRC IRIO measurements.

Table 13 PFS (Months) Subgroup Analysis Based on IRC IRIO Measurements

	Diff in Median PFS	Event/Censor (TRT: KMO)	HR (95% CI)*	HR (95% CI)**
Male	3.3	57/63: 35/18	0.47 (0.29 , 0.77)	0.46 (0.30, 0.71)
Female	2.6	43/51:41/14	0.38 (0.23 , 0.61)	0.36 (0.23, 0.55)
Age <65	3.5	76/89: 62/24	0.38 (0.26 , 0.57)	0.37 (0.26, 0.52)
≥ 65	2.0	24/25: 14/8	0.64 (0.31 , 1.31)	0.63 (0.32, 1.23)
East Europe	3.5	16/15: 10/7	0.40 (0.15 , 1.04)	0.36 (0.16, 0.83)
North America	0.5	12/10: 8/5	0.77 (0.31 , 1.95)	0.74 (0.29, 1.92)
Oceania	3.7	7/12: 12/1	0.22 (0.08 , 0.61)	0.21 (0.08, 0.53)
West Europe	2.8	64/77: 45/18	0.43 (0.28 , 0.67)	0.42 (0.29, 0.62)

*HRs were estimated using unstratified Pike Estimate; ** HRs were estimated using unstratified Cox Estimate; TRT: Trametinib; KMO: chemotherapy; Oceania: Australia and New Zealand

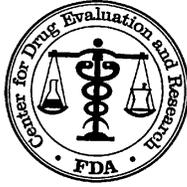
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/s/

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04/10/2013

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U.S. Department of Health and Human Services
Food and Drug Administration
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA #: 204,114

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Indication(s): Unresectable or Metastatic Melanoma

Applicant: The GlaxoSmithKline Group of Companies

Date(s): Submission: 8/3/2012
PDUFA: 6/2/2012

Review Priority: Regular

Biometrics Division: Division of Biometrics V

Statistical Reviewer: Huanyu (Jade) Chen

Concurring Reviewers: Kun He, Team Leader
Rajeshwari Sridhara, Division Director

Medical Division: Division of Oncology Products 2

Clinical Team: Marc Theoret, Medical Reviewer
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1 EXECUTIVE SUMMARY

In this New Drug Application (NDA), the applicant is seeking a regular approval of Mekinist® (trametinib, formerly GSK1120212 and JTP-74057), a kinase inhibitor, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations.

The pivotal study (MEK114267) supporting the application was a randomized, open-label, active-controlled multinational phase III trial evaluating the efficacy and safety of trametinib relative to chemotherapy (dacarbazine or paclitaxel). Patients on the chemotherapy arm were allowed to cross-over to trametinib upon progression. The primary endpoint was progression-free survival (PFS). The secondary endpoints include overall survival (OS) and best overall response rate (ORR). A total of 322 patients were randomized in a 2:1 allocation (trametinib: 214; chemotherapy: 108).

The data and analyses from the study MEK114267 demonstrated that the trametinib had statistically significant improvement in the PFS when compared with chemotherapy. Per investigator assessment, the unstratified log-rank test p-value for PFS comparison was <0.0001. The median PFS was 4.8 (95% CI: 4.3, 4.9) months for the trametinib arm and 1.5 (95% CI: 1.4, 2.7) months for the chemotherapy arm. The unstratified Pike HR was 0.47 with 95% CI (0.34, 0.65). The unstratified Cox proportional hazard ratio (HR) was 0.46 with 95% CI (0.34, 0.61). The results of independent radiologist assessed PFS and independent radiologist and oncologist assessed PFS were similar. Longer OS and bigger ORR were observed in trametinib when compared with chemotherapy.

Based on the data and analyses from the study MEK114267, the trametinib arm demonstrated a statistically significant improvement in PFS, compared with the chemotherapy arm. Whether the data and analyses from the current submission demonstrate an overall favorable benefit vs. risk profile is deferred to the clinical team reviewing this application.

Of note, the quality of the original data submission was not adequate to evaluate and review the application. Problems included poor data organization and management, missing data variables, data sets and documents, unexecutable SAS programs, and lack of documentation on every part of the data submission. More than 10 formal data quality related information requests were sent to the applicant to request additional data, documentations, programs, and results. The reviewers had multiple face-to-face meetings, telephone-conferences and email communications with the applicant. These problems caused inefficient review of this application. As a result, the applicant withdrew the priority review request voluntarily and a standard review was conducted. The final analysis data used in this review were derived by the reviewer from raw data.

2 INTRODUCTION

In this New Drug Application (NDA), the applicant was seeking regular approval of Mekinist® (trametinib, formerly GSK1120212 and JTP-74057), a kinase inhibitor, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test indicated for this use, who have not received BRAF inhibitor therapy. Initially the applicant had requested for a priority review of the application.

2.1 Overview

2.1.1 Class and Indication

According to the applicant's report, trametinib is a pyrido-pyrimidine derivative that was selected on the basis of its potent and highly selective allosteric inhibition of MEK1 and MEK2 activation and kinase activity. Trametinib was reported to have anti-proliferative activity against a broad range of tumor cell lines, xenograft models, and BRAF-activating mutations.

2.1.2 Regulatory History

Trametinib was studied under IND 102175, which was submitted on April 14, 2008. This study was conducted at 84 centers within 19 countries from November 23, 2010 to October 26, 2011.

On 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 statistically related agreements and comments from this meeting were:

- FDA recommended that GSK enroll BRAF wildtype patients 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 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

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

- On October 18, 2010, the primary endpoint was changed to PFS only
- On October 21, 2011, the primary analysis population was changed from the intent to treatment population (ITT) to the primary efficacy (PE) population, which was defined as patients with a

BRAF V600E mutation status without a history of prior brain metastases (a subgroup of ITT population)

- The final statistical analysis plan (SAP) was submitted on December 16, 2011. As stated by the applicant's email on Sep. 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."

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

- FDA agreed to consider labeling the efficacy results on the ITT population, if safety and efficacy in the subgroups are adequately supported by clinical study results and mechanism of action of trametinib

2.1.3 Study Reviewed

Trametinib (2 mg QD) compared with chemotherapy (dacarbazine 1000 mg/m² Q3W, or Paclitaxel 175 mg/m² Q3W) was evaluated in study MEK114267 for patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, who have not received BRAF inhibitor therapy. This study was randomized, open-label, active-controlled multinational phase III comparing the efficacy and safety of trametinib.

A total of 322 patients were randomized in a 2:1 allocation (trametinib: 214; chemotherapy: 108). The randomization was centralized and stratified by lactate dehydrogenase (LDH) (> upper limit of normal [ULN] vs. ≤ ULN) and prior chemotherapy for advanced or metastatic disease (yes vs. no). Patients continued treatments until disease progression, death or withdrawal. Patients randomized to the chemotherapy arm were allowed to crossover to receive trametinib after independent confirmation of progression.

The primary endpoint was PFS. The secondary endpoints were OS, over all response rate (ORR), and duration of response (DoR). The cut-off date for the efficacy analysis was October 26, 2011.

2.2 Data Sources

The electronic submission including Protocols, SAP, Clinical Study Reports (CSR), and analysis data for the original NDA submission and four major amendments are located in the following network paths:

- Original submission: <\\Cdsub1\evsprod\NDA204114\0001>
- Second amendment: <\\Cdsub1\evsprod\NDA204114\0009>
- Third amendment: <\\Cdsub1\evsprod\NDA204114\0024>
- Forth amendment: <\\Cdsub1\evsprod\NDA204114\0047>
- Fifth amendment: <\\Cdsub1\evsprod\NDA204114\0050>

3 STATISTICAL EVALUATION OF STUDY MEK114267

Part of the text, tables and figures presented in this section are adapted from the Applicant's CSR.

3.1 Data and Analysis Quality

The data quality for this submission was not optimal.

Data quality related issues were identified throughout the review process. Problems included poor data organization and management, missing data variables, data sets and documents, un-executable SAS programs, and lack of documentation throughout the whole data submission. More than ten formal data quality related information requests were sent to the applicant to request additional data, documentations, and programs. In addition, face to face meetings, telephone-conferences, and emails were used to discuss solutions on ways to conduct a thorough review due to the limitation of the data in the original submission and amendments.

In the Original data submission:

1. The applicant did not submit the meeting minutes and reports of the independent data monitoring committee (IDMC)
2. The applicant did not provide functional hyperlinks in the annotated electronic case report form (eCRF)
3. Issues related to the datasets include:
 - a. The raw/derived data were not submitted as separate data files. The raw data were embedded within the derived datasets. Some of the raw and derived variable/data used the same variable/data name.
 - b. The primary efficacy data was in the long format, which needed extra data manipulation to conduct efficacy analysis.
 - c. A lot of missing values were captured in the submission without adequate explanation.
 - d. The applicant did not provide a separate data with complete demographic, baseline characteristics and screening information at subject level. The reviewer had to derive key demographic characteristics variables based on the limited reviewer guide and define file.
 - e. Data format was not consistent. Multiple variables were coded by a mixture of numerical and character values.
 - f. In the efficacy analysis data set for some observations, date of event used imputed date without adequate documentation in the submission.
4. Issues related to the documentation include:
 - a. Overview/user guide for the contents of each data set was not provided.
 - b. Many bookmarks/hyperlinks were incorrect for the contents of data files, derivations of the variables, coding of the variables.
 - c. The columns of comment and code were empty in the key efficacy analysis datasets
 - d. Some of the data derivations in the comment column were incorrect.
 - e. For some variables classification did not match what was shown in the code column
 - f. Some variables with the same variable label had different values. For example, there were two sets baseline ECOG variables (ECOGB* and ECOGPE*), which had discordant values.
 - g. Some variables with the same data had multiple variable names. For example, there were five variable recording the gender of the patients (sex, sexcd sexcr, sexcrd, and sextxt).
5. Issues related to the SAS programs include:

The SAS programs provided by the applicant did not have sufficient details and were not executable SAS programs to verify the derivation of the analysis dataset from raw dataset, and the analyses associated with the results presented in the proposed package insert.

The applicant's responses to information requests were disappointing. In many cases the responses were inadequate, and the timelines for submission were not met. For example, the applicant once responded an information request with only a cover letter stating that the required information will be submitted. Response to the information request sent in September was not provided until late November and finally the reviewer found that the November submission did not correct the data as requested and discussed in face-to-face meetings.

After information requests and meetings, with multiple rounds of data amendments, some basic problems remained unsolved and unaddressed, as of March 11, 2013:

1. Raw datasets still contained derived data and IRC (external) data. The applicant' stated that the external data were provided by the vendor. All of the response data sets contained derived data and external data. The applicant did not provide sufficient documentation to support the external data.
2. Multiple variables were still coded by a mixture of numerical values and character values. The datasets submitted on Nov, 2012 were not useful.
3. In the response to FDA's information request dated 11/02/2012, the applicant stated that "GSK has conducted a full quality check of the Define Files in the NDA as well as updated the by-patient datasets to include the additional requested variables. We have identified a small number of minor errors in the Define files (mostly resulting from transcription). While GSK regrets the existence of errors in the Define files, these do not impact the programs, the datasets used by the programs and the analyses." However, throughout the whole database many variables lacked comments and explanation. For example, dataset RRESP2E1 contained best overall response per independent oncologist assessments and most of its variables were simply coded as 'EXTERNAL DATA' without any explanation on the meaning of the variables. Similar cases were captured in many other data.
4. Some of information requests were never addressed
 - a. For example, a full list of visitnum code was not submitted as FDA requested. The reviewer had to do one to one tabulation to understand the meaning of visit number, which was time consuming and labor intensive.
 - b. Similar situations were observed on the clarification of other variables throughout this submission.
5. Most SAS programs submitted were not usable. For example, in the tumor assessment derivation program, more than 10 SAS macros were called in loops. None of the macros contained documentation/comments within the macro to help understand the logic and algorithms involved.

These problems caused inefficient review of this NDA. Significant amount of time was wasted to wait for responses from the applicant, manually clean the data and search for documentation in the submission. With insufficient documentations and poor data quality, this reviewer could not duplicate data derivations and analysis. The applicant withdrew the priority review request voluntarily. The review clock had to be extended from 6 months to 10 months.

The key efficacy data and analysis had to be re-derived from raw data by this reviewer. The applicant agreed to use FDA reviewer's algorithm to derive the primary analysis data using the RECIST 1.1 criteria based on raw-lesion data. In addition, the last set of required data was submitted on April 4, 2013, which resulted in review completion later than the due date according to the PDUFA calendar.

3.2 Evaluation of Efficacy

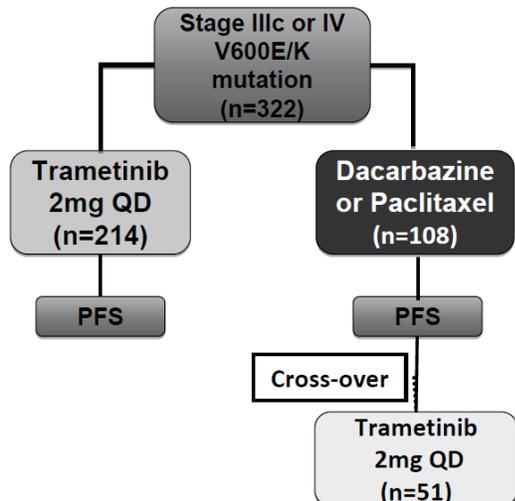
3.2.1 Objective

The primary objective of MEK114267 was to evaluate whether patients receiving trametinib would have improvement in PFS compared to those receiving the chemotherapy. The secondary objectives were to compare OS, ORR, and DoR between the two treatment groups.

3.2.2 Study Design

Study MEK114267 was a randomized, open-label, active-controlled multinational phase III trial to evaluate the efficacy and safety of trametinib (2 mg QD) compared to chemotherapy (dacarbazine 1000 mg/m² Q3W, or Paclitaxel 175 mg/m² Q3W) in patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test indicated for this use, who have not received BRAF inhibitor therapy. Figure 1 presents the trial schema.

Figure 1. Study MEK 114267 Scheme



This study consisted of a screening/baseline phase, a randomization phase, and a cross-over phase for patients randomized to chemotherapy who elect to receive trametinib following disease progression on chemotherapy, and a post-treatment follow-up period. Study treatment was continued until disease progression, unacceptable toxicity, discontinued, or death. Post discontinuation of study treatment, patients remained on the study for follow-up assessment of disease status and survival until 80% patients died or were lost to follow-up.

Approximately 297 patients were planned to be randomized in a 2:1 ratio (trametinib: 198; chemotherapy: 99) in order to observe 145 PFS events. The randomization was centralized and stratified by LDH (> ULN vs. ≤ ULN) and prior chemotherapy for advanced or metastatic disease (yes vs. no).

The main inclusion criteria were:

- Measurable disease according to RECIST v1.1
- Histologically confirmed, stage III unresectable (Stage IIIC) or metastatic (Stage IV) cutaneous melanoma, which is also determined to be BRAF V600E/K mutation-positive by the central reference laboratory
- No prior treatment or up to 1 prior regimen of chemotherapy for advanced or metastatic melanoma.
- ECOG performance status 0–1
- Adequate screening organ function
- No history or current evidence / risk of retinal vein occlusion (RVO) or central serous retinopathy

3.2.3 Efficacy Measures

PFS was defined as the time from randomization to the earliest date of investigator (INV)-assessed radiological disease progression per RECIST V1.1 or death due to any cause. The time interval between tumor response assessments increased during the treatment course. Specifically, the protocol specified tumor assessments at baseline, Weeks 6, 12, 21, 30, and every 12 weeks thereafter.

In general the applicant's analysis plan followed the FDA's Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics.

As stated by the applicant, the date of new anti-cancer therapy (including chemotherapy, hormonal therapy, immunotherapy, biologic therapy, radiotherapy) were planned to be imputed when the date of new anti-cancer therapy were missing. The following rules were used when only partial dates were recorded:

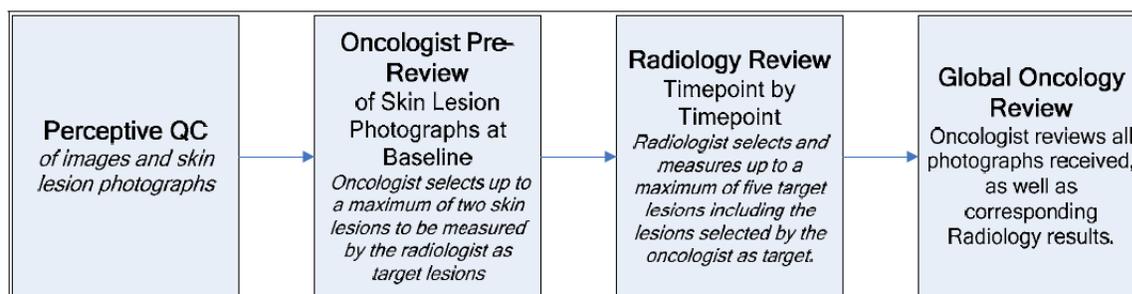
- If partial date falls in the same month as the last dose of study treatment (either randomized therapy or crossover therapy as appropriate), then assigned to earlier of (date of last dose of study treatment+1, last day of month)
- If partial date falls in the same month as the subject's last assessment and the subject's last assessment is progressive disease (PD), then assigned to earlier of (date of PD+1, last day of month)
- If both rules above apply, then assign to latest of the 2 dates
- Otherwise, impute missing day to the first of the month

PFS was also assessed by a blinded independent review committee (IRC). The IRC charter specified two sequential stages of review: (1) the Independent Radiology Review, a central blinded assessment of medical imaging data by one qualified radiologist and (2) the Independent Oncology Review, in which one independent qualified oncologist will assess the skin lesion photographs in

addition to the independent radiology findings to make a final determination for the case, if applicable.

As shown in Figure 2, following quality control inspection and verification, the primary radiologist assessed study imaging to determine overall radiographic tumor response at each timepoint using modified RECIST 1.1. If applicable, the radiologist included target skin lesions, as selected by the independent oncologist, in the timepoint assessments. The oncologist assessed any additional skin lesions and determined relevant endpoints based on a combined assessment of radiologic and skin lesions.

Figure 2. Procedure of IRC Lesion Assessment



Source: Section 7.1 of IRC charter for MEK 114267 (P18 of 50)

OS was defined as the time from randomization to death by any cause. After discontinuation, all the patients were planned to be followed monthly for survival until approximately 80% of the total number of randomized patients had died or otherwise lost to follow-up. For patients who had not died, duration of survival was censored at the date the patient was last known to be alive. The OS included all deaths including those who crossed over to trametinib.

ORR was defined as the percentage of subjects with a confirmed or unconfirmed complete response (CR) or partial response (PR) documented by the INV as per RECIST v1.1.

DoR was defined as the time from first documented evidence of CR or PR until first documented disease progression or death due to any cause.

Reviewer's Comments:

1. As discussed in section 2.1.2, FDA did not review the applicant's final SAP.
2. The reviewer conducted two kinds of IRC PFS analyses: the independent radiologist (IR) assessed PFS and Independent Radiologist and Independent Oncologist (IRIO) assessed PFS. The Independent Oncologist included additional information concerning skin lesions that the Independent Radiologist did not have—i.e., non-target disease of the skin, measurements from subcutaneous disease.
3. According to the applicant's SAP, an adequate assessment was defined as an assessment where the investigator determined response was CR, PR, or SD. In the case of non-RECIST (e.g. symptomatic) progression, the derived lesion response was used to determine if the assessment was adequate (i.e., a derived lesion response of CR, PR, or SD were considered

adequate). Therefore, the non-measurable lesion assessments were excluded in the PFS, ORR, and DoR analyses.

4. For the IRC PFS, the PFS would be censored at the last “adequate” assessment prior to IRC determined PD, death, new anti-cancer therapy, or two consecutive missing tumor assessments.
5. The date of new anti-cancer therapy would impact the PFS and DoR analysis. The imputation method proposed in the SAP was not acceptable. The date of new anti-cancer therapy was embedded within the derived dataset RESP2 (best overall response per INV assessment). Due to inadequate documentation of the program and data files, it is not clear if the imputation was implemented according to the analysis plan. Only four patients (0401252, 0402014, 0402235, and 0402626) used imputed date. The reviewer used the date of new anti-cancer therapy as the imputed date in the FDA’s analysis.
6. Similar to PFS analysis, ORR and DoR results based on IRC measurement (IR and IRIO) are reported in this review.

3.2.4 Sample Size Considerations

The trial was designed to have 99% power to detect a hazard ratio (HR) of 0.4286 with a two-sided alpha of 0.05 and 2:1 randomization ratio, assuming a median PFS of 3 months for the chemotherapy arm and 7 months for the trametinib arm. Assuming an accrual rate of 6 patients in month 1, 15 patients in month 2, 20 patients in month 4, and uniform accrual of 40 patients per month thereafter with 2% and 10% projected drop out rate on the trametinib and chemotherapy arms respectively, it was estimated that 145 PFS events were needed at the final PFS analysis, which could be expected from a total accrual of 297 patients.

At the final PFS analysis, the following subgroups were designed to have 87% power to detect a HR of 0.4286 with the same assumption on the ITT population:

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

Secondary endpoints and subgroup analyses were considered as supportive and were to be tested if the primary analysis of PFS in the ITT population was statistically significant. SAP was not planned to adjust type I error rate for the secondary endpoints and subgroup analyses.

Reviewer’s Comments:

1. Despite the over powered (99%) design for PFS on the ITT population, this study enrolled more patients than the pre-specified number of patients and had more PFS events than the required number of events.
2. Since SAP does not propose a multiplicity adjustment, the secondary endpoints and subgroup analyses were considered as exploratory.

3.2.5 Statistical Methodologies

Intent to Treat (ITT) population was defined as all randomized patients. The ITT population was planned to be the primary analysis population for the efficacy analyses at the original protocol submission and at Pre-NDA meeting.

Primary efficacy (PE) population, a subset of the ITT population, was defined as BRAF V600E patients without a prior history of brain metastases.

Efficacy Analysis Method for PFS

The analysis for PFS was performed using a stratified log-rank test, stratified by the same stratification factors as used for randomization: LDH (>ULN vs. ≤ ULN) and prior chemotherapy for advanced or metastatic disease (yes vs. no). The median PFS with corresponding 95% CIs and survival curves were estimated using the Kaplan-Meier (KM) method. The Pike estimator (Berry, Kitchin, & Mock, 1991) of HR with 95% CI of the trametinib over the chemotherapy were provided.

Efficacy Analysis Method for OS

The OS analysis method was identical to PFS analysis.

Efficacy Analysis Method for ORR

The analysis for ORR was performed using a Fisher's exact test adjusting for the same stratification factors at randomization. ORR estimates and exact 95% CIs were to be estimated for each treatment group. The difference of ORR between the trametinib and chemotherapy arms and the corresponding 95% confidence intervals would also be calculated.

Efficacy Analysis Method for DoR

As stated by the applicant, if sample size permits, the median DoR with corresponding 95% CI were estimated using the KM method.

Reviewer's Comments:

1. *As discussed in section 2.1.2, the primary analysis population was defined as ITT, PE, and ITT at the original protocol, Amendment 3, and Pre-NDA submission, respectively. This reviewer focuses on the efficacy results on the ITT population.*
2. *The DOR analysis is limited to responder and has nothing to do with the sample size. Therefore, no comparison can be made to the responder analysis.*

3.2.6 Applicant's Results and FDA Statistical Reviewer's Findings/ Comments

3.2.6.1 Patient Population and Disposition

A total of 322 patients were randomized in a 2:1 allocation (trametinib: 214; chemotherapy: 108). Table 1 presents the study population and patient disposition.

Table 1 Patient Population and Disposition (ITT)

	Trametinib	Chemotherapy
ITT population, N	214	108
PE population, N (%)	178 (83)	95 (88)
Crossover Population	0	51 (47)
Never treated, n (%)	3 (1)	9 (8)
Died, n (%)	35 (16)	29 (27)
Ongoing, n (%)	169 (79)	65 (60)
On study treatment	65 (30)	13 (12)
On crossover therapy	0	17 (16)
Follow up	104 (49)	35 (32)
Withdrawn from study, n (%)	10 (5)	14 (13)
Loss follow up	2 (<1)	1 (<1)
Investigator Discretion	2 (<1)	3 (3)
Withdrew consent	6 (3)	10 (9)
Treatment discontinuation, n (%)	146 (68)	86 (80)
Adverse event (non-treatment related)	21 (10)	6 (6)
Progressive disease (including death)	116 (54)	72 (67)
Investigator Discretion	5 (2)	4 (4)
Withdrawal by subject or proxy	4 (2)	4 (4)
Protocol Deviation	17 (8)	7 (6)

Reviewer's Comments:

1. A total of 1059 subjects were screened. The most common reason for screening failure was a negative test for the V600E/K BRAF mutation.
2. Three (1%) patients randomized to the Trametinib arm and 9 (8%) patients randomized to the chemotherapy arm did not receive their allocated treatments..
3. At the time of data cut-off date, there were approximately 30% and 12% patients still on study treatment in the trametinib arm and the chemotherapy arm.
4. The majority of the discontinuations were associated with progressive disease (PD).
5. Discontinuations were imbalanced between the trametinib and the chemotherapy arms. The chemotherapy arm had more PD, and trametinib arm had more AE.

3.2.6.2 Baseline Characteristics

Table 2 presents the patient baseline demographic characteristics.

Table 2. Baseline Demographics Characteristics (ITT)

	Trametinib N=214	Chemotherapy N=108
Age (yr) mean (SD)	54.3 (13.0)	52.8 (13.6)
median (min - max)	54.5 (23-85)	54.0 (21-77)
≥ 65	49 (23)	22 (20)
Female	94 (44)	55 (51)
Race White	214 (100)	108 (100)
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)

East Europe: Czech Republic, Poland, Russian Federation, and Ukraine; Latin America: Argentina; North America: Canada and United States; Oceania: Australia and New Zealand; West Europe: Austria, Belgium, France, Germany, Greece, Italy, Norway, Sweden, Switzerland, and UK - CMD

Reviewer's Comments:

1. *All of the patients were white.*
2. *There were more patients with age of 65 years or older and male in the trametinib arm*

Table 3 summarizes the CRF stratification factors and misclassifications per IVRS system.

Table 3. CRF Stratification Factors and Misclassifications

	Trametinib N=214	Chemotherapy N=108
GSK reported LDH > ULN	77 (36)	42 (39)
≤ ULN	134 (63)	66 (61)
missing	3 (1)	0
FDA Derived LDH > ULN	75 (35)	40 (37)
≤ ULN	134 (63)	67 (62)
missing	5 (2)	1 (1)
Prior chemotherapy for advanced or metastatic disease Yes	71 (33)	38 (35)
No	143 (67)	70 (65)
IVRS Misclassification	24 (11)	9 (8)

Reviewer's Comments:

1. *The baseline LDH derivation was unclear and inconsistent.*
 - a. *On the Section 9.2.6 of SAP, the applicant stated that "the baseline LDH would use day 1 values if available otherwise use (the value at) screening."*
 - b. *On the Section 8.2 of SAP, the applicant stated that "for analysis purposes, the strata were defined according to data captured on the eCRF, instead of strata captured from the Interactive Voice Response System (IVRS)".*

- c. *On Section 4.8.2.2 of CSR, the applicant stated that “In the stratified efficacy analyses, missing LDH were imputed based on the stratification reported in the IVRS at the time of randomization.”*
2. *This reviewer derived baseline LDH value based on lab test results. In addition to the applicant reported three patients with missing baseline LDH value, the reviewer also found 14 discordances between the applicant and the reviewer’s results. These discordances were due to the usage of post randomization lab test results or imputed LDH values from IVRS system.*
3. *There was 11% of strata misclassification between IVRS and CRF stratum.*
4. *Using post-randomization and/or imputed LDH value invalidate the randomization. The applicant, agreed to use either unstratified efficacy analyses or stratified efficacy analyses excluding baseline LDH from the strata during discussion in a face to face meeting with the application.*
5. *This reviewer used the unstratified efficacy analyses as primary analysis method because the LDH data had the above mentioned problems.*

Table 4 summarizes the important baseline disease characteristics in the ITT population.

Table 4 Baseline Disease Characteristics (ITT)

		Trametinib N=214	Chemotherapy N=108
BRAF	V600E	184 (86)	97 (90)
	V600K	29 (14)	11 (10)
Beam mutation	V600E	127 (59)	69 (64)
	V600K	21 (10)	7 (6)
	Wild-type	52 (24)	28 (26)
Prior brain metastatic		9 (4)	2 (2)
ECOG	1	78 (36)	39 (36)
	0	136 (64)	69 (64)
Num of disease sites	≥ 3	123 (57)	56 (52)
Prior immunotherapy		68 (32)	30 (28)
Prior Chemotherapy		71 (33)	38 (35)
Prior Radiotherapy		53 (25)	21 (19)
Prior Cancer related Surgery		193 (90)	98 (91)
Prior Biologic Therapy		16 (7)	13 (12)
Stage	IIIC, IV M1c, or IV M1b	69 (32)	45 (42)
	IV M1c	144 (67)	63 (58)
Histology at Initial Diagnosis:	Malignant melanoma NOS	57 (27)	26 (24)
	Nodular melanoma	51 (24)	24 (22)
	Superficial spreading melanoma	59 (28)	27 (25)
Visceral or non-visceral disease:	No	36 (17)	23 (21)
	Yes	178 (83)	85 (79)
Had Non-target lesion		174 (81)	90 (83)
Child-bearing potential	Post-menopausal	51 (24)	34 (32)
	Potentially able to bear children	32 (15)	16 (15)
	Sterile (of child-bearing age)	8 (4)	5 (5)
Path derm lymph invasion	Absent	138 (65)	67 (62)
	Present	71 (33)	38 (35)
Median duration (months) of metastatic disease (min-max)		7.4 (0.2-204)	6.6 (0.7-146)

Reviewer's Comments:

- 1. The trametinib arm had more patients with Stage IV M1C melanoma.*
- 2. There were 56% of patients who had disease in at least 3 sites. The most common locations of disease were lymph nodes, lung, liver, and subcutaneous tissue.*
- 3. There were only 11 (3.4%) patients who had prior history of brain metastases.*

3.2.6.3 Primary Endpoint – PFS

Table 5 presents the applicant's efficacy analysis for PFS based on the INV measurements. There were a total of 254 (79%) progressive disease or death events. The trametinib demonstrated a statistically significant difference in PFS compared with the chemotherapy based on the unstratified log-rank test with a p-value <0.0001. The median PFS was 4.8 months (95% CI: 4.3, 4.9) for the trametinib arm and 1.5 months (95% CI: 1.4, 2.7) for the chemotherapy arm. The

unstratified Pike HR was 0.47 with 95% CI (0.34, 0.65). The unstratified Cox HR was 0.46 with 95% CI (0.34, 0.61).

Table 5 FDA’s PFS Analyses Based on the INV Assessment (ITT)

	Trametinib N=214	Chemotherapy N=108
Number of Event (%)	117 (55)	77 (71)
PD	107 (50)	70 (65)
Death	10 (5)	7 (6)
Median PFS (months), 95% CI	4.8 (4.3, 4.9)	1.5 (1.4, 2.7)
Unstratified Log-Rank Test P-Value	<0.0001	
Cox Un-Stratified (95% CI) [P]	0.46 (0.34, 0.61) [<0.0001]	
Cox Stratified HR Per CRF (95% CI) [P]	0.42 (0.31, 0.57) [<0.0001]	
Cox Stratified HR Per IVRS (95% CI) [P]	0.41 (0.30, 0.55) [<0.0001]	
Pike Un-Stratified (95% CI) [P]	0.47 (0.34, 0.65) [<0.0001]	
Pike Stratified HR Per CRF (95% CI) [P]	0.45 (0.32, 0.63) [<0.0001]	
Pike Stratified HR Per IVRS (95% CI) [P]	0.44 (0.31, 0.61) [<0.0001]	

Figure 3 present the Kaplan-Meier (K-M) Curves for FDA’s PFS based on the INV Measurements.

Figure 3 K-M Curves for FDA’s PFS Based on the INV Measurements (ITT)

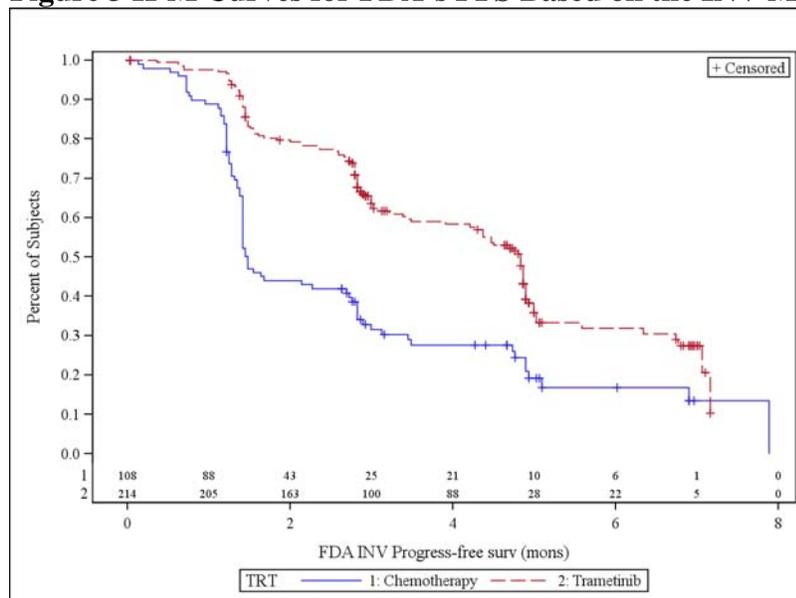


Table 6 presents the applicant’s efficacy analysis for PFS based on the IR and IRIO assessments. Per IR assessment, there were a total of 171 (53%) progressive disease or death events. Trametinib demonstrated a statistically significant difference in PFS compared with the chemotherapy based on the unstratified log-rank test with a p-value <0.0001. The median PFS was 4.9 months (95% CI: 4.6, 5.0) for the trametinib arm and 1.7 months (95% CI: 1.4, 2.8) for the chemotherapy arm. The unstratified Pike HR was 0.43 with 95% CI (0.31, 0.62). The unstratified Cox HR was 0.42 with 95% CI (0.31, 0.57).

Per IRIO assessment, there were a total of 176 (55%) progressive disease or death events. The trametinib demonstrated a statistically significant difference in PFS compared with the chemotherapy based on a unstratified log-rank test with a p-value <0.0001. The median PFS was 4.9 months (95% CI: 4.5, 5.0) for the trametinib arm and 1.5 months (95% CI: 1.4, 2.8) for the chemotherapy arm. The unstratified Pike HR was 0.43 with 95% CI (0.30, 0.60). The unstratified Cox HR was 0.42 with 95% CI (0.31, 0.56).

Table 6 FDA’s PFS Analysis Results based on the IRC Measurements (ITT)

	IR		IRIO	
	Trametinib N=214	Chemotherapy N=108	Trametinib N=214	Chemotherapy N=108
Num of Events	98 (46)	73 (68)	100 (47)	76 (70)
PD	88 (41)	66 (61)	91 (43)	69 (64)
Death	10 (5)	7 (5)	9 (4)	7 (6)
Median PFS (months), 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)
Unstratified Log-Rank Test P-Value	<0.0001		<0.0001	
Cox Un-stratified HR (95% CI) [P]	0.42 (0.31, 0.57) [<0.0001]		0.42 (0.31, 0.56) [<0.0001]	
Cox Stratified HR Per CRF (95% CI) [P]	0.38 (0.28, 0.53) [<0.0001]		0.38 (0.28, 0.52) [<0.0001]	
Cox Stratified HR Per IVRS (95% CI) [P]	0.37 (0.27, 0.51) [<0.0001]		0.37 (0.27, 0.50) [<0.0001]	
Pike Un-stratified HR (95% CI) [P]	0.43 (0.31, 0.62) [<0.0001]		0.43 (0.30, 0.60) [<0.0001]	
Pike Stratified HR Per CRF (95% CI) [P]	0.41 (0.29, 0.59) [<0.0001]		0.41 (0.29, 0.58) [<0.0001]	
Pike Stratified HR Per IVRS (95% CI) [P]	0.40 (0.28, 0.57) [<0.0001]		0.40 (0.28, 0.57) [<0.0001]	

Figures 4 and 5 present the Kaplan-Meier Curves for FDA’s PFS based on the IRC IR and IRIO Measurements.

Figure 4 K-M Curves for FDA’s PFS Based on the IRC IR Measurements (ITT)

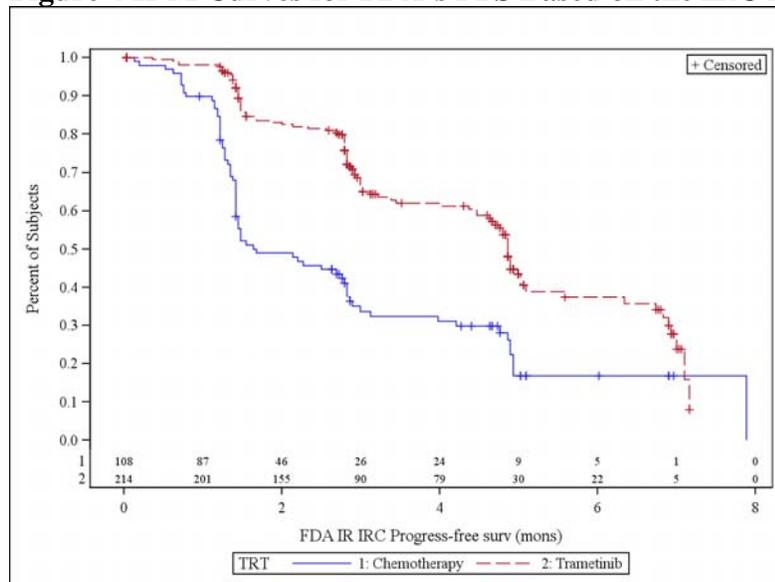
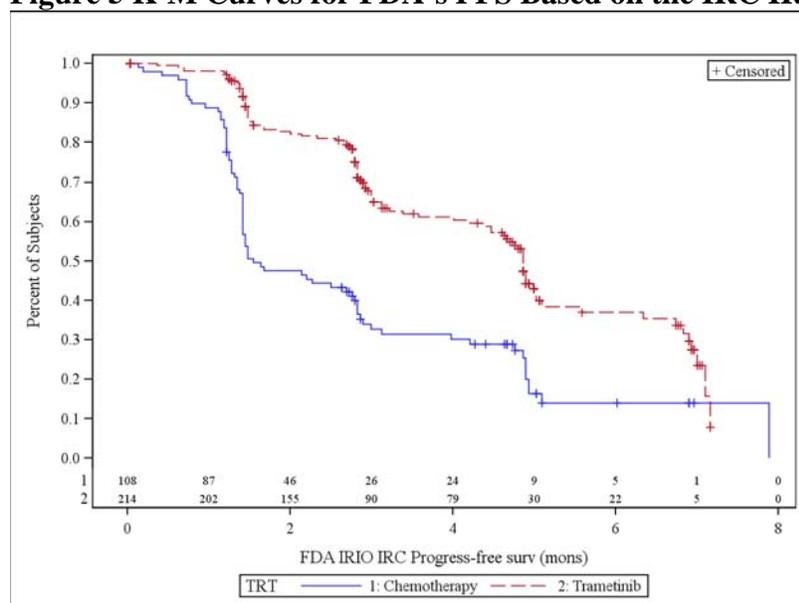


Figure 5 K-M Curves for FDA’s PFS Based on the IRC IRIO Measurements (ITT)



Reviewer’s Comments:

1. The applicant stated that “Due to the processes outlined in the IRC charter, the applicant utilized the response assessment and the response assessment date provided by the IRC.” Although the IRC response datasets (*e1) were claimed to be raw data, these datasets contained derived information without sufficient documentation to support tumor response durations based on the IRC IR and IRIO measurements.
2. The applicant suggested the reviewer to get independent oncologist evaluated PD from data RRESP2E1 without clear documentation (Figures A1 and A2). During the face to face meeting, even the applicant’s statisticians and programmers could not explain the meaning of variables and values in this data. In this reviewer’s opinion, it is unreliable to use independent oncologist assessment results with so many uncertainties.
3. With insufficient documentations and poor data quality, the reviewer could not duplicate data derivations and analysis. The key efficacy data and analysis had to be derived from raw IRC lesion assessment. The reviewer spent an inordinate amount of time, writing several thousand lines of SAS code, and deriving all the major efficacy endpoints from the raw data using SAP stated RECIST v1.1 criteria. After further IRs, face to face meeting, responses to IR, and amendments, the applicant agreed with the reviewer’s algorithm.
4. This reviewer conducted two sets of PFS analyses based on IRC IR and IRIO measurements as discussed in 3.2.3. Due to the uncertainties in IO measurement data, the reviewer considered PFS analysis based on IRIO results as the sensitivity PFS analyses.
5. Per FDA’s IRC PFS analysis, the magnitudes of treatment effect in terms of the difference in PFS medians were 3.2 and 3.4 months for IR and IRIO respectively. The results were similar to FDA’s INV PFS analysis.
6. Sensitivity analyses of PFS using different censoring rules ($p\text{-value} < 0.0001$) were similar to this reviewer’s IRC PFS analyses, as well as this reviewer’s INV PFS analyses.

7. *Time to INV and IRC tumor assessment was examined by this reviewer to detect systematic differences or substantial outliers. There was no difference in the time to scheduled visits between treatment arms.*

3.2.6.4 PFS Subgroup Analysis by BRAF Mutation

Tables 7-10 summarize PFS subgroup analysis results per INV, IRC IR, and IRC IRIO assessment by BRAF mutation.

Table 7 Subgroup PFS Analysis Results Based on the INV Measurements by BRAF Mutation Status

Mutation	Treatment	Event/ Censored	Median PFS (95%CI, Months)	Unstratified HR (95%CI)	
				Pike	Cox
V600E	Chemotherapy	69/28	1.4 (1.4, 2.7)	0.47 (0.33, 0.67)	0.45 (0.33, 0.62)
	Trametinib	99/85	4.8 (4.2, 4.9)		
V600K	Chemotherapy	8/3	1.5 (0.8, 4.9)	0.50 (0.18, 1.35)	0.48 (0.21, 1.12)
	Trametinib	18/9	4.8 (2.8, 4.9)		

Table 8 Subgroup PFS Analysis Results Based on the IRC IR Measurements by BRAF Mutation Status

Mutation	Treatment	Event/ Censored	Median PFS (95%CI, Months)	Unstratified HR (95%CI) [P]	
				Pike	Cox
V600E	Chemotherapy	65/32	2.1 (1.4, 2.8)	0.44 (0.31 , 0.64)	0.43 (0.31, 0.60)
	Trametinib	84/100	4.9 (4.7, 5.1)		
V600K	Chemotherapy	8/3	1.5 (0.8, 4.9)	0.41 (0.14 , 1.19)	0.39 (0.16, 0.95)
	Trametinib	14/15	4.9 (2.8, 5.6)		

Table 9 Subgroup PFS Analysis Results Based on the IRC IRIO Measurements by BRAF Mutation Status

Mutation	Treatment	Event/ Censored	Median PFS (95%CI, Months)	Unstratified HR (95%CI)	
				Pike	Cox
V600E	Chemotherapy	68/29	1.6 (1.4, 2.8)	0.44 (0.30 , 0.62)	0.42 (0.31, 0.58)
	Trametinib	86/98	4.9 (4.5, 5.0)		
V600K	Chemotherapy	8/3	1.5 (0.8, 4.9)	0.41 (0.14 , 1.19)	0.39 (0.16, 0.95)
	Trametinib	14/15	4.9 (2.8, 5.6)		

Reviewer's Comments:

These subgroup analyses are exploratory as discussed in section 3.2.4.

3.2.6.5 Secondary Endpoint - OS

Table 10 presents the efficacy analysis for OS with a total of 64 (20%) death events. The trametinib treated patients demonstrated a statistically significant difference in OS compared with the chemotherapy treated patients based on an unstratified log-rank test with a nominal p-value 0.0136. With a total of 64 (20%) deaths, the median survivals in the two study arms were not estimable. The unstratified Pike HR was 0.56 with 95% CI (0.33, 0.89). The unstratified Cox HR was 0.56 with 95% CI (0.34, 0.91). The median OS had not been reached. The OS data is immature and need further follow up.

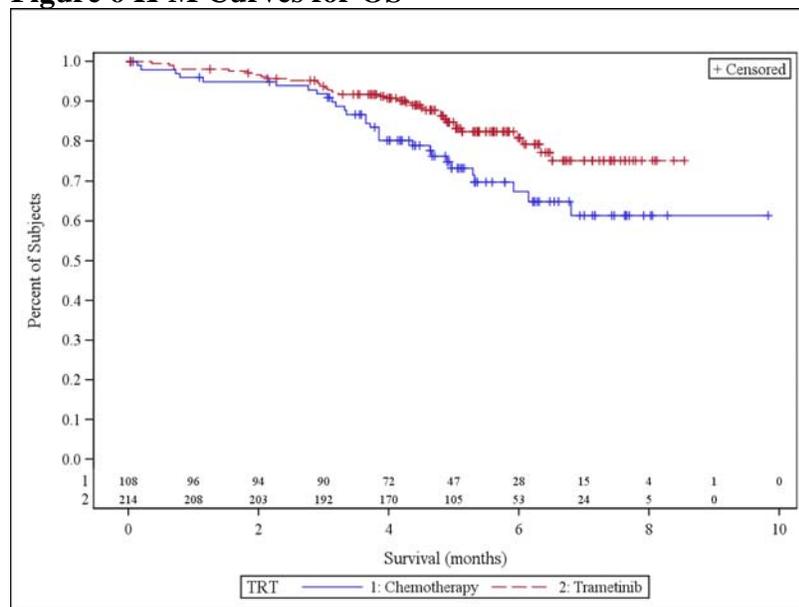
Table 10. OS Analyses (ITT)

	Trametinib N=214	Chemotherapy N=108
Number of deaths, n (%)	35 (16)	29 (27)
Median OS in months (95% CI)	NR(NR, NR)	NR(6.8, NR)
Unstratified Cox HR (95% CI) b	0.54 (0.33, 0.89)	
Un-stratified Log-Rank Test P-value	0.0136	
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 Per IVRS (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)	

NR: Not reached

Figure 6 presents the Kaplan-Meier Curves for OS.

Figure 6 K-M Curves for OS



Reviewer's Comments:

This OS analyses are exploratory as discussed in section 3.2.4.

3.2.6.6 OS subgroup analysis by BRAF Mutation

Table 11 summarizes OS subgroup analysis results by BRAF mutation.

Table 11 OS Subgroup Analyses by BRAF Mutation Status

Mutation	Treatment	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)		

NR: Not reached

Reviewer's Comments:*These subgroup analyses are exploratory as discussed in section 3.2.4.***3.2.6.7 Secondary Endpoint – ORR**

Table 13 presents the ORR analyses based on the INV measurements. Per INV assessments, trametinib demonstrated improvement in ORR (trametinib: 22.0% vs. chemotherapy: 8.3%) based on the nominal Fisher's exact test p-value 0.01. The ORR difference between the treatment arms was 13.7% (95%CI: 3.1%, 25.1%).

Table 12 ORR Results Based on the INV Measurements (ITT)

	Trametinib (N=214)	Chemotherapy (N=108)
Overall Response	47 (22.0%)	9 (8.3%)
Complete Response	4 (1.9%)	0
Partial Response	43 (20.1%)	9 (8.3%)
95% CI	(16.8%, 28.1%)	(3.9%, 15.2%)
Difference (95% CI)	13.7% (3.1%, 25.1%)	
Fisher's Exact Test P-value	0.01	

Table 12 presents the ORR analyses based on the IRC measurements. Per IR assessments, trametinib demonstrated improvement in ORR (trametinib: 19.2% vs. chemotherapy: 5.6%) based on the nominal Fisher's exact test p-value 0.003. The ORR difference between the treatment arms was 13.6% (95% CI: 3.5%, 24.7%). Per IRIO assessments, trametinib also demonstrated improvement in ORR (trametinib: 19.2% vs. chemotherapy: 4.6%) based on the nominal Fisher's exact p-value=0.007. The ORR difference between the treatment arms was 14.6% (95% CI: 2.6%, 25.5%).

Table 13 ORR Results Based on the IRC Measurements (ITT)

	IR		IRIO	
	Trametinib (N=214)	Chemotherapy (N=108)	Trametinib (N=214)	Chemotherapy (N=108)
Overall Response	41 (19.2%)	6 (5.6%)	41 (19.2%)	5 (4.6%)
Complete Response	0	1 (<1%)	0	1 (<1%)
Partial Response	41 (19%)	5 (5%)	41 (19%)	4 (4%)
95% CI	(14.1%, 25.1%)	(2.1%, 11.7%)	(14.1%, 25.1%)	(1.5%, 10.5%)
Difference (95% CI)	13.6% (3.5%, 24.7%)		14.6% (2.6%, 25.5%)	
Fisher's Exact Test P-value	0.007		0.003	

Reviewer's Comments:

ORR analyses are exploratory as discussed in section 3.2.4.

3.2.6.8 Subgroup Analyses for ORR by BRAF Mutation Status

Table 14 summarizes ORR subgroup analysis results based on INV measurements by BRAF mutation.

Table 14 ORR Subgroup Analyses Based on the INV Measurements by BRAF Mutation

	V600E		V600K	
	Trametinib (N=184)	Chemotherapy (N=97)	Trametinib (N=29)	Chemotherapy (N=11)
Overall Response	44 (23.9%)	7 (7.2%)	3 (10.3%)	2 (18.2%)
Complete Response	4 (2.2%)	0	0	0
Partial Response	40 (21.7%)	7 (7.2%)	3 (10.3%)	2 (18.2%)
95% CI	(17.9%, 30.7%)	(3.0%, 14.3%)	(2.3%, 27.4%)	(2.3%, 51.8%)

Table 15 summarizes ORR subgroup analysis results based on the IRC IR measurements by BRAF mutation.

Table 15 ORR Subgroup Analyses Based on the IRC IR Measurements by BRAF Mutation

	V600E		V600K	
	Trametinib (N=184)	Chemotherapy (N=97)	Trametinib (N=29)	Chemotherapy (N=11)
Overall Response	34 (18.5%)	4 (4.1%)	7 (24.1%)	2 (18.2%)
Complete Response	0	0	0	1 (9.1%)
Partial Response	34 (18.5%)	4 (4.1%)	7 (24.1%)	1 (9.1%)
95% CI	(13.1%, 24.9%)	(1.1%, 10.2%)	(10.3%, 43.5%)	(2.3%, 51.8%)

Table 16 summarizes ORR subgroup analysis results based on IRC IRIO measurements by BRAF mutation.

Table 16 ORR Subgroup Analyses Based on the IRC IRIO Measurements by BRAF Mutation

	V600E		V600K	
	Trametinib (N=184)	Chemotherapy (N=97)	Trametinib (N=29)	Chemotherapy (N=11)
Overall Response	34 (18.5%)	3 (3.1%)	7 (24.1%)	2 (18.2%)
Complete Response	0	0	0	1 (9.1%)
Partial Response	34 (18.5%)	3 (3.1%)	7 (24.1%)	1 (9.1%)
95% CI	(13.1%, 24.9%)	(0.6%, 8.8%)	(10.3%, 43.5%)	(2.3%, 51.8%)

Reviewer's Comments:

ORR subgroup analyses are exploratory as the issue discussed in section 3.2.4.

3.2.6.9 Secondary Endpoint – DoR

Table 17 presents the DoR analyses results based on the INV measurements. This data is immature and need further follow up.

Table 17 DoR Analyses Based on the INV Measurements

	Trametinib (N=47)	Chemotherapy (N=9)
Events	12	2
PD	12	2
Death	0	0
Median in months (95% CI)	5.5 (4.1, 5.9)	NR (3.5, NR)

NR: Not reached

Table 18 presents the DoR analysis results based on the IRC measurements. This data is immature and needs further follow up.

Table 18 DoR Analyses Based on the IRC Measurements

	IR		IRIO	
	Trametinib (N=41)	Chemotherapy (N=6)	Trametinib (N=41)	Chemotherapy (N=5)
Events	8	1	8	1
PD	8	1	8	1
Death	0	0	0	0
Median in months (95% CI)	5.6 (3.8, 5.9)	NR (3.5, NR)	5.6 (3.8, 5.9)	NR (3.5, NR)

NR: Not reached

3.2.6.10 DoR Subgroup Analysis by BRAF Mutation Status

Table 19 presents the DoR subgroup analysis Results based on the INV measurements. This DoR information was immature and needs further follow up.

Table 19 DoR Subgroup Analysis Based on INV Measurements by BRAF Mutation Status

	V600E		V600K	
	Trametinib (N=44)	Chemotherapy (N=7)	Trametinib (N=3)	Chemotherapy (N=2)
Median in months (95% CI)	5.5 (3.6, 5.9)	NR (3.5, NR)	4.1 (NR, NR)	NR (NR, NR)

NR: Not reached

Table 20 presents the DoR subgroup analysis results based on the IRC IR measurements by BRAF mutation status. This DoR results were immature and needs further follow up.

Table 20 DoR Subgroup Analysis Based on IRC IR Measurements by BRAF Mutation Status

	V600E		V600K	
	Trametinib (N=34)	Chemotherapy (N=4)	Trametinib (N=7)	Chemotherapy (N=2)
Median in months (95% CI)	5.6 (3.8, 5.9)	NR (3.5, NR)	4.1 (NR, NR)	NR (NR, NR)

NR: Not reached

Table 21 presents the DoR subgroup analysis Results based on the IRC IRIO measurements. This DoR information was immature and needs further follow up.

Table 21 DoR Subgroup Analysis Based on IRC IRIO Measurements by BRAF Mutation Status

	V600E		V600K	
	Trametinib (N=34)	Chemotherapy (N=3)	Trametinib (N=7)	Chemotherapy (N=2)
Median in months (95% CI)	5.6 (3.8, 5.9)	NR (3.5, NR)	4.1 (NR, NR)	NR (NR, NR)

NR: Not reached

Reviewer's Comments:

DoR subgroup analyses are exploratory due to lack of randomization and also as discussed in section 3.2.4.

3.3 Evaluation of Safety

Please refer the clinical review of this application for safety evaluation.

3.4 Benefit/Risk Ratio

Trametinib arm demonstrated a statistically significant improvement in the primary endpoint PFS per INV assessment compared with the chemotherapy arm. Longer OS and bigger ORR were observed. Whether the submission demonstrated an overall favorable benefit vs. risk profile for trametinib arm is deferred to the clinical team reviewing this submission.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 PFS Subgroup Analysis

Table 22 summarizes PFS subgroup analysis results based on INV measurements..

Table 22 PFS (Months) Subgroup Analysis Based on INV Measurements

		Diff in Median PFS	Event/Censor (TRT: KMO)	HR (95% CI)*	HR (95% CI)**
Male		3.0	73/47: 36/17	0.52 (0.33 , 0.83)	0.51 (0.34, 0.77)
Female		3.4	44/50:41/14	0.38 (0.24 , 0.62)	0.36 (0.24, 0.56)
Age	<65	3.4	90/75: 62/24	0.44 (0.30 , 0.64)	0.43 (0.31, 0.59)
	≥ 65	2.9	27/22: 15/7	0.58 (0.29 , 1.18)	0.58 (0.31, 1.09)
East Europe		3.4	13/18: 12/5	0.32 (0.12 , 0.81)	0.29 (0.13, 0.66)
North America		0.5	16/6: 8/4	0.58 (0.23 , 1.44)	0.55 (0.23, 1.29)
Oceania		3.6	10/9: 12/1	0.37 (0.15 , 0.91)	0.34 (0.14, 0.80)
West Europe		3.2	78/63: 43/20	0.52 (0.34 , 0.80)	0.51 (0.35, 0.74)

*HRs were estimated using unstratified Pike Estimate; ** HRs were estimated using unstratified Cox Estimate; TRT: Trametinib; KMO: chemotherapy; Oceania: Australia and New Zealand

Table 23 summarizes PFS subgroup analysis results based on IRC IR measurements..

Table 23 PFS (Months) Subgroup Analysis Based on IRC IR Measurements

		Diff in Median PFS	Event/Censor (TRT: KMO)	HR (95% CI)*	HR (95% CI)**
Male		3.3	57/63: 35/18	0.47 (0.29 , 0.77)	0.46 (0.30, 0.71)
Female		2.6	43/51:41/14	0.38 (0.23 , 0.61)	0.36 (0.23, 0.55)
Age	<65	3.5	76/89: 62/24	0.38 (0.26 , 0.57)	0.37 (0.26, 0.52)
	≥ 65	2.0	24/25: 14/8	0.64 (0.31 , 1.31)	0.63 (0.32, 1.23)
East Europe		3.5	16/15: 10/7	0.40 (0.15 , 1.04)	0.36 (0.16, 0.83)
North America		0.5	12/10: 8/5	0.77 (0.31 , 1.95)	0.74 (0.29, 1.92)
Oceania		3.7	7/12: 12/1	0.22 (0.08 , 0.61)	0.21 (0.08, 0.53)
West Europe		2.8	64/77: 45/18	0.43 (0.28 , 0.67)	0.42 (0.29, 0.62)

*HRs were estimated using unstratified Pike Estimate; ** HRs were estimated using unstratified Cox Estimate; TRT: Trametinib; KMO: chemotherapy; Oceania: Australia and New Zealand

Table 24 summarizes PFS subgroup analysis results based on IRC IRIO measurements.

Table 24 PFS (Months) Subgroup Analysis Based on IRC IRIO Measurements

		Diff in Median PFS	Event/Censor (TRT: KMO)	HR (95% CI)*	HR (95% CI)**
Male		3.3	55/65: 33/ 20	0.48 (0.29 , 0.79)	0.47 (0.30, 0.73)
Female		2.6	43/51:40/15	0.38 (0.23 , 0.62)	0.36 (0.23, 0.56)
Age	<65	3.4	74/91: 60/26	0.39 (0.26 , 0.57)	0.37 (0.26, 0.52)
	≥ 65	2.0	24/ 25: 13/9	0.67 (0.32 , 1.39)	0.66 (0.33, 1.31)
East Europe		2.7	16/15: 8/9	0.45 (0.16 , 1.27)	0.42 (0.17, 1.04)

	Diff in Median PFS	Event/Censor (TRT: KMO)	HR (95% CI)*	HR (95% CI)**
North America	0.5	12/10: 8/5	0.77 (0.31 , 1.95)	0.75 (0.29, 1.92)
Oceania	3.7	6/13: 11/2	0.21 (0.07 , 0.60)	0.19 (0.07, 0.52)
West Europe	2.8	63/78: 45/the 18	0.43 (0.27 , 0.67)	0.42 (0.28, 0.61)

* HRs were estimated using unstratified Pike Estimate; ** HRs were estimated using unstratified Cox Estimate the; TRT: Trametinib; KMO: chemotherapy; Oceania: Australia and New Zealand

Reviewer's comment:

The HRs of PFS in the subgroup analyses are less than 1. However, these analyses are exploratory due to small sample size.

5 SUMMARY AND CONCLUSIONS

In this New Drug Application (NDA), the applicant is seeking a regular approval of Mekinist® (trametinib, formerly GSK1120212 and JTP-74057), a kinase inhibitor, for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations as detected by an FDA-approved test indicated for this use, who have not received BRAF inhibitor therapy. The pivotal study MEK114267 supporting the application was a randomized, open-label, active-controlled multinational phase III trial.

5.1 Statistical Issues

The following are some statistical issues in the submission:

- The quality of the original data submission was not acceptable. Problems included poor data organization and management, missing data variables, data sets and documents, un-executable SAS programs, and lack of documentation on every part of the data submission.
- The applicant failed to submit a complete set of adequate and reviewable information despite multiple and repeated requests by the review team. The applicant also failed to provide information at the requested timeline.
- The applicant could not provide adequate documentation to validate their analysis data, the final PFS, ORR, and DoR information used in this review was derived by the reviewer from raw lesion visit data per IRC IR measurement using RECIST 1.1 criteria under that assumption that the submitted raw data were valid and reliable.
- The primary analysis population was defined as ITT, PE, and ITT populations in protocol, Amendment 3, and Pre-NDA submission, respectively. This reviewer used the ITT population as the primary analysis set for efficacy results.
- FDA did not review the applicant's final SAP
 - Without SAP to do multiplicity adjustment, the secondary endpoints and subgroup analyses were considered as exploratory.
 - The stratification factor baseline LDH used post randomization lab test results and/or imputed from baseline LDH value per IVRS system. This invalidated the randomization and caused potential bias. *This reviewer used the unstratified efficacy analyses as primary efficacy analysis methods.*

5.2 Collective Evidence

The data and analyses from the study MEK114267 demonstrated that the trametinib had statistically significant improvement in the PFS when compared with chemotherapy.

Per INV assessment, the un-stratified log-rank test p-value for PFS comparison was <0.0001. The median PFS was 4.8 (95% CI: 4.3, 4.9) months for the trametinib arm and 1.3 (95% CI: 1.4, 2.7) months for the chemotherapy arm. The un-stratified Cox proportional hazard ratio (HR) was 0.46 with 95% CI (0.34, 0.61). The un-stratified Pike HR was 0.47 with 95% CI (0.34, 0.65).

Per independent radiologist (IR) assessment, the un-stratified log-rank test p-value for PFS comparison was <0.0001. The median PFS was 4.9 (95% CI: 4.7, 5.1) months for the trametinib arm and 2.2 (95% CI: 1.4, 2.8) months for the chemotherapy arm. The un-stratified Cox proportional hazard ratio (HR) was 0.43 with 95% CI (0.31, 0.58). The un-stratified Pike HR was 0.44 with 95% CI (0.31, 0.62).

Per IRIO assessment, there were a total of 176 (55%) progressive disease or death events. Trametinib demonstrated a statistically significant difference in PFS compared with the chemotherapy based on a unstratified log-rank test with a p-value <0.0001. The median PFS was 4.9 months (95% CI: 4.5, 5.0) for the trametinib arm and 1.5 months (95% CI: 1.4, 2.8) for the chemotherapy arm. The unstratified Pike HR was 0.43 with 95% CI (0.30, 0.60).

Trametinib had longer OS compared with chemotherapy. With a total of 64 (20%) deaths, the median survivals in the two study arms were not estimable. The OS data was immature and needs further follow up. The nominal p-value from an unstratified log-rank test was 0.0136. The unstratified Cox proportional HR was 0.56 with 95% CI (0.34, 0.91). The unstratified Pike HR was 0.56 with 95% CI (0.33, 0.95). The median OS had not been reached.

Trametinib also showed bigger ORR (22.0%) compared with chemotherapy (8.3%) per INV measurement. Based on the Fisher's exact, the nominal p-value is 0.007. The ORR difference between the treatment arms was 13.7% (95%CI: 3.1%, 25.17%).

The median DoR in the two study arms were not estimable. Further follow up is needed to collect more information on DoR.

5.3 Conclusions and Recommendations

Trametinib arm demonstrated a statistically significant improvement in the primary endpoint PFS per INV assessment. Longer OS and bigger ORR were observed. Whether the submission demonstrated an overall favorable benefit vs. risk profile for trametinib arm is deferred to the clinical team reviewing this submission.

5.4 Labeling recommendation

- The primary analysis set for the efficacy results are the ITT population
- The PFS results should be updated based on this reviewer's calculation which was derived from raw lesion assessment per IRC IR measurements.
- The [REDACTED] (b) (4) It is recommended not include these [REDACTED] (b) (4)
- The results of ORR (exclude the Fisher Exact test p-value) per INV measurements may be included in the label to provide further information to the clinician.
- Because very few responders' disease had progressed (14/56), DoR can not be reliable estimated.

APPENDIX 1: Summary of Raw Lesion and Raw Response Data

The following table summarizes the raw lesion datasets and response datasets submitted. These datasets contain the key data variables for the derivation of the efficacy analysis including PFS and ORR. As discussed in the review, the applicant’s analysis datasets were derived based on the raw response data, while this review used the raw lesion data for the derivation of the analysis datasets. This review does not consider the submitted response data as raw data but external data that lack of necessary documentations.

Table A1 Summary of Raw Lesion and Response Data

Dataset Name	Assessment	Definition	Included Information	Comments
Rlesion	INV	lesion	date, longest diameter, lesion location, organ name, scan type	A total of 6257 records for 322 patients.
Rlesioe1	IRC	lesion	date, longest diameter, location, organ name, scan type	A total of 5157 records for 319 patients.
Rresp1	INV	visit response	non-target lesion response, target lesion response type, response assessment type, response index code, all lymph node short axis < 10 mm, sum of lesion diameters, sum of lesion diameter at nadir, % change from baseline, % change from nadir, abs change from nadir, new lesion (equivocal: Y/N)	A total of 766 records for 300 patients. This is not a raw data set and it lacks information for derivation of the key variables. Missing documentation on: <ul style="list-style-type: none"> • meaning of nadir • % change from baseline • % change from nadir, • response index code • how to define new lesion based on external data • How to calculate the sum of lesion diameters at nadir
Rresp1e1	IR	IRC visit response	Non-target lesion response, Target lesion response type, response assessment type, response index code (best vs. other), Sum of lesion diameters, Sum of lesion diameter at baseline, % change from baseline, % change from nadir, New lesion (equivocal: Y/N)	A total of 5157 records for 319 patients. This is not a raw data set and it lacks information for derivation of the key variables. Missing documentation on: <ul style="list-style-type: none"> • meaning of nadir • abs change from nadir • lymph node short axis <10mm • % change from baseline • % change from nadir, • meaning of response index code • derive PD without abs change?
Rresp2e1 (Figures A1 and A2)	IR and IO	IRC best Overall Response	“read type” , “Clinical information impact the radio. Assessment?”, “response index code, “clinical radiologic data quality acceptable?”, date of progression	A total of 318 records for 318 patients. All variables except subject id were labeled as external data. Missing documentation on every variable except subject id.

IR: Independent radiologist IO: Independent Oncologist; INV: Investigator assessment

Figure A1 Snapshot of RRESP2E1 in SAS Format

	Unique identifier for the study	Subject ID	Clinical radiologic data quality acpt?	Clinical info impact the radiologic asmt	Date of progression	Response index code	Oncology assessment source code	Oncology criteria type code	Oncology independent review vendor code	Read type code
1	MEK114267	400076	Y	N	12SEP2011	2	3	11	3	11
2	MEK114267	400241	Y		12AUG2011	2	3	11	3	11
3	MEK114267	400251	Y		23SEP2011	2	3	11	3	11
4	MEK114267	400252	Y		22SEP2011	2	3	11	3	11
5	MEK114267	400261	Y		10JUN2011	2	3	11	3	11
6	MEK114267	400263	Y		07JUL2011	2	3	11	3	11
7	MEK114267	400264	Y	N	13JUN2011	2	3	11	3	11
8	MEK114267	400265	Y		04OCT2011	2	3	11	3	11
9	MEK114267	400377	N		24AUG2011	2	3	11	3	11
10	MEK114267	400512	Y		14JUN2011	2	3	11	3	11
11	MEK114267	400576	Y		05JUL2011	2	3	11	3	11
12	MEK114267	400578	Y		23AUG2011	2	3	11	3	11
13	MEK114267	400700	N		29JUN2011	2	3	11	3	11
14	MEK114267	400706	Y		01AUG2011	2	3	11	3	11
15	MEK114267	400712	Y		13JUL2011	2	3	11	3	11
16	MEK114267	400827	Y		12AUG2011	2	3	11	3	11
17	MEK114267	400850	Y		27JUL2011	2	3	11	3	11
18	MEK114267	400853	Y		27JUL2011	2	3	11	3	11
19	MEK114267	401004	Y		21JUL2011	2	3	11	3	11
20	MEK114267	401085	Y		07JUN2011	2	3	11	3	11
21	MEK114267	401106	Y	N	24AUG2011	2	3	11	3	11
22	MEK114267	401206	Y		18AUG2011	2	3	11	3	11
23	MEK114267	401209	Y		26OCT2011	2	3	11	3	11
24	MEK114267	401210	Y	N	07SEP2011	2	3	11	3	11
25	MEK114267	401227	N		09AUG2011	2	3	11	3	11
26	MEK114267	401254	Y		23MAY2011	2	3	11	3	11
27	MEK114267	401271	Y	N	17OCT2011	2	3	11	3	11
28	MEK114267	401277	Y		14APR2011	2	3	11	3	11
29	MEK114267	401278	Y	N	02MAY2011	2	3	11	3	11

Figure A2 Snapshot of the Define File for RRESP2E1

Study mek114267 - rresp2e1(IRC best overall response)				
Variable	Type	Label	Codes	Comments
STUDYID	Char	Unique identifier for the study		EXTERNAL DATA: Data provided by external vendor blankcrf, Page 1
USUBJID	Char	Unique subject ID		DERIVED DATA: STUDYID ':' SUBJID
SUBJID	Num	Subject ID		EXTERNAL DATA: Data provided by external vendor blankcrf, Page 8
ONSRCCD	Char	Oncology assessment source code	1=Investigator 2=Independent radiologist 3=Independent oncologist	EXTERNAL DATA: Data provided by external vendor
ONTYPECD	Char	Oncology criteria type code	11=RECIST 1.1	EXTERNAL DATA: Data provided by external vendor
PROGDT	Date	Date of progression		EXTERNAL DATA: Data provided by external vendor
ONVENDCD	Char	Oncology independent review vendor code	3=Perceptive	EXTERNAL DATA: Data provided by external vendor
CLIMPACT	Char	Clinical info impact the radiologic asm		EXTERNAL DATA: Data provided by external vendor
RDTYPECD	Char	Read type code		EXTERNAL DATA: Data provided by external vendor
REVID	Char	Reviewer ID		EXTERNAL DATA: Data provided by external vendor
RSPIXCD	Char	Response index code		EXTERNAL DATA: Data provided by external vendor
ACQUAL	Char	Clinical radiologic data quality acpt?		EXTERNAL DATA: Data provided by external vendor

APPENDIX 2: Formal Information Requests Sent to The Applicant

Information Request 1: 07/30/2012

From: Griffin, Norma [mailto:Norma.Griffin@fda.hhs.gov]

Sent: Monday, July 30, 2012 11:31 AM

To: Eric Richards

Subject: NDA 204114 GSK for Trametinib - Information Request - Clinical Site Selection Model Dataset

Importance: High

Good Morning Eric,

I refer to the revised clinical site datasets received on 7/13/2012. Our OSI Team notes the following:

"We continue to have difficulties with load of the dataset provided into the site selection model. Why is endpoint "Progression Free Survival" not included for the Chemotherapy arm for Study 114267 in the dataset submitted in response to OSI request (Part 3 of OSI requests)?"

Thank you in advance for a response,

Norma S. Griffin

Regulatory Health Project Manager

Division of Oncology Products 2

Office of Hematology and Oncology Products

Center for Drug Evaluation and Research

Email: Norma.Griffin@fda.hhs.gov

Telephone 301.796.4255

Information Request 2: 08/13/2012



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

Memorandum

Date: August 13, 2012
From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDAs 202806 and 204114; GlaxoSmithKline, LLC
Comments and Information Request

GlaxoSmithKline, LLC
Eric Richards / Ellen S. Cutler
Global Regulatory Affairs
1250 South Collegeville Road
Collegeville, PA, 19426

Dear Eric / Ellen:

Please refer to your New Drug Applications (NDAs) NDA 202806 and NDA 204114 for products: (b) (4) dabrafenib and Mekinist (trametinib)."

We are currently reviewing your submissions of July 30, 2012, and August 2, 2012, and have the following comments. These are being provided to you in advance of our teleconference scheduled for this afternoon, August 13, 2012 (3:00 pm ET).

1. Please identify the location and the names of all raw datasets in the NDAs since a separate folder containing the raw datasets could not be located.
2. Provide clarification of the structure of the primary dataset, e.g., onctte.
3. Please clarify whether the "Annotated Design For Trial" is identical to the Annotated CRF because the file is under the "blankcrf.pdf".
4. Provide the SAS programs as well as format library files used to create the derived datasets for the efficacy endpoints and the SAS programs used for efficacy data analysis. If the SAS programs use any SAS macro, please provide all necessary macro programs.
5. Provide SAS programs for derived datasets and the analyses associated with the results presented in the proposed package insert.
6. Provide the location in NDA 202806 that identifies the version of MedDRA used to code adverse event terms for each trial included in the integrated summary of safety.

Please contact me if you have any questions or concerns at (301) 796-4255 or at Norma.Griffin@fda.hhs.gov.

Reference ID: 3173698

Information Request 3: 08/14/2012



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

Memorandum

Date: August 14, 2012
From: Nomma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDAs 202806 and 204114; GlaxoSmithKline, LLC
FDA Response to GSK Questions

GlaxoSmithKline, LLC
Eric Richards / Ellen S. Cutler
Global Regulatory Affairs
1250 South Collegeville Road
Collegeville, PA, 19426

Dear Eric / Ellen:

Please refer to your New Drug Applications (NDAs) NDA 202806 and NDA 204114 for products (b) (4) (dabrafenib) and Mekinist (trametinib)."

We refer to our teleconference of August 13, 2012 (3:00 pm ET) and to your email correspondence of August 13 and August 14, 2012, as follow up inquiries to the August 13, 2012, teleconference. Please see FDA responses to your questions below:

1. **GSK Question (via August 13, 2012 email correspondence):** On request #4 [Comment #4], it was our understand that the review team wanted to receive SAS programming that supports section 5 and 6 of the Phase III clinical study reports. Sections 5 and 6 of the reports are Study Population Results and Efficacy Results. But we thought it was clear on the phone that the reviewers wanted the SAS programming that supported the Efficacy and Safety Results from each Phase III clinical study report; in which case, that would be Section 6 and 7. Would it be possible to get clarity on this?

FDA Response of August 14, 2012: For Comment #4, the request is for SAS codes which produce results in sections 5 and 6. For Comment #5, the request is for SAS codes which produce the efficacy and safety presented in the labeling.

For efficacy, SAS codes which produce the results in sections 5 and 6 usually cover those in the labeling.

For safety, SAS codes which produce section 7 may not be identical to those in the labeling. If the SAS codes which produce section 7 cover those in the labeling, then please just submit the SAS codes which produce the results in section 7.

2. **GSK Question (via August 13, 2012 email correspondence)**: I'm [GSK is] going to follow-up with our clinical pharmacology group, but would it possible to find out from the FDA clinical pharmacology team if they will need similar SAS programs? This is a tremendous amount of work and while we are happy to give the Division what it needs, we also want to ensure that the individual reviewers need it.

FDA Response August 14, 2012: Datasets as SAS transport files should be submitted for all the clinical pharmacology studies. Please refer to the pre-NDA meeting minutes. In addition, please submit all the major program codes (e.g. SAS, NONMEM, S-PLUS, WinNonLin, etc) for each individual and population PK analyses.

3. **GSK Question (via August 14, 2012 email correspondence)**: Through our discussions the differences between PC-SAS versions 9.1 and 9.2 (let alone 9.3) was noted. We want to make sure we are testing the programs in the same environment as the FDA will be executing them. We presently have versions 9.1 and 9.2 available to us. Can the Agency confirm which version will be acceptable?

FDA Response August 14, 2012: Please use version 9.2

Please contact me if you have any questions or concerns at (301) 796-4255 or at Norma.Griffin@fda.hhs.gov.

Information Request 4: 09/06/2012



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

Memorandum

Date: September 6, 2012
From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 204114; GlaxoSmithKline, LLC
Clinical Comments and Information Request

GlaxoSmithKline, LLC
Eric Richards
Global Regulatory Affairs
1250 South Collegeville Road
Collegeville, PA, 19426

Dear Mr. Richards:

We refer to your amendment to NDA 204114 submitted on August 3, 2012, which completed the NDA rolling submission. On review of NDA 204114, we have the following information request:

1. Submit the raw datasets, in SAS transport file format, for trial MEK113583.
2. Submit narrative summaries for all deaths that occurred, including deaths attributed to disease progression, on trials included in the safety population. In the narratives, include the following information:
 - a. subject age and gender
 - b. signs and symptoms related to the adverse event being discussed
 - c. an assessment of the relationship of exposure duration to the development of the adverse event
 - d. pertinent medical history
 - e. concomitant medications with start dates relative to the adverse event
 - f. pertinent physical exam findings
 - g. pertinent test results (for example: lab data, ECG data, biopsy data)
 - h. discussion of the diagnosis as supported by available clinical data

Reference ID: 3185808

- i. a list of the differential diagnoses, for events without a definitive diagnosis
 - j. treatment provided
 - k. re-challenge and de-challenge results (if performed)
 - l. outcomes and follow-up information
 - m. an informed discussion of the case, allowing a better understanding of what the subject experienced.
3. Submit revised annotated CRFs for each trial which contain links (functional hyperlinks) to the document that defines the variable name and lists the raw dataset that contains the specific item. Please note that each link should be at the level of the individual variable.
4. The raw datasets provided for trial MEK114267 do not appear to include the serious adverse event criteria met by the AE. Please identify the location of the dataset for trial MEK114267 that contains the following SAE variables:
 - a. AESERDTH
 - b. AESERLIF
 - c. AESERHOS
 - d. AESERDIS
 - e. AESERCON
 - f. AESEROTH
 - g. AESERNPR

If this information is not included in the submission, submit a revised raw AE dataset for trial MEK114267 that includes all data for these variables.

5. For investigators that have selected multiple actions taken for the investigational product as a result of the AE on the CRF, i.e. variables “AE.ADACTCD” and “AE_SER.ADACTCD, how was the most clinically significant action taken as a result of the AE, i.e. variables “AE.AEACTRCD” and “AE_SER.AEACTRCD” assigned either by the investigator or GSK.
6. The “Adverse event detail” raw dataset for trial MEK114267 includes a variable “ADTYPCD” which could not be found in the corresponding define file or in the annotated blank CRF. Please define this variable.

7. In regard to the “Time and Events Schedule for Study: MEK114267_jrm7” on Pages 2-5 of the annotated CRF for trial MEK114267, please provide a detailed description of the information that is listed under each visit column for each row (CRF). For example, under the Unscheduled (UNSH) [S/O/R] column, there is a “1” listed in the “Date of Visit/Assessment” row, a “4-DF” listed in the “ECOG Performance Status Scale” row, an “11-DF” listed in the Echocardiogram row, and “9-DF” listed in the “Biomarker samples using Covance” row, etc.

Please note that I will be out of the office the week of September 10-14, 2012, and my colleague Meredith Libeg will be covering this for me. Please ensure that your response is emailed to both Meredith Libeg (Meredith.Libeg@fda.hhs.gov), and myself at Norma.Griffin@fda.hhs.gov

Please contact me if you have any questions or concerns at (301) 796-4255 or at Norma.Griffin@fda.hhs.gov.

Information Request 5: 09/10/2012



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

Memorandum

Date: September 10, 2012
From: Meredith Libeg, RPM DOP2/OHOP/CDER/FDA
Subject: NDAs 202806 and 204114; GlaxoSmithKline, LLC (GSK)
Statistical Comments and Information Request

GlaxoSmithKline, LLC
Eric Richards / Ellen S. Cutler
Global Regulatory Affairs
1250 South Collegeville Road
Collegeville, PA, 19426

Dear Eric / Ellen:

Please refer to your New Drug Applications (NDAs) NDA 202806 and NDA 204114 for products (b) (4) (dabrafenib) and Mekinist (trametinib)."

We also refer to your August 15, 2012, August 17, 2012, August 23, 2012, and September 6, 2012 amendments containing your response to our Statistical Information Request of August 13, 2012. Based on our review of these submissions, our Statistical Reviewer has the following comments and requests for information as the previous submissions did not meet the requirements of the Information Request:

The following items apply to Studies BRF113683, BRF113929, and BRF113710 for NDA 202806 and Studies MEK114267 and MEK113583 for NDA 204114.

1. Identify the locations and all the names of all raw data sets and variables in the NDAs since a separate folder containing the raw datasets could not be located. For example, add a column in your define file to identify each variable as raw or derived.
2. Provide clarification and description of the structure of all datasets submitted, i.e. provide a pdf document that summarizes the contents of each dataset, including but not limited to, the sort key(s), number of observations per patient.
3. All datasets should use "usubjid" as the unique patient identifier.
4. Differentiate the dataset names for raw datasets and derived datasets.

Reference ID: 3186985

5. In the define file, provide the hyperlinks of the variables and datasets that have been used in deriving the analysis data, and the hyperlinks of the raw data variables in the annotated CRF. Provide adequate comment for variable label, data format decode of categorical and numerical variable(s), and algorithm(s) to derive new variable from raw data to derived data. Consolidate the define file for all datasets into one pdf file. Provide a dataset for efficacy analyses at subject level, i.e., each patient has one record.
6. Provide a dataset for efficacy analyses at subject level, i.e., each patient has one record.
7. Provide a dataset with complete demographic, baseline characteristics and screening information at subject level.
8. Provide the SAS programs as well as format library files used to create the derived datasets for the efficacy endpoints and the SAS programs used for efficacy data analysis. If the SAS programs use any SAS macro, please provide all necessary macro programs. Provide an all-in-one SAS format library.
9. Provide SAS programs for derived datasets and the analyses associated with the results presented in the proposed package insert.
10. Provide adequate documentation for all SAS programs.
11. Provide a document that clarifies the imputation methods. If GSK did not impute the data for efficacy analysis, it should be clearly stated and explained.
12. Provide the locations of the meeting minutes and reports to DSMB in the CSR.

Please provide a response to the above comments and requested information to your **NDA** (NDA 202806 and NDA 204114) by Friday, September 21, 2012, or sooner if possible. All information should be contained in one submission for each application. Additionally, the cover letter should detail the volume and page number, (i.e., specific location) where each response can be located.

Please contact your assigned RPM if you have any questions or concerns at (301) 796-4255 or at Norma.Griffin@fda.hhs.gov. During her absence, please free to contact me at meredith.libeg@fda.hhs.gov or (301.796.1721)

Information Request 6: 10/25/2012



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

Memorandum

Date: October 25, 2012
From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 204114; GlaxoSmithKline, LLC
 Statistical Comments and Request for Teleconference

GlaxoSmithKline, LLC
 Eric Richards
 Global Regulatory Affairs
 1250 South Collegeville Road
 Collegeville, PA, 19426

Dear Mr. Richards:

We refer to your amendment to NDA 204114 submitted on August 3, 2012, for Mekinist (trametinib). Our Statistical Reviewer has the following comments and requests a teleconference for Friday, October 26, 2012 to discuss the following issues in this information request and to obtain responses:

1. Reference is made to the “Response to September 10, 2010 FDA Request –Statistical”.
 - For FDA Request 8: GSK stated that “GSK is proposed to submit . . .All Programs which create the derived datasets from the raw data. . .” Please identify the location of program to derive the dataset DEMOBASE and ONCTTERN.
 - For FDA Request 12. Please identify the location of reports to IDMC.
2. As you stated in the final SAP (dated on Nov 4th 2011), there was no plan for interim analysis. However, based on IDMC meeting minutes, two interim analyses were conducted on Study MEK114267 (dated on June 13, 2011 and Oct 24, 2011). Please clarify whether you had conducted efficacy interim efficacy analyses. If yes, please provide detailed interim analysis reports to IDMC.
3. The statistical reviewer thought that your calculation was incorrect on VNBTC D since the pop.ptxmet should be replaced by pop. PRCTX (On Page 133 of 528 define.pdf)

VNBTC D	Num	V600E No Brain Mets/Prior Chemo code	DERIVED DATA: POP.V600E='Y' and POP.PBMET='N' and POP.PTXMET='Y', then VNBTC D=1; else VNBTC D=0.
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If you do not agree, please provide your rationale. Otherwise, please update all the related analysis results.

4. On Section 4.8.2.2 of CSR, you stated that “In the stratified efficacy analyses, missing LDH were imputed based on the stratification reported in the IVRS at the time of randomization.”
- Please clarify whether your stratification factors were CRF based?
 - If so, please provide a dataset in transport format which includes IVRS based stratification factors as well as sort key USUBJID.
5. Please clarify the algorithm to derived baseline variable LDHCD in the DEMOBASE dataset from the raw lab test results (LAB). Based on the statistical reviewer’s calculation, there were $(2+1+7+4)=14$ discordances.

BASELDH_HIGH	LDHCD(Baseline LDH code)			Total
Frequency	0	1		
Percent				
Row Pct				
Col Pct				
3	2	1		6
0.93	0.62	0.31		1.86
50.00	33.33	16.67		
100.00	1.00	0.84		
0	194	7		201
0.00	60.25	2.17		62.42
0.00	96.52	3.48		
0.00	97.00	5.88		
1	4	111		115
0.00	1.24	34.47		35.71
0.00	3.48	96.52		
0.00	2.00	93.28		
Total	3	200	119	322
	0.93	62.11	36.96	100.00

```

/* Used SAS program */
/*Eval % missing in baseline LDH*/

proc sort data=der.mstone; by usubjid; run;
proc contents data=der.mstone; run;
proc contents data=der.lab; run;

/*Get randomization date per patient*/
data mstone; set der.mstone;
keep usubjid randdt;
run;

data lab; set der.lab;
if lbtestcd="LDH_PLC" ; /*limited to LDH test*/
run;

proc sort data=lab out=lab; by usubjid LBDT; run; /*sorted by patient and lab test date*/
data baseLDH;
merge mstone lab;
by usubjid;
day=randdt-lbdt+1;
if lbdt<=randdt and lbstresn ~.; /*limited non-missing baseline test results*/
run;

proc means data=baseLDH min max; var day; run; (up to 43 day prior trt LDH test)
proc sort data=baseLDH; by usubjid lbdt; run;

data baseldh1;
set baseLDH;
by usubjid lbdt;
retain maxldh; /*carry the max baseline LDH value*/
if visit="DAY 1" then baseldh=lbstresn; /*LDH value at day 1*/

```

Reference ID: 3208377

```

if first.usubjid then maxldh=lbstresn;
  maxldh=max(lbstresn, maxldh);
if last.usubjid;

if maxldh>lbstnrhi then maxldh_high=1;
else maxldh_high=0;

/*Following SAP page 27, LDHCD will used day 1 non-missing value otherwise using screening */
if base1dh= . and maxldh ne . then base1dh=maxldh;
if base1dh>lbstnrhi then base1dh_high=1;
else base1dh_high=0;
run;

proc sort data=der.demobase; by usubjid; run;
data LDHbase; set der.demobase; by usubjid;
  keep usubjid trtcd trtgrp LDH; /*keep all LDH related variables from DEMOBASE*/
run;

data LDH_compare;
  merge LDHbase base1dh1(keep=usubjid randdt maxldh maxldh_high base1dh base1dh_high);
  by usubjid;
run;

proc freq data=LDH_compare;
  TITLE "Baseline LDH Analysis";
  tables base1dh_high*LDHCD (maxldh_high base1dh_high LDHCD)*trtgrp /MISSING;
run;

proc print data=LDH_COMPARE;
  where maxldh_high =. and LDHCD ne .;
run;

/*
Obs      MAXLDH_ BASELDH_
MAXLDH  USUBJID  HIGH  TRTCD  TRTGRP  LDHCD LDH          LDHBRESN LDHBULN LDHUNIT
              HIGH
30 MEK114267.0400706  1  GSK1120212  0  equal to or below ULN  195  234  IU/L
91 MEK114267.0402122  2  Chemotherapy  1  above ULN  410  234  IU/L
107 MEK114267.0402229  1  GSK1120212  0  equal to or below ULN  223  234  IU/L*/

proc print data=der.tab;
  where (usubjid="MEK114267.0400706" or usubjid="MEK114267.0402122" or
  usubjid="MEK114267.0402229") and lbtestcd="LDH_PLC";
run;

```

Please contact me if you have any questions or concerns at (301) 796-4255 or at Norma.Griffin@fda.hhs.gov.

Information Request 7: 10/31/2012



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

Memorandum

Date: October 31, 2012
From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 204114; GlaxoSmithKline, LLC
Statistical Comments and Clarification from 10.26.2012 TCON

GlaxoSmithKline, LLC
Eric Richards
Global Regulatory Affairs
1250 South Collegeville Road
Collegeville, PA, 19426

Dear Mr. Richards:

We refer to the teleconference (TCON) held on October 26, 2012 regarding statistical comments and request for information for NDA 204114 Mekinist (trametinib). Our Statistical Reviewers have the following additional comments provided as a follow up to the TCON of October 26, 2012:

1. All datasets, regardless of being re-coded or not, have to be resubmitted, together with an updated define file. The define file should have been reviewed and corrected for all mistakes, and contain the recode information for each variable. For example, the current definition for the stratification factor was incorrect in the current define file.
2. All updated SAS programs for efficacy, baseline, and population analyses should be re-submitted.
3. If there are any variable derivations or analyses that were performed differently from what was defined in the protocol or SAP, a stand-alone document indicating what the changes are, and the rationale should be submitted.

Note: All of the above should be submitted in one submission. **This information request applies to both NDAs, 204114 and 202806.** The cover letter should clearly indicate where the related documents are located.

Please contact me if you have any questions or concerns at (301) 796-4255 or at Norma.Griffin@fda.hhs.gov.

Information Request 8: 11/27/2012



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

Memorandum

Date: November 27, 2012
From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 204114; GlaxoSmithKline, LLC
 Statistical Comments and Information Request

GlaxoSmithKline, LLC
 Eric Richards
 Global Regulatory Affairs
 1250 South Collegeville Road
 Collegeville, PA, 19426

Dear Mr. Richards:

We refer to your November 21, 2012 submission (sequence number 0024) containing statistical information – updated datasets/programs/define file for MEK114267. Out Statistical Reviewer has the following comments and request for information:

Reference is made to the define file in your November 21, 2012 submission. Variable VISITNUM is an essential variable and had been cross referenced in multiple datasets (lesion, exposure...etc) to derive multiple efficacy variables. However, the meaning of the variable visitnum is unclear. Please provide a response to the following:

1. Clarify the meaning of visitnum in each dataset.
2. Clarify whether this variable is consistently derived from the same resource across the whole submitted database. If so, which data contains the raw/original information for visit (exposure or visit)?
3. What is the meaning of QOL?

VISITNUM(Visit sequence number)		VISIT(Visit description)								
Frequency	Col Pct	QOL WEEK 10 UNSC HEDULED	QOL WEEK 11 UNSC HEDULED	QOL WEEK 12	QOL WEEK 13 UNSC HEDULED	QOL WEEK 17 UNSC HEDULED	QOL WEEK 18 UNSC HEDULED	QOL WEEK 19 UNSC HEDULED	QOL WEEK 21	Total
0.01		0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	2
5.00		0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	0 0.00	303

Please provide your response as soon as possible and follow it with a formal submission to the NDA. Please contact me if you have any questions or concerns at (301) 796-4255 or at Norma.Griffin@fda.hhs.gov.

Information Request 9: 02/12/2013



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

Memorandum

Date: February 12, 2013
From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 204114; GlaxoSmithKline, LLC
Statistical Comments and Information Request

GlaxoSmithKline, LLC
Eric Richards
Global Regulatory Affairs
1250 South Collegeville Road
Collegeville, PA, 19426

Dear Mr. Richards:

We refer to your NDA 204114 for Mekinist (trametinib) submitted on August 3, 2012. Our Statistical Reviewer has the following comments and request for information.

Based on the RECIST (version 1.1), the statistical reviewer found that there were 6 patients whose date of PD or status were different than that of GSK. Among these 6 patients, 2 were due to non-target lesion and 4 were due to new lesion. Please explain the discrepancy.

FDA statistical reviewer's calculation

Obs	USUBJID	NONTGPD_DATE	NEWPD_DATE	FDAPD_DATE
1	MEK114267.0400252		02AUG2011	02AUG2011
2	MEK114267.0400258		20MAY2011	20MAY2011
3	MEK114267.0401104		02JUN2011	02JUN2011
4	MEK114267.0402110		07APR2011	07APR2011
5	MEK114267.0402327	07JUN2011		07JUN2011
6	MEK114267.0403689	19AUG2011	07OCT2011	19AUG2011

GSK IRC results

Obs	PFSCT5	PFSDT5	PROGDT5
1	Progressed or Died (event)	22SEP2011	22SEP2011
2	Censored, Follow-up ongoing	23SEP2011	
3	Progressed or Died (event)	13JUL2011	13JUL2011
4	Progressed or Died (event)	12APR2011	
5	Progressed or Died (event)	04AUG2011	
6	Progressed or Died (event)	07OCT2011	07OCT2011

Please provide your response as soon as possible and follow it with a formal submission to the NDA. Please contact me if you have any questions or concerns at (301) 796-4255 or at Norma.Griffin@fda.hhs.gov.

Reference ID: 3260010

Information Request 10: 02/21/2013



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

Memorandum

Date: February 21, 2013
From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 204114; GlaxoSmithKline, LLC
 Statistical Comments and Information Request

GlaxoSmithKline, LLC
 Eric Richards; Global Regulatory Affairs
 1250 South Collegeville Road
 Collegeville, PA, 19426

Dear Mr. Richards:

We refer to your NDA 204114 for Mekinist (trametinib) submitted on August 3, 2012. Our Statistical Reviewer has the following comments and request for response.

Based on the define.pdf, the dataset resp2ex1 is the IRC best overall response data.

BRSPCD	Char	Best response assessment code	1=Complete response 2=Partial response 3=Stable disease 31=Non-CR/Non-PD 4=Progressive disease 41=Progressive disease (downgraded) 6=Not evaluable X=Not applicable	DERIVED DATA: Use last RESP1EX1.RSPCFCD when BRSPDFCD =1; else last RESP1EX1.URSCFCD when BRSPDFCD =2; else if subject not in RESP1EX1 assign to 6 (NE) for both confirmed and unconfirmed response
PROGDT	Date	Date of progression		DERIVED DATA: Date or progression as assessed by the independent review committee. Assign to the first RESP1EX1.RSPDT where RESP1EX1.RSPCD in (4,41) and RESP1EX1.ADEQFL =1

We found that 81 patients had date of progression. However, these patients were coded as non-pd response status in the BRSP or BRSPCD. Please note, the date of PD (PROGDT) was used to do the PFS related calculation in GSK's macro OC_onctte_m.sas. The variable BRSPCD was used to calculate the IRC best response (CSR Table 21) in SAS marco OD_re1.SAS (RespCriteria = brspcd in ('1','2')).

Please explain the discrepancy as soon as possible.

FLAG	BRSP(Best response)							Total
Frequency Percent Row Pct Col Pct	Complete response	Non-CR/N on-PD	Not appl icable	Not eval uable	Partial response	Progress ive dise ase	Stable d isease	
no pd	1 0.31 0.62 100.00	17 5.28 10.49 80.95	2 0.62 1.23 66.67	28 8.70 17.28 96.55	36 11.18 22.22 80.00	0 0.00 0.00 0.00	78 24.22 48.15 54.17	162 50.31
other pd	0 0.00 0.00 0.00	4 1.24 4.94 19.05	1 0.31 1.23 33.33	1 0.31 1.23 3.45	9 2.80 11.11 20.00	0 0.00 0.00 0.00	66 20.50 81.48 45.83	81 25.16
pd	0 0.00 0.00 0.00	0 0.00 0.00 0.00	0 0.00 0.00 0.00	0 0.00 0.00 0.00	0 0.00 0.00 0.00	79 24.53 100.00 100.00	0 0.00 0.00 0.00	79 24.53
Total	1 0.31	21 6.52	3 0.93	29 9.01	45 13.98	79 24.53	144 44.72	322 100.00

Please provide your response as soon as possible and follow it with a formal submission to the NDA. Please contact me if you have any questions or concerns at (301) 796-4255 or at Norma.Griffin@fda.hhs.gov.

Information Request 11: 02/27/2013



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

Memorandum

Date: February 27, 2013
From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 204114; GlaxoSmithKline, LLC
Statistical Comments and Information Request

GlaxoSmithKline, LLC
Eric Richards; Global Regulatory Affairs
1250 South Collegeville Road
Collegeville, PA, 19426

Dear Mr. Richards:

We refer to your NDA 204114 for Mekinist (trametinib) submitted on August 3, 2012. Our Statistical Reviewer has the following comments and request for response. Please provide your response by Wednesday, March 6, 2013, or sooner if possible and follow it with a formal submission to the NDA. Please contact me if you have any questions or concerns at (301) 796-4255 or at Norma.Griffin@fda.hhs.gov.

The statistical reviewer conducted IRC PFS analysis using RECIST 1.1 criteria (Table 1). If you do not agree with FDA's calculation, please comment and insert modified SAS code in the attached SAS code.

Information Request 12: 03/06/2013



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

Memorandum

Date: March 6, 2013
From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 202806 and NDA 204114; GlaxoSmithKline, LLC
Statistical Comments and Information Request

GlaxoSmithKline, LLC
Ellen S. Cutler
Eric Richards
Global Regulatory Affairs
1250 South Collegeville Road
Collegeville, PA, 19426

Dear Ms. Cutler/Mr. Richards:

Please refer to your New Drug Application (NDA) NDA 202806 for product “(dabrafenib)” and NDA 204114 for product “(trametinib)” received on July 31, 2012 and August 3, 2012, respectively.

Our Statistical Reviewers have the following comments and information request and requests a response by Thursday, March 7, 2012, **or sooner if possible.**

1. For both NDAs, provide the detailed definitions of the codings of the variables DSSCATCD, DSRSCD. Currently, DSSCATCD is included in the derived data set of NDA 204114, but not in NDA202806. It is included in the raw data set of NDA 202806 but did not have any documentation.
2. Provide the location of the Independent Review Charter. Submit the charter if it has not been submitted.
3. For Study 113683 of NDA 202806, the data set *trt* was not submitted but it was referenced in the dataset overview Section 3.3.1. Submit this dataset.

Please contact me if you have any questions or concerns at (301) 796-4255 or at Norma.Griffin@fda.hhs.gov.

Information Request 13: 03/11/2013



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

Memorandum

Date: March 11, 2013
From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 204114; GlaxoSmithKline, LLC
Statistical Comments and Information Request

GlaxoSmithKline, LLC
Eric Richards
Global Regulatory Affairs
1250 South Collegeville Road
Collegeville, PA, 19426

Dear Ms. Cutler/Mr. Richards:

Please refer to your New Drug Application (NDA) NDA 204114 for product “(trametinib)” received on August 3, 2012, respectively.

Our Statistical Reviewer has the following comments and information request and requests a response by Wednesday, March 13, 2012, **or sooner if possible**.

Please contact me if you have any questions or concerns at (301) 796-4255 or at Norma.Griffin@fda.hhs.gov.

Please comment and insert modified SAS code in the statistical reviewer’s macro on Stratified/Un-stratified Pike estimate of HR (95%). As noted, the un-stratified/stratified pike estimates of HR results were different. Please provide the stratified and un-stratified HR (95% CI) on 1) on PFS 1) per independent radiologist assessment, and 2) per independent radiologist and oncologist assessment.

Information Request 14: 3/13/2013



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

Memorandum

Date: March 13, 2013
From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 204114; GlaxoSmithKline, LLC
Statistical Comments and Information Request

GlaxoSmithKline, LLC
Eric Richards
Global Regulatory Affairs
1250 South Collegeville Road
Collegeville, PA, 19426

Dear Mr. Richards:

Please refer to your New Drug Application (NDA) NDA 204114 for product "(trametinib)" received on August 3, 2012.

Our Statistical Reviewer has the following comments and information request and requests a response by Friday, March 15, 2013, **or sooner if possible**. Please contact me if you have any questions or concerns at (301) 796-4255 or at Norma.Griffin@fda.hhs.gov.

In response to your response and FDA Request/Comments of March 12, 2013, please find our SAS code attached for NDA 204114. In addition, we have the following comments:

1. For NDAs 202806 and NDA 204114, we agree to exclude not measurable lesion assessments from the algorithm in the last adequate assessment calculation.
2. For NDA 204114, we will use un-stratified log-rank test as the primary analysis on PFS. The rationale was discussed during the meeting on March 8, 2013.
3. Whether or not we will exclude independent oncologist assessments from PFS analysis is still a pending review issue and needs further internal team discussion.

We also have the following information request:

4. Please provide PFS analysis results in the following Table 1 and Table 2.

Table 1. PFS Analysis per Independent Radiologist Assessment

	Trametinib n=214	Chemotherapy n=108
Num of Events		
PD		
Death		
Median PFS (months), 95%CI		
Cox Stratified HR Per CRF (95% CI) [P]		
Cox Stratified HR Per IVRS (95% CI) [P]		
Cox Un- stratified HR (95% CI) [P]		
Pike Stratified HR Per CRF (95% CI) [P]		
Pike Stratified HR Per IVRS (95% CI) [P]		
Pike Un-stratified HR (95% CI) [P]		

Table 2. PFS Analysis per Independent Radiologist and Oncologist Assessments

	Trametinib n=214	Chemotherapy n=108
Num of Events		
PD		
Death		
Median PFS (months), 95%CI		
Cox Stratified HR Per CRF (95% CI) [P]		
Cox Stratified HR Per IVRS (95% CI) [P]		
Cox Un- stratified HR (95% CI) [P]		
Pike Stratified HR Per CRF (95% CI) [P]		
Pike Stratified HR Per IVRS (95% CI) [P]		
Pike Un-stratified HR (95% CI) [P]		

Information Request 15: 3/13/2013



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

Memorandum

Date: March 13, 2013
From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDAs 202806 and 204114; GlaxoSmithKline, LLC
Statistical Comments and Information Request

GlaxoSmithKline, LLC
Ellen Cutler
Eric Richards
Global Regulatory Affairs
1250 South Collegeville Road
Collegeville, PA, 19426

Dear Ms. Cutler/Mr. Richards:

Please refer to your New Drug Applications (NDA) 202806 and 204114 for products "dabrafenib" and "(trametinib)" received on July 30, 2012 and August 3, 2012 respectively.

In response to E. Cutler's 'Response algorithms' email of 2:35 pm 3/13/2013, our Statistical Reviewers have the following comments and information request. We request a response by Friday, March 15, 2013, **or sooner if possible**.

Please provide the SAS program used to calculate the blinded, independent committee review (BICR)-assessed ORR and DoR per RECIST 1.1 criteria. The program should not contain any SAS macros. Provide sufficient comments to explain the algorithm in the program. Given the time limitations, please submit this program by close of business, Friday, March 13, 2013.

Please contact me if you have any questions or concerns at (301) 796-4255 or at Norma.Griffin@fda.hhs.gov.

Information Request 16: 3/17/2013



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

Memorandum

Date: March 17, 2013
From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 202806 and NDA 204114; GlaxoSmithKline, LLC
Statistical Comments and Information Request

GlaxoSmithKline, LLC
Ellen S. Cutler
Eric Richards
Global Regulatory Affairs
1250 South Collegeville Road
Collegeville, PA, 19426

Dear Ms. Cutler/Mr. Richards:

Please refer to your New Drug Application (NDA) NDA 202806 for product “(dabrafenib)” and NDA 204114 for product “(trametinib)” received on July 31, 2012 and August 3, 2012, respectively.

The SAS programs that you submitted on March 15, 2013, cannot be utilized in the review of NDAs 202806 and 204114. These programs derived objective response rates (ORR) and duration of response (DoR) based on the response datasets, which were not raw datasets. In the meeting on March 8, 2013, GSK agreed that the PFS analyses data should be derived based on raw lesion data, and therefore, ORR and DoR should be derived on raw lesion data to be consistent with the primary analysis approach.

You should resubmit the programs for deriving confirmed ORR and DoR for both NDAs based on raw IRC lesion data set (rlesioe1) and the programs should meet the following requirements:

1. The SAS programs should not contain any macros.
2. Derivations of complete response (CR) and partial response (PR) should follow RECIST 1.1 guidelines. For example, in the evaluation of target lesions, a CR is defined as disappearance of all target lesions—pathologic lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm; a PR is defined as at least a 30% decrease in the sum of diameters of target lesions from the baseline sum of diameters.
3. Adequate documentation should be provided to explain the procedure of the derivation in the programs. Every SAS procedure in the program should have comments to explain its purpose. Additional documentation can be provided in a separate document if necessary.
4. State whether the derivation of a confirmed best overall response of CR or PR requires the standard 4 weeks as the minimum time that must have elapsed prior to the confirmatory measurement.

Reference ID: 3277544

5. Since different patterns of CR, PR, PD, NE were observed at different visits, clearly explain how these different patterns of CR, PR, NE and PD were processed in the derivation of the confirmed best overall CR/PR and in the derivation of the duration of overall response. Follow Table 3 and Section 4.4.4 in RECIST 1.1 guidelines (<http://www.eortc.be/recist/documents/RECISTGuidelines.pdf>) for these derivations and clarify the procedure for handling of missing data/assessments (e.g., not evaluable) in the determination of confirmed best overall response as well as duration of response. In addition, clarify the determination of confirmed best overall response for patients with overall response determinations of CR at the first time point and PR at the subsequent time point.
6. Two versions of ORR derivation should be provided: one that excludes assessments by the independent oncologists and one that includes the assessments by the independent oncologists. The ORR and DoR results calculated by the programs described above should be reported in tables for both NDA's 202806 and 204114.

If you need clarification on any of the items above, please discuss with us as soon as possible. Given the review time left, the programs should be submitted no later than close of business **March 20, 2013, or sooner than that if possible.**

Please contact me if you have any questions at (301) 796-4255 or at Norma.Griffin@fda.hhs.gov.

Information Request 17: 3/27/2013



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

Memorandum

Date: March 27, 2013
From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 202806 and NDA 204114; GlaxoSmithKline, LLC
Statistical Comments and Information Request

GlaxoSmithKline, LLC
Amita Chaudhari, Ellen S. Cutler, and Eric Richards
Global Regulatory Affairs
1250 South Collegeville Road
Collegeville, PA, 19426

Dear Ms. Chaudhari:

Please refer to GSK's New Drug Application (NDA) NDA 202806 for product "(dabrafenib)" and NDA 204114 for product "(trametinib)" received on July 31, 2012 and August 3, 2012, respectively.

For NDAs 202806 and 204114:

1. Submit a dataset that contains the analysis data for IRC assessed PFS, OS, IRC assessed ORR and DoR analyses. Include the following variables in the dataset:
 - a) Unique subject ID
 - b) Important variables that are currently listed in oncctern
 - c) PFS analyses variables: PFS_GSK, PFS_IR, PFS_IRIO
 - d) OS analyses variable
 - e) ORR analysis variables and corresponding DoR variables : ORR_GSK, DoR_GSK, ORR_IR, DoR_IR, ORR_IRIO, DoR_IRIO

Please submit the SAS programs that generated the Tables 1-4 in GSK's March 20, 2013 submission.

2. Using the same algorithm to calculate ORR for the Phase III studies, analyze and report ORR and DoR analyses based on raw lesion data for Study BRF 113929 in NDA 202806. Report results for each cohort and combined cohorts, and report results based on investigator's assessments and IRC assessments separately.

Reference ID: 3283815

3. Using the same algorithm to calculate ORR for the Phase III studies, analyze and report ORR and DoR analyses based on raw lesion data for Study MEK113583 in NDA 202806. Report results for each cohort and combined cohorts.

Given the review time left, please submit your response by **Friday, March 29, 2013, or sooner if possible.**

Please contact me if you have any questions at (301) 796-4255 or at Norma.Griffin@fda.hhs.gov.

Information Request 18: 04/02/2013



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

Memorandum

Date: April 2, 2013
From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 202806 and NDA 204114; GlaxoSmithKline, LLC
Statistical Comments and Information Request

GlaxoSmithKline, LLC
Amita Chaudhari, Ellen S. Cutler, and Eric Richards
Global Regulatory Affairs
1250 South Collegeville Road
Collegeville, PA, 19426

Dear All:

Please refer to GSK's New Drug Application (NDA) NDA 202806 for product "(dabrafenib)" and NDA 204114 for product "(trametinib)" received on July 31, 2012 and August 3, 2012, respectively.

For NDAs 202806 and 204114:

1. Please derive the Investigator assessed PFS, ORR, and DoR based on raw lesion data. Submit the analysis data and results.

For NDA 204114:

2. In NDA 204114, please provide subgroup analyses by V600E/K for PFS (include INV, IRC_IR and IRC_IRIO), ORR (include INV, IRC_IR and IRC_IRIO), and OS.

Please submit your response by **noon tomorrow, Wednesday, April 3, 2013.**

Please contact me if you have any questions at (301) 796-4255 or at Norma.Griffin@fda.hhs.gov.

Information Request 19: 04/03/2013



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

Memorandum

Date: April 3, 2013
From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 204114; GlaxoSmithKline, LLC
Statistical Follow Up Comments and Information Request

GlaxoSmithKline, LLC
Eric Richards / Amita Chaudhari
Global Regulatory Affairs
1250 South Collegeville Road
Collegeville, PA, 19426

Dear All:

Please refer to GSK's New Drug Application (NDA) NDA 204114 for product "(trametinib)" received on August 3, 2012.

We also refer to your response of April 3, 2013 (to Item #2 of FDA's 4.2.2013 STATS IR).

1. Please provide the respective unstratified Pike HR (95% CI) and unstratified Cox HR (95% CI) in the Tables 4, 7, 10, and 14.

Please submit your response by **3:00 pm tomorrow, Thursday, April 4, 2013.**

Please contact me if you have any questions at (301) 796-4255 or at Norma.Griffin@fda.hhs.gov.

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

/s/

HUANYU CHEN
04/08/2013

KUN HE
04/08/2013
Accepted as a complete review

RAJESHWARI SRIDHARA
04/09/2013

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 204114

Applicant: GSK

Stamp Date: 8/2/2012

Drug Name: Mekinist (trametinib) NDA/BLA Type: Standard

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.	X			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

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

/s/

HUANYU CHEN
08/31/2012

KUN HE
08/31/2012