CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204114Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 204114 SUPPL # HFD # 107

Trade Name MEKINIST

Generic Name trametinib

Applicant Name GlaxoSmithKline, LLC

Approval Date, If Known May 29, 2013

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☒ NO ☐

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES ☒ NO ☐

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5-year New Chemical Entity Exclusivity

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☐ NO ☒

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered “NO” for original approvals of new molecular entities.)
IF “YES,” GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☐ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☐

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES ☐ NO ☐

Investigation #2 YES ☐ NO ☐

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 ! !
IND # YES ☐ ! NO ☐
! Explain:

Investigation #2 ! !
IND # YES ☐ ! NO ☐
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

==========

Name of person completing form: Norma Griffin
Title: Regulatory Health Project Manager
Date: April 24, 2013

Name of Office/Division Director signing form: Patricia Keegan, M.D.
Title: Director, Division of Oncology Products 2/OHOP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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

/s/

NORMA S GRIFFIN
05/28/2013

PATRICIA KEEGAN
05/29/2013

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 204114 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DOP2/OHOP PDUFA Goal Date: 02/01/2013 Stamp Date: 8/3/2012

Proprietary Name: Mekinist

Established/Generic Name: trametinib

Dosage Form: tablets, 0.5 mg, 1.0 mg, 2.0 mg

Applicant/Sponsor: GlaxoSmithKline, LLC

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) N/A
(2) _____
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation as detected by an FDA approved test.

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☒ active ingredient(s) (includes new combination); ☒ indication(s); ☒ dosage form; ☒ dosing regimen; or ☒ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☒ Yes. PREA does not apply. **Skip to signature block.**

☐ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☒ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed∆
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

˙ Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

ɜction C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification** †
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):					
Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: ____

Q1: Does this indication have orphan designation?

- ☐ Yes. PREA does not apply. **Skip to signature block.**
- ☐ No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- ☐ Yes: (Complete Section A.)
- ☐ No: Please check all that apply:
  - ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
  - ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
  - ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
  - ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
  - ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

  (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failed∆
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

∆ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

	Population	minimum	maximum	PeRC Pediatric Assessment form attached?	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

ction F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

	Population	minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

DEBARMENT CERTIFICATION

GlaxoSmithKline certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application (NDA 204114 Original NDA for Trametinib (GSK1120212) Tablets for the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation).

Craig Wozniak

May 2012

Head, Americas Clinical Operations

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 204114 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Mekinist Established/Proper Name: trametinib Dosage Form: Tablet		Applicant: GlaxoSmithKline, LLC Agent for Applicant (if applicable):
RPM: Norma Griffin		Division: Division of Oncology Products 2 (DOP2)

NDAs and NDA Efficacy Supplements:

NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:

Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ This application does not reply upon a listed drug.
☐ This application relies on literature.
☐ This application relies on a final OTC monograph.
☐ This application relies on (explain)

For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is September 3, 2013	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.
[2] For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., nrew listed drug, patent certification revised).

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [3]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☒ Fast Track
☒ Rolling Review
☒ Orphan drug designation

☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☐ Yes, dates
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☒ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other OHOP ASCO Burst

[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist[4]	FINAL 5/31/2013
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	5/29/2013
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	5/29/2013
• Original applicant-proposed labeling	8/3/2012
• Example of class labeling, if applicable	N/A

[4] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)* ***Please note: This is attached with the PI.***	☐ Medication Guide ☒ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	5/29/2013
• Original applicant-proposed labeling	8/3/2012
• Example of class labeling, if applicable	N/A
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	5/7/2013
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)* • *Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.*	4/10/2013 (final review) 9/20/2012 (conditionally accepted letter) 9/19/2012 (initial review)
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 5/22/2013 ☒ DMEPA 11/15/2012 ☒ DMPP/PLT (DRISK) 5/14/2013 ☒ ODPD (DDMAC) 5/14/2013 ☐ SEALD ☐ CSS ☒ Other reviews 5/8/2013 (W.Chambers – ophth consult) 4/18/2013 (PMH)
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[5]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	10/2/2012 (RPM Filing Review) ☒ Not a (b)(2) ☒ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ Included 5/2/2013
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP ○ If yes, Center Director's Exception for Review memo *(indicate date)* ○ If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action

[5] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before finalized)*	☒ Included *Orphan Drug status – does not trigger PREA.*
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Outgoing communications *(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)*	5/29/2013 Labeling 6thRound 5/28/2013 (evening) Labeling 5th Round 5/28/2013 Labeling 4th Round 5/24/2013 Labeling 3rd Round 5/22/2013 Labeling - 2nd Round 5/21/2013 Proposed Clinical PMR 5/10/2013 Labeling – 1st Round FDA Proposed 5/6/2013 Advice – Shelf-Life Statement 5/3/2013 Container Labeling Comments (new storage temp) 4/12/2013 Clinical (ophthalmology IR 4/9/2013 Compliance Letter (blending uniformity) 4/8/2013 Clinical (ophthalmology) IR 4/5/2013 Clinical IR 4/4/2013 Clinical IR 4/3/2013 STATS IR 4/2/2013 STATS IR 3/27/2013 STATS IR 3/27/2013 Clinical IR 3/26/2013 Clinical IR 3/20/2013 Methods Val. IR (2nd) 3/20/2013 Labeling - DMEPA Container Comments 3/17/2013 STATS IR 3/15/2013 Clinical IR 3/13/2013 STATS IR *(in response to GSK email for algorithms)* 3/13/2013 STAT IR *(follow on to* 3.8.2013 STATS working session) – *memo to file for this request uploaded on 5/8/2013* 3/11/2013 STATS IR 3/5/2013 STATS IR **3/1/2013 CMC AI Letter** 2/27/2013 STATS IR 2/21/2013 STATS IR 2/21/2013 ClinPharm IR – proposed PMR language 2/12/2013 STATS IR 12/21/2012 ClinPharm IR 12/19/2012 CMC IR (biopharmaceutics) 12/5/2012 CMC IR 11/27/2012 STATS IR

	11/21/2012 CMC IR (biopharmaceutics) 11/7/2012 Labeling DMEPA Comments 11/1/2012 Method Val IR 10/31/2012 STATS IR 10/31/2012 Nonclinical IR 10/25/2012 STATS IR **10/14/2012 Filing/74 Def. Letter** 9/27/2012 CMC IR 9/21/2012 Labeling IR DMEPA 9/19/2012 CMC Micro IR 9/17/2012 Labeling IR (SPL) 9/17/2012 CDRH and BIMO 9/14/2012 OSI and IRC Charters 9/10/2012 STATS IR 9/6/2012 Clinical IR 9/4/2012 Labeling IR (Carton inquiry) 8/29/2012 ClinPharm IR (pharmacometrics) **8/15/2012 NDA Ack Letter** 8/14/2012 ClinPharm/STATS IR 8/13/2012 STATS IR **7/20/2012 Presub Ack Letter**
❖ Internal memoranda, telecons, etc.	5/31/2013 Memo to File – STATS TCON/Mtgs 5/21/2013 TCON Mtg Summary with SGE 5/3/2013 Team Mtg 7 Final Issues (uploaded in DARRTS 5/8/2013) 4/5/2013 Wrap-Up Mtg (uploaded in DARRTS 4/17/2013) 3/12/2013 Team Mtg (uploaded in DARRTS 4/17/2013) 2/12/2013 Team Mtg (uploaded in DARRTS 4/17/2013) 1/18/2013 Labeling Mtg 6 (uploaded in DARRTS 4/17/2013) 12/18/2012 Team Mtg 4 (uploaded in DARRTS 4/17/2013) 12/6/2012 Labeling Mtg 5 (uploaded in DARRTS 4/17/2013) 11/19/2012 Labeling Mtg 4 (uploaded in DARRTS 4/17/2013) 11/14/2012 Team Mtg 3 (uploaded in DARRTS 4/17/2013) 11/14/2012 Labeling Mtg 3 (uploaded in DARRTS 4/17/2013) 11/13/2012 Labeling Mtg 2 (uploaded in DARRTS 4/17/2013) 11/6/2012 Labeling Mtg 1 (uploaded in DARRTS 4/17/2013) 11/1/2012 Mid-Cycle Mtg (uploaded in DARRTS 4/17/2013) 10/16/2012 Team Mtg 2 (uploaded

	in DARRTS 4/17/2013) 9/19/2012 Team Mtg 1 (uploaded in DARRTS 4/17/2013) 8/31/2012 Filing Mtg (uploaded in DARRTS 4/17/2013) 8/15/2012 Initial Planning Mtg (uploaded in DARRTS 4/17/2013)
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☐ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg 5/9/2012 Pre-NDA w/ IND 105032 2/15/2012 Pre-NDA CMC;
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg 2/24/2011 (EOP1/PP3) with IND 105032 7/30/2010 (EOP1 / PP3)
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	11/9/2010 (EOP1/PP3 CMC)
❖ Advisory Committee Meeting(s) ***Not needed - the application did not raise significant safety or efficacy issues***	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☐ None 5/28/2013
Division Director Summary Review *(indicate date for each review)*	☐ None 5/28/2013
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 5/16/2013
PMR/PMC Development Templates *(indicate total number)* – Total # PMR/PMCs = 4	☐ None 5/24/2013 (Clinical) 4/10/2013 (ClinPharm)
Clinical Information[6]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	5/24/2013 (concurrence)
• Clinical review(s) *(indicate date for each review)*	5/23/2013 (final) 9/27/2012 (filing)
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	5/23/2013 [See page 20 of 5/23/2013 Clinical Review (final)]
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None

[6] Filing reviews should be filed with the discipline reviews.

❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☐ None 3/14/2013
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☐ None requested 3/20/2013 (NAI-Russia) 1/22/2013 (NAI-France) 1/3/2013 (Clinical Inspection Summary) 1/2/2013 (NAI-GSK US) 12/17/2012 (NAI-US)
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None Concurred 4/10/2013 (addendum) Concurred 4/9/2013
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None Concurred 4/10/2013 (addendum) Concurred 4/8/2013
Statistical Review(s) *(indicate date for each review)*	☐ None 4/10/2013 (addendum) 4/9/2013 (primary review) 8/31/2012 (filing)
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None Concurred 4/8/2013
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None Concurred 4/8/2013
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 4/8/2013 9/27/2012 (filing)
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None 4/25/2013
• Supervisory Review(s) *(indicate date for each review)*	☐ None 4/19/2103
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 4/16/2013 9/5/2012 (filing)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None 5/28/2013
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None Concurred 4/8/2013 (for drug substance and drug product) Concurred 4/5/2013 (biopharmaceutics)
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 4/8/2013 (drug product) 4/8/2013 (drug substance) 4/5/2013 (biopharmaceutics) 8/31/2012 (filing) 8/17/2012 (biopharmaceutics filing)
❖ Microbiology Reviews ☒ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) *(indicate date of each review)*	☐ Not needed 11/30/2012 8/29/2012 (filing)
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None 2/5/2013 (Nonclinical review) 1/29/2013 (request)
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	4/8/2013 (drug product review) – see page 92 of 102
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

❖ Facilities Review/Inspection	
☒ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[7])*	Date completed: 5/21/2013 ☒ Acceptable – 5/9/2013 ☐ Withhold recommendation ☐ Not applicable
☐ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☒ Requested ☐ Not yet requested ☐ Not needed (per review)

[7] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

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

Memorandum

Date: May 31, 2013

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

Subject: NDAs 202806 and 204114 – Memo to File
TCON/Meetings Regarding Statistical Issues

The following are the dates that teleconferences and/or working session meetings were held between FDA and GSK to discuss statistical issues with these NDA applications:

8/13/2012	Teleconference to discuss datasets
9/7/2012	Face-to-face working session after Application Orientation meeting to discuss datasets
9/19/2012	Teleconference to discuss datasets
10/26/2012	Teleconference to discuss datasets
11/7/2012	Teleconference to discuss datasets
11/15/2013	Face-to-face to discuss and understand how Sponsor can assist in resolving specific dataset issues experienced during the review.
3/8/2013	All day on-site working session to confirm the derived dataset from the raw data

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/s/

NORMA S GRIFFIN
05/31/2013

From: Griffin, Norma
Sent: Wednesday, May 29, 2013 12:05 PM
To: 'Eric Richards'
Cc: Hughes, Monica L; Ellen Cutler
Subject: NDAs 202806 and 204114-Final Agreed Labeling

Importance: High

Attachments: FDA Proposed 5.29.2013.doc; MEKINIST FDA Proposed 5.29.2013.docx

Eric/Ellen,

Attached are our final psoposed changes for both NDAs. We need to speak with you in 15 minutes (12:20 pm) to obtain final agreement.

Please provide a call in number.

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

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/s/

NORMA S GRIFFIN
05/30/2013

From: Griffin, Norma
Sent: Tuesday, May 28, 2013 8:23 PM
To: 'Eric Richards'
Cc: Hughes, Monica L; 'Ellen Cutler'
Subject: NDA 204114 MEKINIST (trmetinib) - Final Agreed Labeling

Attachments: MEKINIST FDA Proposed Edits 5.28.2013 to GSK Final Agreed.pdf; MEKINIST FDA Proposed Edits 5.28.2013 to GSK Final Agreed.docx

Good Evening Eric,

Attached is the final labeling for NDA 204114 MEKINIST (trametinib) that was agreed to during our TCON this afternoon. I've included the WORD and PDF version.

Kindly respond to confirm receipt of this email and the attached labeling. In addition in your email, please provide your response (agreement). Finally, ensure that you formally submit your agreement of the labeling to the NDA and that your cover letter is dated the same day as the date of your email agreement.
If you have any questions, please contact me via email.

Thanks,

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

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NORMA S GRIFFIN
05/30/2013

From: Griffin, Norma
Sent: Tuesday, May 28, 2013 12:39 PM
To: 'Eric Richards'; Ellen Cutler
Cc: Hughes, Monica L; Libeg, Meredith
Subject: NDA 204114 - FDA Request for TCON to finalize Labels

Importance: High

Attachments: MEKINIST FDA Proposed Edits 5.28.2013 to GSK.pdf; MEKINIST FDA Proposed Edits 5.28.2013 to GSK CLEAN.docx

Eric,

Please see the attached FDA proposed labeling for NDA 204114 - included is both CLEAN (WORD) and PDF tracked changes. This will be discussed and finalized during out TCON at 2:30 pm today.

Please confirm receipt.

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

From: Eric Richards [mailto:eric.2.richards@gsk.com]
Sent: Tuesday, May 28, 2013 12:18 PM
To: Griffin, Norma; Ellen Cutler
Cc: Hughes, Monica L; Libeg, Meredith
Subject: RE: NDAs 202806 and 204114 - FDA Request for TCON to finalize Labels

Hi Norma – We can certainly meet at 2:30. We can use my TC number:

Participant code	(b) (4)
US dial-in number	

Thanks,

Eric Richards

Global Regulatory Affairs
Internal phone: 8-202-6842
External: 610-917-6842
Mobile: (b) (6)

From: Griffin, Norma [mailto:Norma.Griffin@fda.hhs.gov]
Sent: Tuesday, May 28, 2013 12:04 PM
To: Eric Richards; Ellen Cutler
Cc: Hughes, Monica L; Libeg, Meredith
Subject: NDAs 202806 and 204114 - FDA Request for TCON to finalize Labels
Importance: High

Eric/Ellen,

Can we have a TCON to finalize both labels? Today at 2:30 pm? Please respond to confirm and provide a call-in number.

I'm working on sending you both the labeling now.

Thanks,

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

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/s/

NORMA S GRIFFIN
05/30/2013

From: Griffin, Norma
Sent: Friday, May 24, 2013 11:17 AM
To: 'Eric Richards'; 'Ellen Cutler'
Cc: Libeg, Meredith; Hughes, Monica L; Jones, Karen
Subject: NDA 204114 MEKINIST (trametinib) - FDA Proposed Edits 5.24.2013 (inclusion of Dose Modification Table

Importance: High

Attachments: FDA 5.24.2013 Edits to GSK Tracked Changes.pdf; FDA 5.24.2013 Edits to GSK CLEAN.doc

Eric,

Please see our attached proposed labeling edits (5.24.2013) for NDA 204114 MEKINIST (trametinib). I have included both the Tracked Changes (PDF) and CLEAN WORD versions.

Kindly respond to confirm receipt of this email and the attached labeling and provide your response as soon as possible.
Thanks,

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

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/s/

NORMA S GRIFFIN
05/30/2013

From: Griffin, Norma
Sent: Wednesday, May 22, 2013 9:40 AM
To: 'eric.2.richards@gsk.com'
Cc: 'ellen.s.cutler@gsk.com'; Libeg, Meredith; Hughes, Monica L
Subject: NDA 204114 MEKINIST (trametinib) - FDA Proposed Edits 5.22.2013

Importance: High

Attachments: FDA 5.22.2013 Edits to GSK CLEAN.doc; FDA 5.22.2013 Edits to GSK.pdf

Good Morning Eric,

Please see the attached proposed labeling edits (5.22.2013) for NDA 204114. I have included both a CLEAN WORD document and a Tracked Changes PDF document. Please ensure that you address the formatting for the links in the Table of Contents.

We ask that you provide a response as soon as possible.

FDA 5.22.2013 Edits to GSK CLE...

FDA 5.22.2013 Edits to GSK.pdf...

Kindly respond to confirm receipt of this email and the attached labeling.

Thanks,

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

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/s/

NORMA S GRIFFIN
05/22/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

MEMORANDUM OF MEETING MINUTES

MEETING DATE: May 21, 2013

TIME: 1:30-2:00 PM ET

LOCATION: Teleconference, WO 22, RM 2376

APPLICATION: NDA 204114

DRUG NAME: MEKINIST (trametinib)

TYPE OF MEETING: Teleconference with Special Government Employee (SGE), Dr. Janice Dutcher, cleared for participation by CDER's Division of Advisory Committee and Consultant Management (DACCM).

FDA ATTENDEES:

Patricia Keegan – DOP2 Division Director

Suzanne Demko – DOP2 Clinical Team Leader and CDTL

Marc Theoret – DOP2 Clinical Reviewer

Norma Griffin - Regulatory Health Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Dr. Janice Dutcher

BACKGROUND: Dr. Janice Dutcher agreed to serve and was cleared as an SGE for this NDA. Prior to this teleconference, background materials and draft product labeling were provided to Dr. Dutcher along with three specific questions from the Division for Dr. Dutcher to address during this teleconference. Those materials are attached to this document.

DISCUSSION POINTS:

FDA Questions for Discussion During Teleconference:

1. Does the 3.3-month improvement in median progression-free survival observed on the trametinib arm of the MEK114267 trial represent a clinically meaningful benefit?

   Discussion During Teleconference: Dr. Dutcher agreed that this does represent a clinically meaningful benefit and that, as a single agent, trametinib is better than chemotherapy. She believes that it will be used off-label in combination with a BRAF inhibitor by the medical community.

2. Based upon the data in this study, does the risk-benefit ratio favor treating the proposed indicated population with trametinib?

   Discussion During Teleconference: Dr. Dutcher offered the opinion that there is a favorable benefit: risk assessment for this drug, as long as the risk for cardiomyopathy does not increase. She also noted that patients with metastatic melanoma are likely to accept the risks of taking this drug.

3. Does the proposed product label adequately inform patients and physicians of the potential risks and benefits of trametinib treatment?

   Discussion During Teleconference: Dr. Dutcher mentioned the following with regard to the trametinib label:

   - It needs to be noted in the label that it is not recommended in patients who have received prior BRAF-inhibitor therapy, but that patients who were previously treated with chemotherapy do respond. FDA stated that this is included in the current wording of the labeling (the version provided to Dr. Dutcher on 5.17.2013 (b) (4) ; FDA has added this in the current version).

   - Physician and patient labeling should display prominently information on the risks of cardiomyopathy and ocular toxicities, including the risk of blindness. Dr. Dutcher also recommended that the label identify patient demographics and characteristics associated with greatest risk of cardiomyopathy, if known, to decrease the burden of cardiac monitoring for the indicated patient population.

FDA said that the final draft label would be provided to her and asked Dr. Dutcher to provide feedback on Section 17 (Patient Counseling Information).

ATTACHMENTS: Background information provided to Dr. Dutcher via email (jpd4401@aol.com) on Friday, May 17, 2013 which included:

- Briefing Document for FDA Teleconference to Discuss NDA 204114
- Draft Labeling of 5.10.2013

Briefing Document for FDA Teleconference to Discuss NDA 204114
Mekinist (trametinib), Tablets
GlaxoSmithKline

I. Introduction

- On August 3, 2012, GSK submitted NDA 204114 seeking approval of trametinib for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutations, as detected by an FDA-approved test.
- Trametinib is a small molecule inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK-2 activation and of MEK1 and MEK2 kinase activity.
- NDA 204114 includes data from a single randomized clinical trial, MEK114267, titled "a Phase III randomized, open-label study comparing GSK1120212 to chemotherapy in subjects with advanced or metastatic BRAF V600E/K mutation-positive melanoma."
- Trametinib has been administered to over 1700 patients at various doses, either as monotherapy or in combination with approved drugs or experimental compounds, including 211 patients as monotherapy in the MEK114267 trial at the proposed to-be-marketed dose and schedule of 2 mg orally once daily.

II. Design of the MEK114267 Trial

- The MEK114267 trial was an open-label, multicenter, international, randomized (2:1), active-controlled trial comparing single agent trametinib to chemotherapy in 322 patients with previously untreated or treated, histologically confirmed, unresectable (Stage IIIc) or metastatic (Stage IV) cutaneous melanoma determined to be BRAF V600E or V600K mutation-positive based upon centralized testing.
- Patients were randomized to receive trametinib 2 mg orally once daily (n=214) or chemotherapy (n=108), dacarbazine 1000 mg/m^2 or paclitaxel 175 mg/m^2 intravenously once every 3 weeks.
- Patients were stratified at randomization according to:
    - LDH (normal vs. elevated)
    - Prior chemotherapy for advanced or metastatic disease (Yes vs. No)
- At the time of disease progression, patients on the chemotherapy arm were offered the opportunity to take trametinib.
- The primary endpoint was progression-free survival (PFS) based on investigator-assessments and secondary endpoints were overall survival, tumor response rate, and duration of tumor response.
- GSK conducted pre-specified, supportive analyses of PFS, tumor response rates, and duration of response as assessed by blinded independent central review (BICR).
- No interim analyses performed.
- Eligibility criteria included:
    - Male or female patients ≥ 18 years of age.
    - Patients with histologically confirmed, unresectable (Stage IIIc) or metastatic (Stage IV) cutaneous melanoma which was also determined to be BRAF V600E or BRAF V600K mutation-positive by centralized testing.

- No prior treatment or up to one prior regimen of chemotherapy for advanced or metastatic melanoma. Prior treatment with immunotherapy was allowed (except ipilimumab unless given in the adjuvant setting).
- No prior treatment with BRAF inhibitors or MEK inhibitors in the advanced or metastatic setting.
- Patients must have measurable disease according to RECIST, version 1.1.
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.

A. Results of the MEK114267 Trial

- Baseline characteristics of enrolled patients were comparable between treatment arms.
  - Median age: 54 years
  - 100% white
  - All patients had a baseline ECOG performance status of 0 (64%) or 1 (36%).
  - Most patients were from Western Europe (63%), Eastern Europe (15%), and North America (11%).
  - BRAF V600 mutation subtype was V600E in 87% and V600K in 13% of randomized patients. The incidence of BRAF V600K mutation subtype by treatment arm was 14% for trametinib and 10% for chemotherapy.
  - Metastasis stage was M1c in 64% of patients (67% of patients randomized to trametinib arm and 58% of patients randomized to chemotherapy arm)
  - History of brain metastases in 4% of patients on trametinib arm and 2% of patients on the chemotherapy arm
  - Elevated LDH at study entry in 36% of patients
  - Prior use of chemotherapy at study entry at study entry in 34% of patients
- The median duration of follow-up in the randomized phase of the trial was 4.9 months (range 0-9 months) on the trametinib arm and was 4.8 months (range 0-10 months) on the chemotherapy arm.
- At the time of progression, 51 (47%) patients crossed over from the chemotherapy arm to receive trametinib

Table 1. Analyses of Progression-free Survival (PFS). Intent-to-Treat (ITT) Population.

	Trametinib, (n=214)	Chemotherapy, (n=108)
PRIMARY EFFICACY ANALYSIS, INVESTIGATOR-ASSESSMENT		
N	214	108
Events (%)	117 (55)	77 (71)
Progression	107 (50)	70 (65)
Death	10 (5)	7 (6)
Median PFS in months (95% CI)	4.8 (4.3, 4.9)	1.5 (1.4, 2.7)
2-sided p-value (unstratified log-rank)	<0.0001	
Hazard Ratio (95% CI)	0.47 (0.34, 0.65)	
BICR ASSESSMENT		
Events (%)	98 (46)	73 (68)
Progression	88 (41)	66 (61)
Death	10 (5)	7 (5)
Median PFS in months (95% CI)	4.9 (4.6, 5.0)	1.7 (1.4, 2.8)
2-sided p-value (unstratified log-rank)	<0.0001	
Hazard Ratio (95% CI)	0.43 (0.31, 0.62)	

Figure 1. Kaplan-Meier Curves of Investigator-assessed PFS. ITT Population.

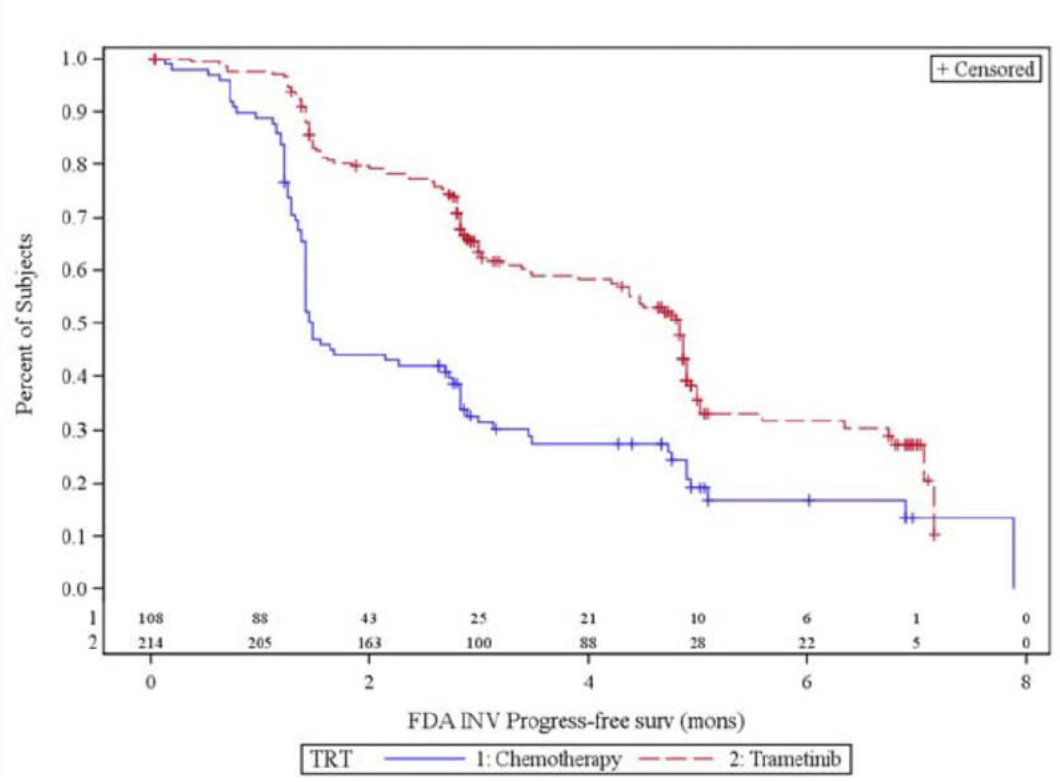

Table 2: Supportive Analyses of Investigator-Assessed PFS by Selected Subgroups.

	Trametinib	Chemotherapy
BRAF V600E		
N	184	97
Events (%)	99 (54)	69 (71)
Median PFS, months (95% CI)	4.8 (4.2, 4.9)	1.4 (1.4, 2.7)
HR (95% CI)	0.47 (0.33, 0.67)	
BRAF V600K		
N	27	11
Events (%)	18 (67)	8 (73)
Median PFS, months (95% CI)	4.8 (2.8, 4.9)	1.5 (0.8, 4.9)
HR (95% CI)	0.50 (0.18, 1.35)	
PRIOR CHEMOTHERAPY-TREATED		
N	71	38
Events (%)	44 (62)	27 (71)
Median PFS, months (95% CI)	4.5 (2.8, 4.9)	2.7 (1.4, 2.9)
HR (95% CI)	0.52 (0.30, 0.90)	
NO PRIOR CHEMOTHERAPY		
N	143	70
Events (%)	73	50
Median PFS, months (95% CI)	4.8 (4.3, 5.0)	1.4 (1.4, 1.7)
HR (95% CI)	0.45 (0.30, 0.68)	

Additional Supportive Analyses of Efficacy

- Subgroup analyses of progression free survival
- Key secondary endpoints were overall survival, response rate, and duration of response

Figure 2: Subgroup Analyses of Investigator-Assessed PFS

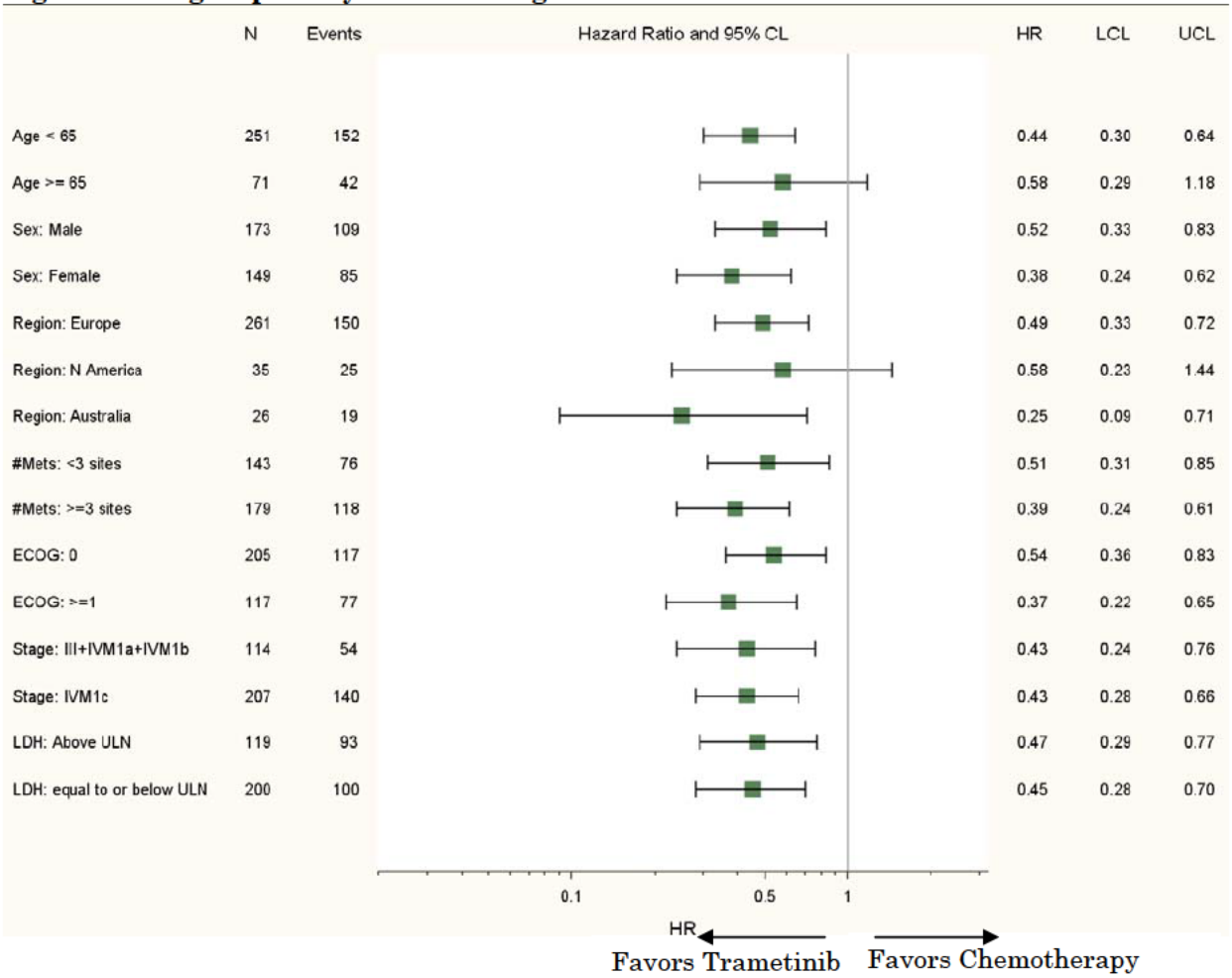

Table 3. Analysis of Overall Survival. ITT Population.

	Trametinib N=214	Chemotherapy N=108
Events	35 (16)	29 (27)
Median OS in months (95% CI)	NR (NR, NR)	NR (6.8, NR)
p-value (unstratified log-rank test)	0.0136	
Hazard Ratio (95% CI)	0.54 (0.33, 0.95)	

Abbreviations in Table: NR, not reached

Figure 3. Kaplan-Meier Curves of Overall Survival. ITT Population.

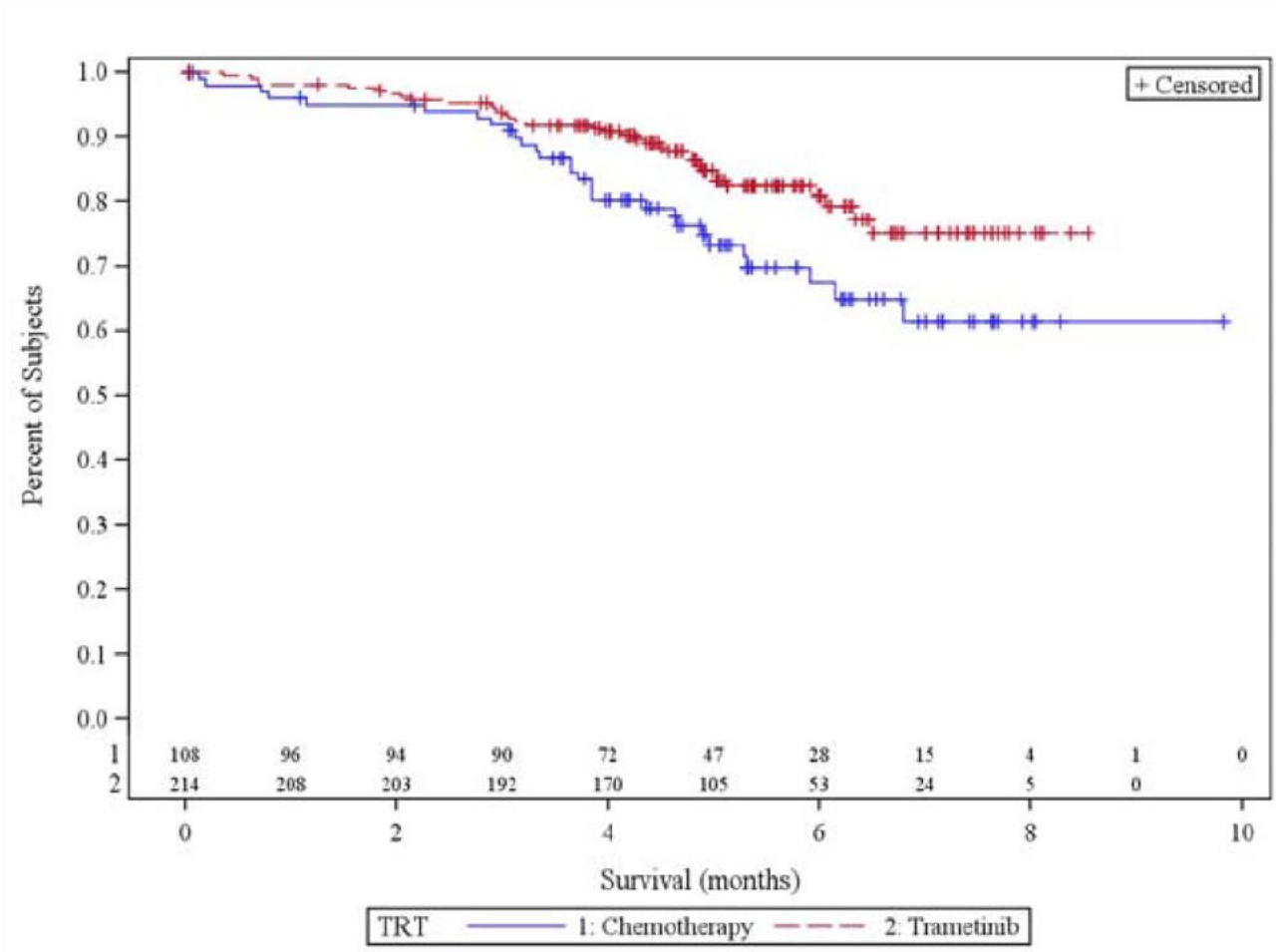

Table 4. Confirmed Objective Response Rates and Duration of Responses by Assessment Method (Investigator or BICR). ITT Population and by BRAF V600 Mutation Subgroups.

	Investigator Assessment		BICR Assessment	
	Trametinib	**Chemo**	**Trametinib**	**Chemo**
ALL				
N	214	108	214	108
ORR, n (%)	47 (22)	9 (8)	41 (19)	6 (6)
95% CI	(17%, 28%)	(4%, 15%)	(14%, 25%)	(2%, 12%)
CR, n (%)	4 (2)	0	0	1 (1)
PR, n (%)	43 (20)	9 (8)	41 (19)	5 (5)
Median DoR[1] (95%CI)	5.5 (4.1, 5.9)	NR (3.5, NR)	5.6 (3.8, 5.9)	NR (3.5, NR)
BRAF V600E SUBGROUP				
N	184	97	184	97
ORR, n (%)	44 (24)	7 (7)	34 (18)	4 (4)
95% CI	(18%, 31%)	(3%, 14%)	(13%, 25%)	(1%, 10%)
CR, n (%)	4 (2)	0	0	0
PR, n (%)	40 (22)	7 (7)	34 (18)	4 (4)
Median DoR[1] (95%CI)	5.5 (3.6, 5.9)	NR (3.5,NR)	5.6 (3.8, 5.9)	NR (3.5, NR)
BRAF V600K SUBGROUP				
N	29	11	29	11
ORR, n (%)	3 (10)	2 (18)	7 (24)	2 (18)
95% CI	(23%, 27%)	(2%, 52%)	(10%, 44%)	(2%, 52%)
CR, n (%)	0	0	0	1 (9)
PR, n (%)	3 (10)	2 (18)	7 (24)	1 (9)
Median DoR[1] (95%CI)	4.1 (NR, NR)	NR (NR, NR)	4.1 (NR, NR)	NR (NR, NR)
PRIOR CHEMOTHERAPY SUBGROUP				
N	71	38	71	38
ORR, n (%)	17 (24)	0	12 (17)	0
95% CI	(15%, 36%)	(0, 9%)	(9%, 28%)	(0, 9%)

	Investigator Assessment		BICR Assessment	
CR, n (%)	1 (1)	0	0	0
PR, n (%)	16 (23)	0	12 (17)	0
Median DoR[1] (95%CI)	4.9 (3, NR)	NR (NR, NR)	5.6 (3.4, 5.6)	NR (NR, NR)
NO PRIOR CHEMOTHERAPY SUBGROUP				
N	143	70	143	70
ORR, n (%)	30 (21)	9 (13)	29 (20)	6 (9)
95% CI	(15%, 29%)	(6%, 23%)	(14%, 28%)	(3%, 18%)
CR, n (%)	3 (2)	0	0	1 (1)
PR, n (%)	27 (19)	9 (13)	29 (20)	5 (7)
Median DoR[1] (95% CI)	5.5 (3.6, 5.9)	NR (3.5, NR)	5.9 (3.8, 5.9)	NR (3.5, NR)

Abbreviations in Table: BICR, Blinded independent central review; CI, confidence interval; CR, complete response; DoR, duration of response; NR, not reached; ORR, objective response rate; PR, partial response
[1] Duration of response in months

B. Analysis of Safety Data from the MEK114267 Trial

- The mean duration on treatment was 4.1 months for trametinib-treated patients compared to 2.9 months for chemotherapy-treated patients.
- The most serious toxicities caused by trametinib were:
  - Cardiomyopathy
  - Interstitial lung disease
  - Retinal pigment epithelial detachments
  - Retinal vein occlusion
  - Dermatologic toxicity [rash, acne, palmar-plantar erythrodysesthesia (PPE), and erythema
- Adverse events leading to treatment interruptions/delays occurred in 20% of trametinib-treated patients and 16% of chemotherapy-treated patients. AEs leading to withholding treatment in more than 1% of the trametinib-treated patients were rash (4.3% in the trametinib treated group vs. 0 in the chemotherapy treated group), diarrhea (2.4% vs. 0), peripheral edema (1.9% vs. 0), ALT/AST increase (1.4% vs. 0), and ejection fraction decreased (1.4% vs. 0). Adverse events led to dose reductions more frequently in the treatment group (27%) than in the chemotherapy treatment group (10%)--the most frequent in trametinib-treated patients were rash (9% vs. 0) and decreased left ventricular ejection fraction (3% vs. 0). Treatment-emergent adverse events resulted in treatment withdrawal in approximately 9% of patients in both treatment groups.
- Grade 5 cardiac event: One trametinib-treated patient experienced a fatal myocardial infarction adverse event compared to none of the chemotherapy-treated patients. This patient was a 77 year old man with a past medical history significant for cardiac shock requiring cardioversion as well as a significant smoking history. He was initially hospitalized on Day 11 for an episode of syncope thought related to vomiting. He subsequently experienced an MI on Day 15 after initiating trametinib and underwent

cardiac catheterization with stent placement as well as medical management. He experienced a second MI on Day 63 and died while receiving comfort measures on Day 65. The patient's last dose of trametinib was Day 63.

[Note: GSK conducted an analysis of fatal SAEs across all clinical trials of trametinib administered as monotherapy or in combination and at the time of the analysis there were 65 fatal SAEs of >1200 patients being treated with various types of malignancies. An independent review panel reviewed all 65 deaths and determined that there were 12 patients who died of a cardiovascular cause (e.g., stroke, heart failure, sudden death, other). Within the cardiovascular deaths, there were five cases of sudden death/cardiac arrest, three of which occurred in patients without identifiable cardiovascular comorbidities or concomitant medications.]

- Cardiomyopathy defined as cardiac failure, left ventricular dysfunction, or decreased ejection fraction occurred in 7% (14/211) of trametinib-treated patients and in none of the chemotherapy-treated patients. Cardiomyopathy was a serious adverse event in 3 (1.4%) trametinib-treated patients. Analyses of routine and unscheduled echocardiograms or MUGA scans based on investigator (INV) or blinded independent review (IR) demonstrated that 10% (INV) to 14% (IR) of trametinib-treated patients compared to 3% of chemotherapy-treated patients met LVEF criteria to withhold treatment [≥ 10% decrease in LVEF which was also below the institutional lower limits of normal (LLN)].
- Pneumonitis occurred in two (1%) trametinib-treated patients and no chemotherapy-treated patients.
- Skin toxicity (including rash, acneiform dermatitis, pustular rash, PPES, erythema) occurred in 87% of trametinib-treated patients and 13% of chemotherapy-treated patients. The incidence of Grade 3 or 4 skin toxicity was 12% in trametinib-treated patients and 0 in chemotherapy-treated patients. Twelve (6%) of trametinib-treated patients required hospitalization for associated skin infections (5%) or for the severity of the rash itself (1%). The data were insufficient to evaluate the efficacy of supportive care measures for skin toxicity, either pre-emptive or as primary treatment.
- Ocular toxicities of trametinib are retinal pigment epithelial detachments (RPED) and retinal vein occlusion.

  [Note, the incidences of RPED and retinal vein occlusion are based on the integrated safety population, i.e., patients with unresectable or metastatic melanoma who received at least one dose of trametinib administered at a dose and schedule of 2 mg orally once daily across three clinical trials]

  RPED occurred in 4% of patients across clinical trials of trametinib (n=329). Generally, these events appear to be reversible with interruption and/or reduction in trametinib dosing. Retinal vein occlusion occurred in 1% (4/329) trametinib-treated patients.

- Other significant adverse reactions of trametinib include:
  - Hepatic-related adverse events:

        - Defined as increased ALT/AST, increased bilirubin, cytolytic hepatitis, increased hepatic enzymes, hepatic failure, hepatic pain, hepatitis, hepatobiliary disease, hepatomegaly, and jaundice were increased in trametinib-treated patients (12%) compared to chemotherapy-treated patients (6%). The most frequent hepatic-related AE were increased ALT (7% in trametinib-treated patients vs. 2% in chemotherapy treated patients) and increased AST (9% vs. 1%). Based on laboratory testing, the incidence of any Grade ALT increase was higher in trametinib-treated patients (67%) than in chemotherapy treated patients (24%) but Grade 3 or 4 increases in ALT were similar between treatment groups, approximately 3% in each.
    - Hypertension:
        - 16% of trametinib-treated patients and 7% of chemotherapy-treated patients experienced hypertension (any Grade) on-treatment. Grade 3-4 hypertension occurred in 13% of trametinib-treated patients and 4% of chemotherapy-treated patients. There were no serious cases of hypertension reported in either treatment group. Most hypertension adverse events occurred in patients with hypertension at baseline: 26/33 (79%) of cases in the trametinib-treatment group and 6/7 (86%) of cases in the chemotherapy-treatment group.
    - Edema
        - 32% of trametinib-treated patients and 4% of chemotherapy-treated patients experienced edema (composite AE of lymphedema, edema, peripheral edema)
    - Rhabdomyolysis
        - The incidence of rhabdomyolysis was 1% in trametinib-treated patients and 0 in chemotherapy-treated patients. All patients experienced the AE within the first month of starting treatment with trametinib. All cases confounded by concomitant medications which are associated with rhabdomyolysis.
- Adverse drug reactions observed in ≥20% of trametinib-treated patients were:
    - Rash
    - Diarrhea
    - Fatigue
    - Peripheral edema
    - Acneiform dermatitis
    - Nausea

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/s/

NORMA S GRIFFIN
05/23/2013

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

Memorandum

Date: May 21, 2013

From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 204114; GlaxoSmithKline, LLC
Proposed Clinical PMRs

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

Dear Mr. Richards:

Please see FDA's post-marketing requirement proposal for the Mekinist (trametinib) NDA application 204114. Please submit your response and provide timelines to our proposal by Wednesday, May 22, 2013.

Post Marketing Requirements (PMRs) Under 505(o)

CLINICAL

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

Milestones

Final Analysis Plan Submission:

Interim Report Submission:

Interim Report Submission:

Interim Report Submission:

Interim Report Submission:

Interim Report Submission:

Interim Report Submission:

Final Report Submission:

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

Milestones

Final Analysis Plan Submission:

Interim Report Submission:

Final Report Submission:

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

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/s/

NORMA S GRIFFIN
05/21/2013

From: Griffin, Norma
Sent: Friday, May 10, 2013 5:25 PM
To: 'eric.2.richards@gsk.com'
Cc: 'ellen.s.cutler@gsk.com'; Libeg, Meredith; Hughes, Monica L
Subject: NDA 204114 MEKINIST (trametinib) - FDA Proposed Edits 5.10.2013

Importance: High

Attachments: FDA Proposed Labeling Mtg as of 5.10.2013 CLEAN.doc; FDA Proposed Labeling Mtg as of 5.10.2013 Tracked Changes.pdf

Good Afternoon Eric,

Please see the attached proposed labeling edits (5.10.2013) for NDA 204114. I have included both a CLEAN WORD document and a Tracked Changes PDF document. In addition, this round of edits does not include edits from Patient Labeling or OPDP - we will provide these later. Please ensure that you address the formatting for the links in the Table of Contents. Also please ensure that the headers for tables are consistent.

We ask that you provide a response by Friday, May 17, 2013, or sooner if possible. Please respond to both Meredith and myself.

FDA Proposed Labeling Mtg as o...

FDA Proposed Labeling Mtg as o...

Kindly respond to confirm receipt of this email and the attached memorandum.

Thanks,

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

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/s/

NORMA S GRIFFIN
05/10/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

INDs 102175 and 105032

MEETING MINUTES

GlaxoSmithKline, LLC
Attention: Eric Richards
Global Regulatory Affairs
1250 South Collegeville Road
UP4110
Collegeville, PA 19426

Dear Dr. Richards:

Please refer to your Investigational New Drug Application (IND) 102175 submitted under section 505(i) of the Federal Food, Drug, and **Cosmetic Act for "trametininb (GSK1120212)" and IND 105032 for "dabrafenib (GSK2118436)".**

We also refer to the meeting between representatives of your firm and the FDA on May 9, 2012. The purpose of the meeting was to discuss in a joint meeting the separate monotherapy marketing applications with a similar proposed **indication of** (b) (4)

(b) (4)

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-4255.

Sincerely,

{See appended electronic signature page}

Norma Griffin
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

MEETING DATE:	Wednesday May 9, 2012
TIME:	10:00-12:00 PM (ET)
APPLICATION:	INDs 102175 and 105032
SPONSOR:	GlaxoSmithKline LLC (GSK)
DRUG NAME:	Dabrafenib (GSK2118436) and trametinib (GSK1120212)
TYPE OF MEETING:	Face-to-Face; Type B Pre-NDA
MEETING CHAIR:	Joseph Gootenberg
MEETING RECORDER:	Norma Griffin

LIST OF FDA ATTENDEES:

CDER

Richard Pazdur, M.D.	Director, OHOP
Anthony Murgo, M.D.	Associate Director for Regulatory Science
Patricia Keegan, M.D.	Director, DOP2/OHOP
Joseph Gootenberg, M.D.	Deputy Director, DOP2/OHOP
Marc Theoret, M.D.	Clinical Reviewer, DOP2/OHOP
Norma Griffin	Regulatory Project Manager, DOP2/OHOP
Sachia Khasar, Ph.D.	Toxicology Reviewer, DHOT/OHOP
Whitney Helms, Ph.D.	Toxicology Team Leader, DHOT/OHOP
Lillian Zhang, Ph.D.	Clinical Pharmacology Reviewer, DCP5/OCP/OTS
Ruby Leong, Ph.D.	Clinical Pharmacology Reviewer, DCP5/OCP/OTS
Hong Zhao, Ph.D.	Clinical Pharmacology Team Leader, DCP5/OCP/OTS
Weishi (Vivian) Yuan, Ph.D.	Statistical Reviewer, DBV5/OB
Jing (Jenny) Zhang, Ph.D.	Statistical Reviewer, DBV5/OB
Kun He, Ph.D.	Statistical Team Leader, DBV5/OB
Jean Mulinde	OC/OSI
Amarilys Vega	OSE/DRISK

CDRH

Donna Roscoe, Ph.D.	Division Director, DIHD/OIVD
Maria Chan	Supervisor Microbiologist, DIHD/OIVD

LIST OF SPONSOR ATTENDEES:

Rafael Amado, M.D.	Clinical Development
Vicki Goodman, M.D.	Clinical Development
Michael Streit, M.D., M.B.A.	Clinical Development
Daniele Ouellet, Ph.D.	CPMS
Michelle Casey, Ph.D.	Biostatistics
Anne-Marie Martin, Ph.D.	Oncology Biomarkers
Jennifer Dudinak, Pharm.D.	Regulatory Affairs
Eric Richards, MS, M.P.H.	Regulatory Affairs
Ellen Cutler	Regulatory Affairs
Amita Chaudhari, M.S.	Regulatory Affairs
Angela Hughes-Earle, D.V.M.	Preclinical safety assessment (by phone)
Kevin French, Ph.D.	Preclinical safety assessment (by phone)
Ajay Singh, M.D.	Global Clinical Safety and Pharmacovigilance (by phone)
Kiran Patel, M.D., M.B.A.	Clinical Development(by phone)
Jeff Legos, PhD, M.B.A.	Clinical Development (by phone)
Steve Lane, M.S.	Biostatistics (by phone)
Laurie Sherman, R.N.	Clinical Development (by phone)
Mary Gucker, M.S.N.	Clinical Development (by phone)
Sandra Perrand	Biomerieux (diagnostic partner) (by phone)

1.0 MEETING OBJECTIVES:

To discuss proposed separate NDA submissions for GSK1120212 (trametinib) and GSK2118436 **(dabrafenib) as individual monotherapy for** (b) (4) (b) (4)

2.0 BACKGROUND:

Dabrafenib (GSK2118436) is a selective inhibitor of B-RAF kinase activity and trametinib (GSK1120212) is a selective inhibitor of MEK1/MEK2 activation and kinase activity. GSK currently has both agents under development (INDs 105032 and 102175) as monotherapy (b) (4) (b) (4) for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma.

On February 14, 2012, GSK requested two Pre-NDA meetings to both INDs 105032 and 102175 to discuss with FDA planned separate monotherapy NDA applications for trametinib (GSK1120212) and dabrafenib (GSK2118436) with a **similar proposed indication of** (b) (4) (b) (4) (b) (4) **Considering the general si**milarity of issues to discuss and to promote efficient meeting management, the Division agreed to an expanded meeting to cover both IND files.

CMC pre-NDA meetings were previous held with FDA on January 31, 2012 (IND 105032) and February 15, 2012 (IND 102175) respectively.

2.1 Trametinib

On July 30, 2010, FDA held a Type B meeting with GSK to discuss the proposed Phase III monotherapy study in BRAF V600 mutation-positive metastatic melanoma. The key issues communicated to GSK were:

- a recommendation that GSK design study MEK114267 with a sole primary endpoint of overall survival (OS) rather than the proposed co-primary endpoints of OS and progression-free survival (PFS)
- an acknowledgement from the Agency that it would be willing to discuss the results of study MEK114267, including the magnitude of the difference between arms and the clinical relevance of this difference, if it were to be designed using PFS as the primary endpoint
- a recommendation that all scans be centrally and independently reviewed if GSK chooses PFS as the primary endpoint of study MEK114267

In the Briefing Document submitted to IND 102175 on April 6, 2012, GSK states that the proposed indication above will be supported by two clinical studies:

- MEK113583, titled "an open-label, multi-center study to investigate the objective response rate, safety, and pharmacokinetics of GSK1120212, a MEK inhibitor, in BRAF mutation-positive melanoma subjects previously treated either with or without a BRAF inhibitor." The trial enrolled patients simultaneously into two cohorts: Cohort A (n=40) enrolled patients who had previously received BRAF-inhibitor therapy, and Cohort B (n=57) enrolled patients who had previously received only prior standard therapy (chemotherapy and/or immunotherapy). Of the patients enrolled in Cohort B, the confirmed response rate (RR) was 25% and the median PFS was 4.0 months (95% CI: 3.6, 5.6). Among the eight Cohort B patients with a $BRAF^{V600K}$ mutation, six had tumor reduction in their target lesions, but only one unconfirmed PR was observed. For the subset of Cohort B patients with a $BRAF^{V600E}$ mutation and no history of brain metastases (n=36), the preliminary median PFS was 5.3 months (95% CI: 3.6, 7.4).

- MEK114267 (METRIC), titled "a phase III randomized, open-label study comparing GSK1120212 to chemotherapy in subjects with advanced or metastatic BRAF V600E/K mutation-positive melanoma."

MEK114267 is a two-arm, open-label, randomized (2:1) Phase III study comparing single agent trametinib to chemotherapy (either dacarbazine or paclitaxel) in 322 patients with histologically confirmed, cutaneous unresectable or metastatic melanoma (Stage IIIc or Stage IV), determined to be BRAF V600 E/K mutation-positive tumor sample based upon centralized testing using the Response Genetics Inc. (RGI) laboratory developed test (LDT). Eligible patients may have received a maximum of one prior regimen of chemotherapy in the advanced or metastatic melanoma setting. The primary endpoint of MEK114267 was PFS— assessed by the

investigator at Week 6, Week 12, Week 21, **Week 30, then every 12 weeks thereafter—in** patients with $BRAF^{V600E}$ mutation-positive melanoma without a prior history of brain metastases. Of note, based on the results from MEK113583, GSK modified the primary endpoint of MEK114267, prior to locking the database and unblinding the trial, in order to exclude from the primary efficacy analysis all patients with $BRAF^{V600K}$ mutation-positive melanoma (n=40) and patients with $BRAF^{V600E}$ (n=8) or $BRAF^{V600E/K}$ (n=1) mutation-positive melanoma and a prior history of brain metastases.

The study has ≥99% power at a 2-sided alpha level of 5% to detect a 133% improvement in PFS [hazard ratio (HR) of 0.43] in patients with $BRAF^{V600E}$ mutation-positive melanoma without a prior history of brain metastases, assuming a median PFS of 3 months in the control arm and 7 months in the experimental arm. The primary analysis is a stratified log-rank test performed on the primary efficacy population ($BRAF^{V600E}$ mutation-positive melanoma without a prior history of brain metastases).

Randomization was stratified based on two factors: (1) LDH [above the upper limit of normal (ULN) vs. equal to or below ULN] and (2) prior chemotherapy for advanced or metastatic disease (Yes vs. No). Patients were randomized to receive trametinib monotherapy (n=214) at a dose of 2 mg administered orally once daily or to receive either of the following two chemotherapies (n=108, combined) at the discretion of the investigator:

- dacarbazine 1000 mg/m^2 administered intravenously (IV) once every 3 weeks
- paclitaxel 175 mg/m^2 administered IV once every 3 weeks

Treatment in either arm continued until disease progression, death, or patient withdrawal from study. Of the 108 patients randomized to the chemotherapy arm, 51 patients crossed over after confirmation of progression by a blinded independent review committee (BIRC) and received trametinib.

According to the Briefing Document, MEK114267 met its primary endpoint; within the primary efficacy analysis population, median PFS as assessed by the investigator was 4.8 months in the trametinib arm vs. 1.4 months on the chemotherapy arm [HR: 0.44 (95% confidence interval: 0.31, 0.64); $p<0.0001$]. Secondary analyses of PFS within the primary efficacy analysis population as assessed by the BIRC and within the ITT population as assessed by the investigator demonstrated similar results.

Efficacy results of MEK 114267, summarized from the Briefing Document, are shown in the following table:

	TRAMETINIB	CHEMOTHERAPY
PROGRESSION-FREE SURVIVAL		
Primary Efficacy Population[a]		
N	**178**	**95**
Events, N (%)	**96 (54%)**	**68 (72%)**
Median, months	**4.8**	**1.4**
HR (95% CI), p-value	**0.44 (0.31, 0.64), p<0.0001**	
Primary Efficacy Population[b]		
Median, months	4.9	1.6
HR (95% CI)	0.41 (0.29, 0.60)	
ITT Population[a]		
N	214	108
Events, N (%)	118 (55%)	77 (71%)
Median, months	4.8	1.5
HR (95% CI)	0.45 (0.33, 0.63)	
OVERALL SURVIVAL[c]		
Events, N (%)	28 (16%)	26 (27%)
Withdrawals from study, (%)	(5%)	(13%)
Median, months	NR	NR
HR (95% CI)	0.53 (0.30, 0.94)	
OBJECTIVE RESPONSE RATES		
Primary Efficacy Population[a,d] % (95% CI)	24% (18.0, 31.1)	7% (3.0, 14.6)
ITT Population[a,e] % (95% CI)	22% (16.6, 28.1)	8% (3.9, 15.2)
ITT Population[b,e] % (95% CI)	19% (14.1, 25.1)	5% (1.5, 10.5)

[a] Investigator assessed; [b] IRC assessed; [c] ITT population; [d] confirmed response rates; [e] confirmed or unconfirmed response rate; NR, Not reached; CI, confidence interval; * Primary endpoint shown in bold

The Briefing Document summarizes the safety results of MEK114267. The safety population comprises 211 patients on the trametinib arm and 99 patients on the chemotherapy arm. The summary of adverse events provided in the Briefing Document is shown in the table below:

	TRAMETINIB N=211	CHEMOTHERAPY N=99
Any AE, n (%)	209 (>99)	91 (92)
AEs related to study treatment	205 (97)	77 (78)
AEs leading to permanent	20 (9)	9 (9)
AEs leading to dose reduction	58 (27)	10 (10)
AEs leading to dose	74 (35)	22 (22)
Any SAE, n (%)	38 (18)	20 (20)
SAEs related to study treatment	19 (9)	11 (11)
Fatal SAEs	4 (2)	2 (2)
Fatal SAEs related to study treatment	1 (<1)	0

According to the Briefing Document, key toxicities (all grades) of trametinib vs. chemotherapy included the following: rash (57% vs. 10%), diarrhea (43% vs. 16%), peripheral edema (26% vs. 3%), hypertension (15% vs. 7%), and ejection fraction decrease (5% vs. 0). Additional adverse events of special interest occurring more frequently in the trametinib treated group compared to the chemotherapy treated group included ocular events (9% vs. 3%) and pneumonitis (1% vs. 0). The Briefing Document reports that no cases of cutaneous squamous cell carcinoma or hyperproliferative skin lesions were observed with trametinib.

2.2 Dabrafenib

On July 6, 2010, FDA held a Type B, End of Phase 1 (EOP1)/Pre-Phase 3 meeting with GSK to discuss the development program for dabrafenib in the proposed indication treatment of patients with BRAF V600E/K (b) (4) [redacted] (b) (4) or metastatic melanoma. GSK proposed to conduct two clinical studies to support the proposed indication: (1) study BRF113710, a Phase 2 single-arm, open label, study of GSK2118436 in 100 patients with BRAF mutant metastatic melanoma (Stage IV) who received prior systemic therapy to evaluate an overall response rate primary endpoint and (2) study BRF113683, a two-arm, open-label, randomized Phase 3 study comparing dacarbazine (DTIC) to the single agent GSK2118436 in 600 patients to evaluate co-primary endpoints of PFS and OS. The key agreements and issues communicated to GSK were:

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

FDA held a Type A Meeting on October 7, 2010, to **discuss GSK's revised clinical development** plan. Key issues communicated to GSK were:

- if an approval in BRAF mutant melanoma is granted based on an improvement in OS, ORR would not be considered an acceptable endpoint for FDA approval in this population
- an improvement in PFS of sufficient magnitude may be an appropriate endpoint for the proposed phase 3 study (BRF113683) provided that an improvement in OS is not demonstrated in a prior approval of another drug in the proposed population
- use of DTIC may not be an appropriate control for BRF113683 and the Agency suggested that a possible trial design may include a three-arm randomized study of GSK1120212 vs. GSK2118436 vs. the combination

[redacted] (b) (4)

GSK states that the proposed indication, [redacted] (b) (4) (b) (4) (b) (4) **will be primarily supported by** the following three primary clinical studies:

- BRF113710 (BREAK-2), a Phase II, single-arm, open-label study to assess the efficacy, safety, and tolerability of GSK2118436 administered twice daily as a single agent in 92 patients with previously treated, $BRAF^{V600E}$ (n=76) or $BRAF^{V600K}$ (n=16) mutation-positive metastatic melanoma. The overall investigator-assessed confirmed response rate in the $BRAF^{V600E}$ population was 59%, and the overall investigator-assessed confirmed response rate in the $BRAF^{V600K}$ population was 13%.

- BRF113929 (BREAK-MB), a Phase II open-label, two-cohort, multicentre study of GSK2118436 as a single agent in treatment naïve and previously treated subjects with $BRAF^{V600E}$ or $BRAF^{V600K}$ mutation-positive metastatic melanoma to the brain to assess the efficacy, pharmacokinetics, safety, and tolerability of an oral, twice daily dose of 150 mg GSK2118436. Patients were enrolled in two cohorts: (1) no prior local therapy for brain metastases (Cohort A) and (2) prior local therapy for brain metastases (Cohort B). The primary efficacy objective was to assess the overall intracranial response rate (OIRR) in $BRAF^{V600E}$ mutation-positive patients, as assessed by the investigator, in each Cohort. The table below summarizes the response rates, intracranial and overall, based on the addendum to the Pre-NDA Briefing Document submitted to FDA on April 26, 2012:

	$BRAF^{V600E}$		$BRAF^{V600K}$	
	COHORT A N=74 n (%)	COHORT B N=65 n (%)	COHORT A N=15 n (%)	COHORT B N=18 n (%)
INTRACRANIAL[a]				
Investigator				
CR+PR	29 (39%)	20 (31%)	1 (7%)	4 (22%)
CR	2 (3%)	0	0	0
95% CI	28.0%, 51.2%	19.9%, 43.4%	0.2%, 31.9%	6.4%, 47.6%
Independent radiologist				
CR+PR	15 (20%)	12 (18%)	0	2 (11%)
CR	1 (1%)	0	0	0
95% CI	11.8%, 31.2%	9.9%, 30.0%	0, 21.8%	1.4%, 34.7%
OVERALL[a,b]				
CR+PR	28 (38%)	20 (31%)	0	5 (28%)
CR	0	0	0	0
95% CI	26.8%, 49.9%	19.9%, 43.4%	0, 21.8%	9.7%, 53.5%

[a] confirmed objective response rates
[b] investigator assessed

- BRF113683 (BREAK-3), a Phase III randomized, open-label study comparing dabrafenib (GSK2118436) to DTIC in previously untreated subjects with BRAF^{V600E} [redacted] (b) (4) metastatic (Stage IV) melanoma. This study allowed DTIC subjects to cross-over to dabrafenib upon progression.

BRF113683 is a two-arm, open-label, randomized (3:1) Phase III study comparing single agent dabrafenib to dacarbazine in 250 patients with histologically confirmed, cutaneous unresectable or metastatic melanoma (Stage IIIc or Stage IV), determined to be BRAF^{V600E} mutation-positive based upon centralized testing using the RGI LDT. Randomization was stratified for Stage (unresectable III+IVM1a+IVM1b vs. IVM1c). The primary endpoint of investigator-assessed PFS was achieved in subjects with BRAF^{V600E} mutation-positive melanoma.

The study has a >95% power at a one-sided alpha level of 2% to detect a 200% increase in median PFS (HR of 0.33) in patients with BRAF^{V600E} mutation-positive melanoma, assuming a median PFS of 2 months in the DTIC arm and 6 months in the dabrafenib arm. The primary analysis of PFS is estimated using Kaplan-Meier method and compared using a log-rank test stratified on disease staging (unresectable III+IVM1a+IVb vs. IVM1c).

Patients were randomized to receive dabrafenib monotherapy (n=187) at a dose of 150 mg administered orally twice daily or to receive DTIC monotherapy (n=63) at a dose of 1000 mg/m^2 administered intravenously (IV) once every 3 weeks. Treatment in either arm continued until disease progression, death, or patient withdrawal from study. Of the 63 patients randomized to the DTIC arm, 28 patients crossed over to receive dabrafenib after confirmation of radiologic progression.

According to the Briefing Document, BRF113683 met its primary endpoint; dabrafenib demonstrated a 70% reduction in the risk of tumor progression or death compared to DTIC [HR 0.30 (96% CI: 0.18, 0.53); p<0.0001]. Median PFS was 5.1 months on the dabrafenib arm vs. 2.7 months on the DTIC arm. GSK states that median PFS estimate for the GSK2118436 arm is unstable based upon the 40% of the patients on the GSK2118436 arm that were administratively censored for PFS prior to the reported estimated median. The hazard ratio for independent-reviewer (IR) assessment of PFS, a secondary endpoint of the trial, was 0.35 (95% CI: 0.20, 0.61) with a median PFS of 6.7 months on the dabrafenib arm vs. 2.9 months on the DTIC arm. Overall survival was not mature as there were only 30 deaths observed at the time of clinical cut-off; median OS was not reached in either arm. The best overall response rate was higher on the dabrafenib arm compared to the DTIC arm as assessed by the investigator (53% vs. 19%) and as assessed by independent review (50% vs. 6%).

The efficacy results as reported in the Briefing Document are summarized in the following table:

	DABRAFENIB N=187	DTIC N=63
PROGRESSION-FREE SURVIVAL		
Investigator Assessment		
Median, months	**5.1**	**2.7**
HR (95% CI), p-value	**0.30 (0.18, 0.53), p<0.0001**	
Independent Review[b]		
Median, months	6.7	2.9
HR (95% CI)	0.35 (0.20, 0.61)	
OVERALL SURVIVAL[c]		
Events, n (%)	21 (11%)	9 (14%)
Median, months	NR	NR
HR (95% CI)	0.61 (0.25, 1.48)	
OBJECTIVE RESPONSE RATES		
Investigator Assessment[a,d] % (95% CI)	53% (45.5, 60.3)	19% (10.2, 30.9)
CR, n (%)	6 (3%)	0
Independent Review[a,e] % (95% CI)	50% (42.4, 57.1)	6% (1.8, 15.5)

NR, Not reached
* Primary endpoint shown in bold

According to the Briefing Document, the key toxicities (all grades) occurring more frequently with dabrafenib than DTIC include: hyperkeratosis (37% vs. 0), headache (32% vs. 8%) pyrexia (28% vs. 10%), arthralgia (27% vs. 2%), skin papilloma (24% vs. 2%), cutaneous squamous cell carcinoma/keratoacanthoma (8% vs. 0). Adverse events such a neutropenia (1% vs. 17%), anaemia (4% vs. 12%) and abdominal pain (4% vs. 14%) occurred more frequently with DTIC.

2.3 Companion Diagnostic

Within the trametinib and dabrafenib development programs, patients were selected for eligibility for treatment using a CLIA-certified "laboratory developed test" (LDT) which was developed by Response Genetics Inc. (RGI). According to the Briefing Document, the RGI BRAF assay is an allele-specific polymerase chain reaction (PCR) assay, which differentiates the V600E and K mutation forms, and is performed on DNA extracted from fresh frozen paraffin embedded (FFPE) melanoma tumors. Following interactions with the FDA's Office of In Vitro Diagnostics (OIVD) on May 19, 2010, the RGI LDT underwent full analytical validation rendering the assay as an "investigational use only (IUO)" assay which has been used to screen subjects for eligibility onto GSK-sponsored clinical study MEK114267, and the dabrafenib studies in the same patient population; i.e. studies BRF113710, BRF113683 and BRF113929.

Further, GSK states that it has partnered with bioMerieux (bMx) in the co-development of a companion diagnostic (cDx) assay to be available at the time of dabrafenib and trametinib registration. Clinical validation in support of licensure of the cDx will come from the Phase III

study (MEK114267). GSK and partners have worked closely with the OIVD throughout development with regard to the data needed to demonstrate comparability of the RGI IUO to the intended commercial cDx. Concordance and equivalency will be demonstrated using the bMx THxIDTM BRAF assay retrospectively, with the banked samples from the clinical studies. All data will be submitted by bioMerieux as part of a PMA application at the time of the NDA submission.

Preliminary FDA responses were communicated to GSK on May 7, 2012

3.0 DISCUSSION

SPONSOR SUBMITTED TRAMETINIB QUESTIONS AND FDA RESPONSE:

Filing and Labeling

1. The pivotal study MEK114267 will provide the primary evidence to support the proposed indication for trametinib. In this study, the primary endpoint of progression-free survival was achieved in subjects with BRAF V600E mutation-positive melanoma. Median PFS was 4.8 months with trametinib vs. 1.4 months with chemotherapy (HR: 0.44 [95%CI: 0.31, 0.64]; p<0.0001). Overall survival, the secondary endpoint of the study was analyzed at the time of primary endpoint analysis. The median overall survival was not reached in either arm but showed statistical significance HR 0.53 [0.30, 0.94]; p = 0.0181. Very similar results were seen in the ITT population, which included patients with V600K mutations. These data will be supported by results from the Phase II study MEK113583.

   Does the Agency agree that these data, along with other data (i.e. nonclinical, clinical pharmacology, etc.) outlined in this briefing document, provide adequate basis to support the following proposed indication: (b) (4)

   (b) (4)

   FDA RESPONSE: The design and the reported results of Study MEK114267 together with the proposed supportive data appear sufficient to support the filing of an NDA from a clinical perspective. The wording of the final indication statement will be determined based on the NDA review.

   Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

2. On October 3 2011, GSK amended the protocol for MEK114267 to change the population of the primary analysis of this study to only those subjects with a BRAF V600E mutational status without prior brain metastases. This change was made to focus the study on the population most likely to benefit from GSK1120212 based on data from the Phase II study MEK113583, which reported out shortly prior to the protocol amendment. Data from MEK113583 seemed to indicate that the defined population of subjects with BRAF V600E mutational status without a prior history of brain metastases

had a slightly better outcome than subjects with V600K mutational status or those with a prior history of brain metastases. This change to the primary analysis was made prior to Data Base Freeze and unblinding.

As described in section 2.3.3.3 of this briefing document, the primary analysis population for the study (MEK114267), i.e. those with V600E mutational status without prior history of brain metastases, derived clinically meaningful and statistically significant benefit from trametinib compared to chemotherapy; based on the primary endpoint and all secondary endpoints. Notwithstanding the change to the protocol, GSK notes that very similar results are seen in the ITT population, in addition to the all population subgroups (e.g. with and without prior chemotherapy, V600K). Importantly, the hazard ratio for the subgroup of subjects with the BRAF V600K mutation was similar to that of the primary analysis population and the ITT population. While the number of subjects with prior brain metastases in the study (N=11) is too small to make conclusions, and the comparison of subjects with and without prior chemotherapy is of limited value given the current clinical environment, GSK believe that the evidence produced from the ITT population and the V600K sub-population provide substantive evidence of the benefit trametinib may offer to patients with V600K mutations. In addition, the companion diagnostic for trametinib has been validated in subjects with BRAF V600E and V600K mutations. As such, GSK believes that it is reasonable to consider labeling that is inclusive of V600K and V600E mutational status based on the ITT population, V600K subgroup analyses, and the analytically/clinically validated companion diagnostic in BRAF V600E and V600K mutations.

Does the Agency agree?

FDA RESPONSE: FDA agrees to consider labeling that is inclusive of V600K and V600E mutational status and of patients with brain metastases if safety and efficacy in the subgroups are adequately supported by the clinical study results and mechanism of action of trametinib. However, since the majority of patients in the ITT were those with BRAF V600E mutation-positive melanoma without a prior history of brain metastases, FDA would also request to include results from that subset.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

3. Section 3.5.1.1 of this Briefing Document contains a list of the clinical pharmacology studies and population analysis reports to be included in the trametinib NDA submission.

Does the FDA agree that the clinical pharmacology package is sufficient for filing?

FDA RESPONSE: No. Bioanalytical methods with validation reports and final study reports should be included in the trametinib NDA submission to allow assessment of the following:

- *In vitro* ability of trametinib (and its major metabolites) to act as substrates, inhibitors or inducers of cytochrome P450 enzymes, transporters, and conjugating enzymes to determine the need to conduct PK drug interaction trial(s). Refer to

the **Guidance for Industry entitled** "*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf.

- Pathways by which trametinib (and its active metabolites) are eliminated to determine the need to conduct dedicated organ impairment trial(s). Refer to the **Guidances for Industry entitled** "*Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM204959.pdf and "*Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf.

Timelines for completing the planned QTc Study MEK114655 should be provided. In addition, please address the following clinical pharmacology-related questions in the Summary of Clinical Pharmacology Studies in Module 2 of the NDA submission:

- What is the basis for selecting the dose(s) and dosing regimen used in the registration trial(s)?
- What are the exposure-response relationships (dose-response, exposure-response) for efficacy?
- What are the exposure-response relationships (dose-response, exposure-response) for safety?
- How is the QT prolongation potential of trametinib assessed? What are the conclusions and proposed labeling description?
- What are the characteristics of absorption, distribution, metabolism, and excretion of trametinib?
- What are the effects of food on the bioavailability of trametinib, and dosing recommendation with regard to meals or meal types?
- What influence do the intrinsic factors (as listed below but not limited to) have on trametinib exposure and/or its pharmacodynamic response? What is their clinical impact? What dose and dosing regimen adjustments are recommended?
  - gender
  - race
  - weight
  - disease
  - genetic polymorphism
  - hepatic impairment

- renal impairment

- What influence do the extrinsic factors (as listed below but not limited to) have on trametinib exposure and/or its pharmacodynamic response? What is their clinical impact? What dose and dosing regimen adjustments are recommended?
  - concomitant medications
  - CYP and/or transporter based drug-drug interactions
  - diet
  - smoking

Please apply the following advice regarding format and content of datasets related to clinical pharmacology sections of the NDA submission:

i. Provide complete datasets for clinical pharmacology and biopharmaceutics studies. The datasets should not be limited to PK/PD. For example, domains related to safety (e.g., AEs), demographics, non-PK laboratory values, concomitant drug use should be included. All of these are important in identifying patterns of potential clinical pharmacology related causes of clinical safety outcomes and facilitating exploratory exposure-response analyses and population PK analyses.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

ii. Provide all concentration-time and derived PK parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

iii. Present the PK parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate in the study reports.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

iv. Provide a table listing of patients with renal or hepatic impairment who have received trametinib, organized by trial number. Include available renal and hepatic function parameters such as SCr, CLCr calculated by the Cockcroft Gault equation and/or eGFR calculated by MDRD, AST/ALT, total bilirubin, etc. for each patient in the listing. Also, provide a summary of the following information for each patient: PK and PD data, safety, and clinical efficacy.

GSK Email Response of 5/8/2012: GSK will provide a table listing of patients with renal or hepatic impairment including serum creatinine, creatinine clearance (Cockcroft Gault and MDRD), AST, ALT, bilirubin, etc, that are included in the population PK analysis of trametinib. The population PK analysis included 200 subjects from the first-time-in-human study (MEK111054), 96 subjects from the Phase II study (MEK113583) and 197 subjects from the Phase III study (MEK114267) who received trametinib. GSK notes that the Agency has requests summaries of information, per patients, for PK, PD, efficacy and clinical safety. GSK will provide datasets separately for the exposure-response analysis on key adverse events, progression free survival (PFS), objective response, and tumor size, which included 97 subjects from the Phase II study (MEK111583) and 211 subjects from the Phase III study (MEK114267).

Discussion During Meeting 5/9/2012: FDA stated that GSK's response to FDA's comment provided in Section 3.iv is acceptable. GSK agreed to provide the milestone timelines for completion of the QTc study as part of the post marketing requirement.

v. Submit the following datasets to support the population PK analysis:

- SAS transport files (*.xpt) for all datasets used for model development and validation
- Description of each data item provided in a Define.pdf file [any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets]
- Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model [submit these files as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt)]
- Model development decision tree and/or table which gives an overview of modeling steps

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

vi. For the population analysis reports, submit:

- Standard model diagnostic plots
- Individual plots for a representative number of subjects including observed concentrations, the individual prediction line, and the population prediction line
- Model parameter names and units in tables [for example, oral clearance should be presented as CL/F (L/h) and not as THETA(1)]
- Summary of the report describing the clinical application of modeling results.

For or more information, refer to the following pharmacometric data and models submission guidelines at

http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

vii. Explore exposure-response (measures of effectiveness, biomarkers, and toxicity) relationships for trametinib and its active metabolite(s) in the targeted patient population and include the results of this exploratory analysis in the NDA submission.

For more information, refer to Guidance for Industry found at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf and

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

viii. Submit the following items for QT/QTc assessment:

- Copy of the QT/QTc study protocol
- Copy of the Investigator's Brochure
- Annotated CRF
- Define file which describes the contents of the electronic data sets
- Electronic data sets as SAS transport files (in CDISC SDTM format – if possible) and all the SAS codes for the analyses
- ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
- Completed Highlights of Clinical Pharmacology Table

GSK Email Response of 5/8/2012: GSK submitted the proposed QTc protocol to FDA on November 30, 2011 and received comments from FDA February 8, 2012. GSK formally submitted the amended protocol, based on FDA comments, last week. The study will begin shortly. No discussion needed on Question 3viii.

4. Appendix 2 of this Briefing Document contains a summary list of the nonclinical studies to be included in the trametinib NDA submission.

Does the FDA agree that the nonclinical data package is sufficient for filing?

FDA RESPONSE: GSK's list of nonclinical studies appears sufficient for filing. A final decision will be made following review of data submitted with the NDA.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

Content and Format of the NDA

5. Appendix 1 of this Briefing Document describes how GSK plans (b) (4) (b) (4) for the trametinib NDA submission and Section 3.2.2 outlines how the text portions of the ISS/ISE will be handled.

   a) Does the FDA agree with the Summary Document Analysis Plan (SDAP) proposed in Appendix 1?

   FDA RESPONSE: No, the proposal (b) (4) is not acceptable. If possible, the data should be recoded to a single NCI CTCAE version prior to integrating the data across studies.

   GSK Email Response of 5/8/2012: GSK does not believe that recoding to a single NCI CTCAE version prior to integrating the data across studies is warranted or advisable. The data integration plan developed to include as many patients as possible in the indicated population at the recommended dose, in order to provide the most robust assessment of safety. Importantly, the impact of including studies coded with CTCAE v3 is expected to be minimal due to the following:

   - Terms are coded from inv reported term to a PT using MedDra
   - Only severity grading is potentially impacted by CTCAE
   - Most safety outputs including SAEs, AEs leading to dose modifications and withdrawals, laboratory/ECG data will be unaffected
   - For most events there is little or no difference in grading between the two versions

   The consistency of the safety profile between ph 3 and ISS also supports this approach. It should be noted that for the few events that may be impacted by change in CTCAE version, re-coding of events from CTCAE v3 to v4 is not recommended, as details of clinical events which may affect grading between versions are not available; therefore making the recoding of these events an unreliable process.

   In the dabrafenib ISS, only one study (BRF112680) utilized the CTCAE Version 3, which encompasses 47 patients of the ISS dataset. All other studies including the integration utilized CTCAE Version 4. Therefore, for dabrafenib, approximately 8% of the ISS population utilized CTCAE Version 3, all other subjects were assessed with Version 4.

In the trametinib ISS, the phase I (MEK111054, ISS N = 21) and phase II (MEK113583, ISS N = 97) studies utilized CTCAE Version 3, which encompasses 118 patients of the ISS dataset. The phase III study (MEK114267) utilized CTCAE Version 4. Therefore, for trametinib approximately 36% of the ISS population utilized CTCAE Version 3.

Discussion During Meeting 5/9/2012 for Questions 5a and 22a: FDA agreed that GSK should not recode adverse events from one CTCAE version to another version for the proposed NDA submission. However, FDA requested and GSK agreed to provide a tabular summary of the incidence of adverse events grouped by toxicity severity that is limited to clinical trials conducted using the same CTCAE version (i.e., CTCAE version 3 or version 4). GSK also agreed to provide the corresponding pooled data sets with submission of the trametinib NDA.

b) **Does the FDA agree with the approach for utilizing the integrated summaries of efficacy and safety in the module 2.7.3 and 2.7.4 summaries, respectively, with tables and datasets for the pooled analyses of safety included in m5.3.5.3 as outlined in Section 3.2.2?**

FDA RESPONSE: The proposal to include the text portion of the integrated summary of efficacy (ISE) and the integrated summary of safety (ISS) in modules 2.7.3 and 2.7.4, respectively, is acceptable if the narrative portions of modules 2.7.3 and 2.7.4 are sufficiently detailed to serve as the narrative portion of the ISE and the ISS. However, presenting a summary of the individual efficacy results from each study in Module 2.7.3 as proposed in Section 3.2.2 of the Briefing Document may not be sufficient to satisfy the requirements under 21 CFR 314.50. Please refer to the FDA "Guidance for Industry: Integrated Summary of Effectiveness" which can be accessed at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

6. Table 18, in Section 3.5.1, outlines how each of the studies for inclusion into the NDA will be reported within Module 5.

Does the Agency agree with the proposal?

FDA RESPONSE: Yes.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

Listings, Narratives and Case Report Forms

7. **Does the FDA agree with the proposal for submission of listings, narratives and case report forms as described in Section 3.5.1?**

   FDA RESPONSE: The proposal is acceptable to support clinical review of the NDA, but it is not sufficient to provide data necessary to support clinical study site inspections by FDA. Please refer to Appendix 1 (Part I and Part II of OSI pre-NDA Request) for the format in which these data should be provided.

   In addition to those proposed in Section 3.5.1, FDA may request that GSK submit additional listings, narratives, and case report forms during the review of the NDA.

   Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

Risk Management Plan

8. **Does the FDA agree with the proposed content and format of the Risk Management Plan as described in Section 3.1.2?**

   FDA RESPONSE: The proposed risk management plan does not provide sufficient detail for FDA to comment. A complete review of the full risk management plan in conjunction with the full clinical review after the NDA is submitted will be necessary to determine whether it is acceptable, since additional information regarding risks and safe product use may emerge during the review of the NDA.

   Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

Datasets

9. Section 3.5.2 describes the studies for which GSK will provide SAS transport files (i.e. datasets) in the trametinib NDA submission. In addition, the format of the datasets is described.

   Does the Agency agree with these proposals?

   FDA RESPONSE: Yes, the proposal for submission of the clinical and clinical pharmacology datasets appear acceptable, however an additional dataset is requested to support clinical study site selection for inspection (see Appendix 1, Part III of request). **In addition, please refer to FDA's Response** to Question #3 regarding the format and content of datasets for clinical pharmacology sections of the NDA submission.

   Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

Safety Update

10. For the trametinib NDA 120 Day safety update, GSK will submit updated safety information using the data cut-off date June 23, 2012.

Does the FDA agree with this approach for the NDA?

FDA RESPONSE: Yes.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

11. The Agency was recently informed about 5 cases of sudden death/cardiac arrest reported coincident with the administration of trametinib. Assessment of these cases is complicated by the significant underlying co-morbidities and the lack of information regarding the proximate cause of death. At present, association of sudden death/cardiac arrest with trametinib remains unclear. In **evaluating these cases, GSK's internal safety** review board advised that an independent adjudication of cases be conducted to more fully understand these events. GSK plans to have an independent adjudication of relevant cases [redacted] (b) (4) (including review of all SAEs associated with fatal outcomes and cardiac SAEs). The scope of this adjudication and the attendant charter are currently being developed [redacted] (b) (4). GSK anticipates completing the activity by end of third quarter.

GSK is planning to submit the final report of this adjudication to the Agency once completed; under the assumption that the Agency wishes to review the report. As described above, the timing of the adjudication will not permit the final report to be submitted with the initial trametinib NDA, but GSK would like to offer that the report be submitted during the 120-day safety update, or earlier if the Agency wishes (the report will likely be completed prior to the 120-day submission date).

Does the Agency wish GSK to submit the report to NDA at the 120-day safety update or early if feasible?

FDA RESPONSE: FDA requests that GSK submit the report as soon as it becomes available.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

Financial Disclosure

12. For trametinib NDA, GSK has determined that studies MEK113583 and MEK114267 are covered studies under 21 CFR Part 54. Form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) and, if applicable, Form 3455 (Disclosure Financial Interests and Arrangements of Clinical Investigators) will be included in the NDA submission for these studies.

Does the FDA agree with these proposals?

FDA RESPONSE: Yes.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

Diagnostic Question

13. **A PMA submission to CDRH is projected for July 2012. Does the Agency require any documentation or data elements related to the companion diagnostic included in the trametinib NDA submission?**

FDA RESPONSE: Please include in the clinical study report for Study MEK 114267 the results of the exploratory analysis of efficacy based on the population identified as V600K mutation-positive and V600E mutation-positive according to the to-be-marketed diagnostic test. The clinical data sets should include information on the mutation status based on the to-be-marketed test to allow FDA to confirm the exploratory analysis.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

Potential Combination File

14. In Section 4.3, GSK outlines potential timing for the mature data from BRF113220.

a.) **Should the mature data from this study prove compelling, does the Agency agree that a Type A meeting to discuss the results and a potential file based on these results is appropriate?**

FDA RESPONSE: FDA agrees a meeting is appropriate, however, a Type A meeting would not be the correct category as this type of meeting is reserved to "help an otherwise stalled product development program proceed." Please see Guidance for Industry: Formal Meetings Between the FDA and Sponsors for Applicants (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm153222.pdf).

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

b.) **Should the mature data from this study prove compelling, does the Agency agree that the proposed filing strategy described in Section 4.3 is reasonable?**

FDA RESPONSE: The proposed filing strategy should be discussed at the time of the requested meeting.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

Additional Clinical Comment:

15. Please clarify in the trametinib Briefing Document the total number of patients with $BRAF^{V600E}$ mutation-positive melanoma and brain metastases within the ITT population of trial MEK114267. Based on the tabulations provided in Table 4, there were eight such patients. However, page 18 states that there were nine V600E patients with documented brain metastases.

    GSK Email Response of 5/8/2012: As requested by the Agency, GSK is clarifying here the number of patients in the ITT population of MEK114267 with a prior history of brain metastases. In this study, there were 8 patients that had tumors which were BRAF V600e positive with a prior history of brain metastases and 2 patients that had tumors which were BRAF V600k positive with a prior history of brain metastases. No discussion is required for this question.

SPONSOR SUBMITTED DABRAFENIB QUESTIONS AND FDA RESPONSE:

Filing and Labeling

16. The pivotal study BREAK-3 will provide the primary evidence to support the proposed indication for dabrafenib. Headline efficacy and safety data are provided in Section 2.3.3. In the primary analysis of PFS, dabrafenib demonstrated a 70% reduction in the risk of progression or death compared to DTIC (HR 0.30 [96% CI- 0.18, 0.53]; p<0.0001). A consistent benefit was seen by independent radiographic review, as well as across pre-defined subgroup analyses. These data will be supported by results from the Phase II studies BREAK-2 and BREAK-MB.

    Does the Agency agree that these data, along with other data (i.e. nonclinical, clinical pharmacology, etc.) outlined in this briefing document, provide adequate basis to support a filing for the following proposed indication: (b) (4)

    FDA RESPONSE: The design and the reported results of Study BREAK-3 together with the proposed supportive data appear sufficient to support the filing of an NDA from a clinical perspective. The wording of the final indication statement will be determined based on the NDA review.

    Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

17. As noted in section 2.3.3.3 of this briefing document, the hazard ratios for the investigator-assessed PFS (primary endpoint) and the independent review committee (IRC) -assessed PFS were similar; 0 30 (95% CI: 0.18, 0.53) and 0.35 (95% CI: 0.20, 0.61) respectively. There were some small distinctions in the median PFS values. The investigator-assessed median for dabrafenib was 5.1 versus 2.7 on DTIC, while the IRC-assessed values were 6.7 months for dabrafenib versus 2.9 months for DTIC. Similarly, there were some distinctions noted in the best overall response rates (RR) by each assessment: by investigator-assessment the RR was 53% for dabrafenib versus 19% for DTIC, while IRC-assessed values were 50% for dabrafenib and 6% for DTIC. Although both investigator assessed and independent radiologist reviews demonstrated that PFS and RR were significantly higher for dabrafenib compared to DTIC, GSK believes there is value in presenting both and proposes to include both investigator and IRC assessments within the clinical trials section of the label.

Does the Agency agree?

FDA RESPONSE: The Clinical Studies section of the label should provide information from adequate and well-controlled studies that provide primary support for effectiveness and that facilitate an understanding of how to use the drug safety and effectively. Including information from the prespecified, IRC-assessed PFS endpoint in the absence of a pre-specified plan for controlling type I error is not likely to provide additional information useful to prescribing physicians. (b) (4)

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

18. Patients with the BRAF V600K subtype were included in the Phase I study BRF112680, BREAK-2 and BREAK-MB. The literature suggests that approximately 5-15% of the overall BRAF V600 mutation population carry V600K mutations [COSMIC database; Rubinstein, 2010; Long, 2010, and Cheng, 2011]. In the studies noted above, using the RGI test which is specific for both V600E and V600K subtypes, approximately 50 patients with the V600K subtype were enrolled; representing approximately 5-10% of the efficacy population studies with dabrafenib on these studies. Therefore the sample population enrolled in the dabrafenib clinical studies would appear representative of the expected rates based on the current literature.

In BREAK-2 a confirmed investigator-assessed response rate of 13% was observed in patients with BRAF V600K mutations. In addition, 44% of the BRAF V600K population had stable disease for at least 12 weeks. Although these subjects did not meet protocol defined criteria for response as per RECIST, many had shrinkage of tumor. Median duration of response and median PFS for the V600K population were 22.9 weeks and 19.7 weeks, respectively. The Phase II study BREAK-MB also included subjects with BRAF V600K mutations. As noted previously in this document, data from this study will be reported shortly. The Summary of Clinical Efficacy will summarize the outcome

measures for subjects with V600K muations, in terms of response rate and duration of response, across the studies.

(b) (4)

FDA RESPONSE: Under 21 CFR 201.57, indications listed in the *Indications and Usage* Section of the label must be supported by substantial evidence of effectiveness based on adequate and well-controlled trials.

(b) (4)

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

19. The majority, ranging from 20-75%, of patients with advanced melanoma develops brain metastases. The prognosis for these patients is generally very poor; with a median overall survival of 2.8 to 4 months. As these patients are typically excluded from clinical trials, there is currently a lack of proven effective treatment for these patients with concurrent CNS and systemic metastases.

Data from a cohort of patients (n=10) on the Phase I study BRF112680, indicated that dabrafenib was active in the treatment of intracranial metastases; in addition to the effect seen on systemic lesions. On the basis of this early signal of clinical activity, a global, multi-center, open-label, two-cohort, Phase II study (BRF113292) was initiated to evaluate the activity of dabrafenib in subjects with histologically confirmed (Stage IV) BRAF (V600E or V600K) mutation-positive melanoma metastatic to the brain. This study enrolled 172 patients into two cohorts: Cohort A (subjects with no prior local therapy for brain metastasis) or Cohort B (subjects who received prior local therapy for brain metastasis). A description of the study design for BRF113292 is provided in section 2.3.4.1 of this briefing document.

The primary analysis of BRF113929 is nearly completed and as soon as the data is available, GSK proposes to submit the headline data in advance of our 09MAY12 pre-NDA meeting as an addendum to this briefing document. Should the data from BRF113929 be positive, GSK believes that this information would be valuable for prescribers and patients, and would warrant inclusion in the clinical trials section of the label.

Does the agency agree that patients with systemic disease and active brain metastases encompass an unmet medical need and therefore data from this prospective Phase II study could warrant inclusion into the clinical trials section of the label?

FDA RESPONSE: Under 21 CFR 201.57, indications listed in the *Indications and Usage* Section of the label must be supported by substantial evidence of effectiveness based on adequate and well-controlled trials.

FDA agrees to consider labeling that is inclusive of patients with brain metastases if safety and efficacy in this subgroup is adequately supported by clinical study results and mechanism of action of dabrafenib.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

20. Section 3.5.1.1 of this Briefing Document contains a list of the clinical pharmacology studies and population analyses to be included in the dabrafenib NDA submission.

Does the FDA agree that the clinical pharmacology package is sufficient for filing?

FDA RESPONSE: The NDA filing decision will be made in the context of the entirety of the NDA submission. The sufficiency of the clinical pharmacology package is judged by its adequacy to support labeling languages for general pharmacokinetics information, drug-drug interaction, organ dysfunction, specific populations and QT interval evaluation. FDA recommends that GSK include the full study report for the drug-drug interaction study BRF113771 in the NDA submission and provide study protocols and timelines for completing the planned organ dysfunction studies and QTc study. In addition, as FDA communicated at the End-of-Phase 2 meeting on July 6, 2010, please address how GSK is going to evaluate 1) the effect of a strong CYP3A4 inducer on the PK of dabrafenib and its active metabolites, 2) the inhibition potential of dabrafenib and its major metabolites on medications that are substrates of CYP2C19, CYP2C8, OATP1B1, or OATP1B3, and 3) the induction potential of dabrafenib and its major metabolites on medications that are substrates of CYP2B6.

GSK Email Response of 5/8/2012: GSK would like to clarify that study BRF113771 is ongoing. An interim report including complete results on Cohort D (n=13 subjects) which characterize the effect of single and repeat dose dabrafenib administered as HPMC capsules and interim results on Cohort B (n=8 out of 12 subjects) which assess the effect of ketoconazole on the pharmacokinetics of dabrafenib. Results from full Cohort B, Cohort A (effect of dabrafenib on warfarin) and Cohort C (effect of gemfibrozil on dabrafenib) are not yet available. No discussion is needed on this particular point.

Discussion During Meeting of 5/9/2012: GSK stated that they will include interim data for cohort B and complete data for cohort D from Study BRF113771 in the NDA submission for dabrafenib. GSK agreed to provide the anticipated study completion date and submission date for the final study report for Study BRF113771 as milestones for the post marketing requirement addressing potential drug interactions.

With respect to the NDA submission, FDA has the following recommendations:

a. In the NDA submission, please address the following clinical pharmacology related questions:

- What is the basis for selecting the dose(s) and dosing regimen used in the registration trial(s)?
- What are the exposure-response relationships (dose-response, exposure-response) for efficacy?
- What are the exposure-response relationships (dose-response, exposure-response) for safety?
- How is the QT prolongation potential of dabrafenib assessed? What are the conclusion and proposed labeling description?
- What are the characteristics of absorption, distribution, metabolism and excretion of dabrafenib?
- What are the effects of food on the bioavailability of dabrafenib and dosing recommendation with regard to meals or meal types?
- What influence do the intrinsic factors (as listed below but not limited to) have on dabrafenib exposure and/or its pharmacodynamic response? What is their clinical impact? What dose and dosing regimen adjustments are recommended?
  - gender
  - race
  - weight
  - disease
  - genetic polymorphism
  - hepatic impairment
  - renal impairment
- What influence do the extrinsic factors (as listed below but not limited to) have on dabrafenib exposure and/or its pharmacodynamic response? What is their clinical impact? What dose and dosing regimen adjustments are recommended?
  - concomitant medications
  - CYP and/or transporter based drug-drug interactions
  - diet
  - smoking

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

b. Apply the following advice in preparing clinical pharmacology sections of the NDA submission:

i. Submit bioanalytical method(s) and validation reports for clinical pharmacology and biopharmaceutics studies.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

ii. Provide complete datasets for clinical pharmacology and biopharmaceutics studies. The datasets should not be limited to PK/PD. For example, domains related to safety (e.g., AE's), demographics, non-PK laboratory values, concomitant drug use should be included. All of these are important in identifying patterns of potential clinical pharmacology related causes of clinical safety outcomes and facilitating exploratory exposure-response analyses and population PK analyses.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

iii. Provide all concentration-time and derived PK parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

iv. Present the PK parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate in the study reports.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

v. Provide a table listing of patients with renal or hepatic impairment who have received dabrafenib, organized by trial number. Include available renal and hepatic function parameters such as SCr, CLCr calculated by the Cockcroft Gault equation and/or eGFR calculated by MDRD, AST/ALT, Total Bilirubin, etc., for each patient in the listing. Also, provide a summary of the following information for each patient: PK and PD data, safety, and clinical efficacy.

GSK Email Response of 5/8/2012: GSK will provide a table listing of patients with renal or hepatic impairment including creatinine clearance (Cockcroft Gault and MDRD), AST, ALT, bilirubin (when available), etc, that are included in the population PK analysis of dabrafenib. The population PK analysis included 181 subjects from the first-time-in-human study (BRF112680), 87 subjects from the Phase II study (BRF113710), 148 subjects from the Phase II study in subjects with brain metastases (BRF113929), and 179 subjects from the Phase III study (BRF113683) who received dabrafenib. GSK notes that the Agency has requests

summaries of information, per patients, for PK, PD, efficacy and clinical safety. GSK will provide datasets separately for the exposure-response analysis on key adverse events, progression free survival (PFS), objective response, and tumor size, which included 112 subjects from the Phase I study (BID regimen; BRF112680), 92 subjects on the Phase II study (BRF113710), 148 subjects on the Phase II study with brain metastases (AE ONLY; BRF113929) and 188 subjects from the Phase III study (BRF113683).

Discussion During Meeting 5/9/2012: FDA stated that GSK's response to FDA's comment provided in Section 20.b.v is acceptable. GSK agreed to provide milestone timelines for the planned dedicated organ dysfunction studies as part of the proposed post marketing requirements.

vi. Submit the following datasets to support the population PK analysis:

- SAS transport files (*.xpt) for all datasets used for model development and validation
- Description of each data item provided in a Define.pdf file [any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets]
- Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model [submit these files as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt)]
- Model development decision tree and/or table which gives an overview of modeling steps

For the population analysis reports, submit:

- Standard model diagnostic plots
- Individual plots for a representative number of subjects including observed concentrations, the individual prediction line and the population prediction line
- Model parameter names and units in tables [for example, oral clearance should be presented as CL/F (L/h) and not as THETA(1)]
- Summary of the report describing the clinical application of modeling results

For more information, refer to the following pharmacometric data and models submission guidelines at

http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

vii. Explore exposure-response (measures of effectiveness, biomarkers and toxicity relationships for dabrafenib and its active metabolite(s) in the targeted patient population and include the results of this exploratory analysis in the NDA submission. For more information, refer to Guidance for Industry found at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf and

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

viii. Submit the following items for QTc study/assessment:

- Copy of the clinical protocol
- Copy of the Investigator's Brochure
- Annotated CRF
- Define file which describes the contents of the electronic data sets
- Electronic data sets as SAS transport files (in CDISC SDTM format – if possible) and all the SAS codes for the analyses
- ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
- Completed Highlights of Clinical Pharmacology Table

GSK Email Response of 5/8/2012: GSK submitted the proposed QTc protocol (including all components outlined in the preliminary comments) to FDA on April, 19 2012 and is awaiting comments from the Agency. No discussion is needed on question 20viii.

Discussion During Meeting 5/9/2012: FDA acknowledged receipt of GSK's proposed study protocol BRF113773 for evaluation of QTc prolongation potential of dabrafenib which is under review by QT-IRT and a response will be communicated GSK once review is completed. GSK agreed to provide milestone timelines Study BRF113773 as part of the proposed post marketing requirement.

21. Appendix 2 of this Briefing Document contains a summary list of the nonclinical studies to be included in the dabrafenib NDA submission.

Does the FDA agree that the nonclinical data package is sufficient for filing?

FDA RESPONSE: GSK's list of nonclinical studies appears sufficient for filing. A final decision will be made following review of data submitted with the NDA.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

Content and Format of the NDA

22. The Summary Document Analysis Plan included in Appendix 1 and Section 3.2.2 of this Briefing Document outline GSK's plans [redacted] (b) (4) for the dabrafenib NDA submission.

a) Does the FDA agree with the proposed plans?

FDA RESPONSE: No, the proposal [redacted] (b) (4) is not acceptable. If possible, the data should be recoded to a single NCI CTCAE version prior to integrating the data across studies.

GSK Email Response of 5/8/2012: GSK does not believe that recoding to a single NCI CTCAE version prior to integrating the data across studies is warranted or advisable. The data integration plan developed to include as many patients as possible in the indicated population at the recommended dose, in order to provide the most robust assessment of safety. Importantly, the impact of including studies coded with CTCAE v3 is expected to be minimal due to the following:

- Terms are coded from inv reported term to a PT using MedDra
- Only severity grading is potentially impacted by CTCAE
- Most safety outputs including SAEs, AEs leading to dose modifications and withdrawals, laboratory/ECG data will be unaffected
- For most events there is little or no difference in grading between the two versions

The consistency of the safety profile between ph 3 and ISS also supports this approach. It should be noted that for the few events that may be impacted by change in CTCAE version, re-coding of events from CTCAE v3 to v4 is not recommended, as details of clinical events which may affect grading between versions are not available; therefore making the recoding of these events an unreliable process.

In the dabrafenib ISS, only one study (BRF112680) utilized the CTCAE Version 3, which encompasses 47 patients of the ISS dataset. All other studies including the integration utilized CTCAE Version 4. Therefore, for dabrafenib,

approximately 8% of the ISS population utilized CTCAE Version 3, all other subjects were assessed with Version 4.

In the trametinib ISS, the phase I (MEK111054, ISS N = 21) and phase II (MEK113583, ISS N = 97) studies utilized CTCAE Version 3, which encompasses 118 patients of the ISS dataset. The phase III study (MEK114267) utilized CTCAE Version 4. Therefore, for trametinib approximately 36% of the ISS population utilized CTCAE Version 3.

Discussion During Meeting 5/9/2012: FDA requested and GSK agreed to provide a tabular summary of the incidence of adverse events grouped by toxicity severity that is limited to clinical trials conducted using CTCAE version 4 in the trametinib NDA. GSK also agreed to provide the corresponding pooled data set with submission of the dabrafenib NDA.

Also see discussion for Question 5a.

b) Does the FDA agree with the approach for utilizing the integrated summaries of efficacy and safety in the module 2.7.3 and 2.7.4 summaries, respectively, with tables and datasets for the pooled analyses of safety included in m5.3.5.3?

FDA RESPONSE: The proposal to include the text portion of the integrated summary of efficacy (ISE) and the integrated summary of safety (ISS) in modules 2.7.3 and 2.7.4, respectively, is acceptable if the narrative portions of modules 2.7.3 and 2.7.4 are sufficiently detailed to serve as the narrative portion of the ISE and the ISS. However, presenting a summary of the individual efficacy results from each study in Module 2.7.3 as proposed in Section 3.2.2 of the Briefing Document may not be sufficient to satisfy the requirements under 21 CFR 314.50. Please refer to the FDA "Guidance for Industry: Integrated Summary of Effectiveness" which can be accessed at

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079803.pdf.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

Listings, Narratives and Case Report Forms

23. **Does the FDA agree with the proposal for submission of listings, narratives and case report forms as described in Section 3.5.1?**

FDA RESPONSE: The proposal is acceptable to support clinical review of the NDA, but it is not sufficient to provide data necessary to support clinical study site inspections by FDA. Please refer to Appendix 2 (Part I and Part II of OSI pre-NDA Request) for the format in which these data should be provided.

In the NDA submission, please assure that all narratives for patients who develop second primary malignancies include at a minimum the following information:

- Patient age, gender, and race
- Medical history including risk factors relevant to developing the second primary malignancy
- Concomitant medications
- Onset of the second primary malignancy in relation to exposure to the study drug
- A detailed summary of the anatomical/pathological features related to the risk of recurrence or metastasis
- Available results of staging evaluations
- Treatments planned and/or administered
- Outcome of the treatment, if available

In addition to those proposed in Section 3.5.1, FDA may request that GSK submit additional listings, narratives, and case report forms during the review of the NDA.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

Risk Management Plan

24. **Does the FDA agree with the proposed content and format of the Risk Management Plan as described in Section 3.1.2?**

FDA RESPONSE: The proposed risk management plan does not provide sufficient detail for FDA to comment. A complete review of the full risk management plan in conjunction with the full clinical review after the NDA is submitted will be necessary to determine whether it is acceptable, since additional information regarding risks and safe product use may emerge during the review of the NDA.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

Datasets

25. Section 3.5.2 describes the studies for which GSK will provide SAS transport files (i.e. datasets) in the dabrafenib NDA submission. In addition, the format of the datasets is described.

Does the Agency agree with these proposals?

FDA RESPONSE: Yes, the proposal for submission of the clinical and clinical pharmacology datasets appear acceptable, however an additional dataset is requested to

support clinical study site selection for inspection (see Appendix 2, Part III of request). In addition, please refer to FDA's Response to Question #20 regarding the format and content of datasets for clinical pharmacology sections of the NDA submission.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

Safety Update

26. For the dabrafenib NDA four-month safety update, GSK will submit updated safety information using the data cut-off date June 23, 2012.

Does the FDA agree with this approach for the NDA?

FDA RESPONSE: Yes.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

Financial Disclosure

27. For the dabrafenib NDA, GSK has determined that studies BREAK-3, BREAK-MB, BREAK-2 and BRF112680 are covered studies under 21 CFR Part 54. Form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) and, if applicable, Form 3455 (Disclosure Financial Interests and Arrangements of Clinical Investigators) will be included in the NDA submission for these studies.

Does the FDA agree with these proposals?

FDA RESPONSE: Yes.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

Diagnostic Question

28. A PMA submission to CDRH is projected for July 2012.

Does the Agency require any documentation or data elements related to the companion diagnostic included in the dabrafenib NDA submission?

FDA RESPONSE: Please include in the clinical study report for Study BREAK-3 the results of the exploratory analysis of efficacy based on the population identified as V600E mutation-positive according to the to-be-marketed diagnostic test. The clinical data sets should include information on the mutation status based on the to-be-marketed test to allow FDA to confirm the exploratory analysis.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

Additional Chemistry, Manufacturing, and Controls Comments (for both trametinib and dabrafenib)

29. In the forthcoming NDA applications, provide a complete listing of all manufacturing, testing, packaging and labeling sites for the drug substance and drug product. Ensure that all sites are ready for inspection at the time of NDA submission.

Discussion During Meeting 5/9/2012: GSK acknowledged FDA's response. There was no discussion during the meeting.

Additional Discussion

Appendix 1 (trametinib) and Appendix 2 (dabrafenib)

GSK Email Response of 5/8/2012 for Appendix 1: It appears that GSK will be able to provide the vast majority of the requested items for OSI in the initial NDAs. If there are any items that **can't be provided in the initial NDA, GSK will** communicate this to the Agency in the coming weeks, along with estimation of when the items will be available. **Does the Agency concur?**

Discussion During Meeting 5/9/2012: FDA requested and GSK agreed that Part 1 and 3 of the Appendix 2 requests be submitted formally to the preNDA prior to the NDA submission. Part 2 (Line Listings) should come in the initial NDA submission.

Post Meeting Note: As stated in the discussion above for Appendix 2, Appendix 1 items should be similarly submitted.

Filing Strategy

GSK Email Response of 5/8/2012 for Dabrafenib and Trametinib Filing Strategy: GSK would like to communicate the updated filing strategy for dabrafenib and trametinib to the Agency and understand if these proposals raise any topics for discussion during our May 9 meeting.

Based on the results of BREAK-MB, a robust study in patients with brain metastases, GSK intends to request a priority review of dabrafenib. The data from this study demonstrate safety and effectiveness in a population that represent an area of unmet medical need. This NDA submission will occur in July of this year.

GSK believes trametinib monotherapy provides an alternative treatment option for patients with BRAF V600 mutation-positive melanoma. As the planned mono-therapy file is close to the read-out of the Phase II combination study BRF113220, GSK intends to submit the trametinib mono-therapy NDA [redacted] (b) (4) [redacted]; assuming this data is compelling enough to warrant filing. This filing [redacted] (b) (4) monotherapy [redacted] (b) (4) would happen within the fourth quarter of this year.

This proximity of filling the mono-therapy data [redacted] (b) (4) will better align with the anticipated usage of the drug (as single-agent [redacted] (b) (4)), and facilitate greater efficiency in the crafting of submission documents and labeling. [redacted] (b) (4) [redacted]. GSK will reevaluate the timing of an NDA submission for trametinib mono-therapy.

Lastly, the submission of a PMA will be filed concurrently with the dabrafenib NDA submission. To summarize, the following filling timelines are projected as follows:

- Dabrafenib mono-therapy NDA: July, 2012
- Trametinib mono-therapy NDA [redacted] (b) (4) [redacted] 4Q2012
- PMA filing:
  - Manufacturing section: June, 2012
  - Remaining sections: July, 2012

Discussion During Meeting 5/9/2012: GSK intends to submit the dabrafenib NDA in July and BioMerieux will submit the PMA for the companion diagnostic to CDRH in July 2012. FDA stated that this approach is acceptable. FDA **recommended that due to GSK's plans to submit a** single NDA containing results for the trametinib monotherapy [redacted] (b) (4) [redacted]

CDRH stated that whether a PMA supplement would be required for bridging data to support trametinib alone [redacted] (b) (4) depends on the PMA status. CDRH also recommends that BioMerieux or Response Genetics submit an IDE for the companion diagnostic in the event that final action on the PMA is pending at the time of NDA approval for the BRAF inhibitor.

FDA will provide additional advice on whether the trametinib application for monotherapy (b) (4) [redacted]

FDA also requested that GSK develop a proposal [redacted] (b) (4) [redacted]

Post Meeting Note: CDRH has determined that the best path forward is that if the first PMA is approved, BioMerieux should submit a PMA supplement. If the PMA is pending, then BioMerieux should submit a new original PMA and then it will be converted to a supplement after the first PMA is approved.

ACTION ITEMS

- FDA will provide additional advice [redacted] (b) (4)
- GSK's proposed study protocol BRF113773 for evaluation of QTc prolongation potential of dabrafenib is under review by QT-IRT. A response will be communicated GSK once review is completed.
- GSK agreed to submit Parts 1 and 3 of the Appendix 2 to the preNDA prior to the NDA submission and to submit Part 2 (Line Listings) in the initial NDA submission.
- GSK develop a proposal [redacted] (b) (4)

APPENDICES

- Appendix 1 – OSI Pre-NDA Request (for Trametinib-IND 102175)
- Appendix 2 – OSI Pre-NDA Request (for Dabrafenib-IND 105032)
- Appendix 3 – DOP2's End-of-Phase 2 General Advice for Planned Marketing Applications
- Appendix 4 – Additional DBOP CDISC Guidance
- Appendix 5 – Meeting Attendance List

Appendix 1
OSI Pre-NDA Request

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 2/3 clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)

2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 2/3 clinical trials:
   a. Number of subjects screened for each site by site
   b. Number of subjects randomized for each site by site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed Phase 2/3 clinical trials:
   a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
   b. Name, address and contact information of all CROs used in the conduct of the clinical trials
   c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
   d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)

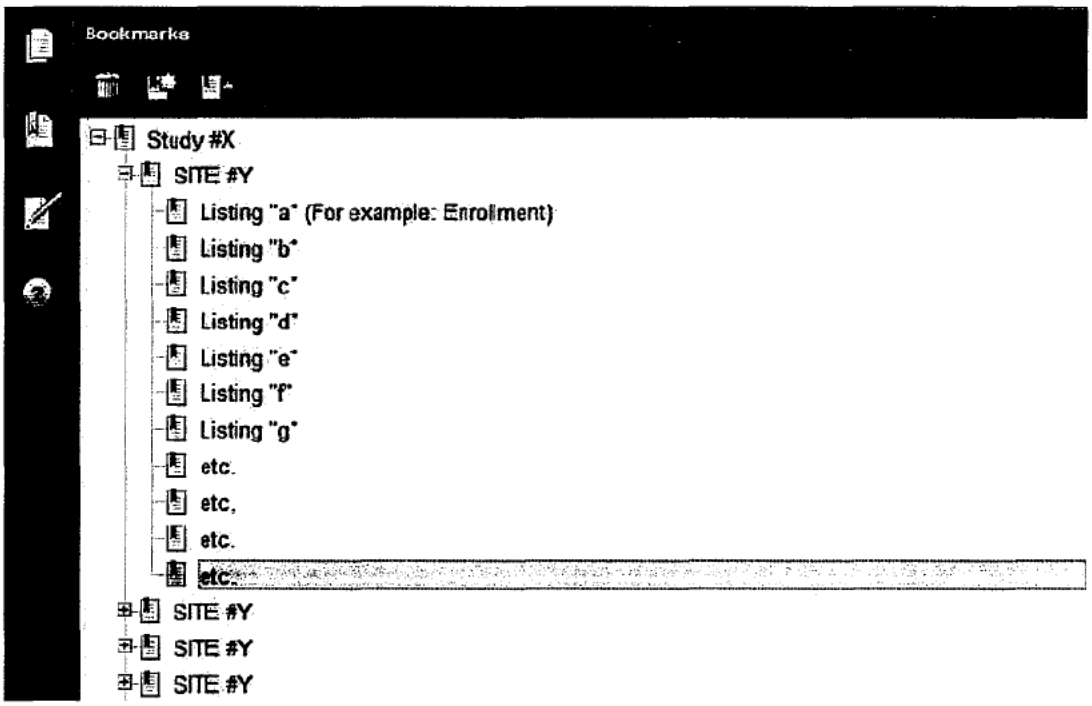
4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data ("line") listings. For each site provide line listings for:
   a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
   b. Subject listing for treatment assignment (randomization)
   c. Subject listing of subjects that crossed over to GSK 1120212 treatment, if applicable
   d. Subject listing of drop-outs and subjects that discontinued with date and reason
   e. Evaluable subjects/ non-evaluable subjects and reason not evaluable
   f. By subject listing of eligibility determination (clinical investigator assessment of each inclusion and exclusion criterion should be included)
   g. Adverse event listings (inclusive of preferred/investigator terms, start/stop time and date, investigator assessment of relatedness to study drug, seriousness/severity, treatment for AE, action taken, and outcome):
      i. By subject listing, of AEs, SAEs, deaths and dates
      ii. By subject listing, of AEs of special interest (Hepatic events, Skin related events, Diarrhea, Visual disorders, Cardiac related events, and Pneumonitis)
   h. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
   i. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint. For example, specific data points (e.g., target/non-target lesion MRI/CT measurements, development of new lesions, non-measurable disease burden assessment, if used, etc.) used by the clinical investigator to make assessment of overall response for subjects should be included as well as the clinical investigator's overall assessment.
   j. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   k. By subject listing of treatment compliance
   l. By subject listing of 12 led ECG results
   m. By subject listing of echocardiogram/MUGA scan results
   n. By subject listing, of laboratory tests performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Attachment 1, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

For pivotal Trametinib studies we request that the site specific efficacy results be reported for both the PFS (progression free survival) and OS (overall survival) endpoints.

Attachment 1

1 Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

1.1 Introduction

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

1.2 Description of the Summary level clinical site dataset

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection to facilitate the evaluation of the application. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)

- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.

- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report.

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) –the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, "TRTEFFR."

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.

- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.

- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).

- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the "endpoint" plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1: *Table 1 Clinical Site Data Elements Summary Listing (DE)*. A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt).

Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description
1	STUDY	Study Number	Char	String	Study or trial identification number.
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation Domain abbreviation is also used as a prefix for the variables to ensure unic datasets are merged.
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in th while the study was ongoing, enter an integer indicating the total number of there was no change in the sponsor while the study was ongoing, enter "1".
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of st completion, as defined in 21 CFR 312.3(a).
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8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not appl 1.
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applic applicable, enter -1.
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, e
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study repo characters).
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.
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Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description
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17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to ever
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.
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21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not ap enter -1.
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm should include multiple events per subject and all event types (i.e., not limite those that are deemed related to study drug or treatment emergent events).
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by arm. This value should include multiple events per subject.
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defin study report. This value should include multiple violations per subject and a type (i.e., not limited to only significant deviations).
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount ($USD) by any single investigator by the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 860). If unable to obtain the information required to the corresponding stater 1.
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount ($USD) by site calculated as the sum of di the principal investigator and all sub-investigators to include all required pari the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 860). If unable to obtain the information required to the corresponding stater 1.

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.
31	MINITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US nu
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicabl
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, eac following example data set and a total of 8 rows for the entire data set.

Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	EN
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FIN
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	1
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0

Appendix 1
OSI Pre-NDA Request

MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville

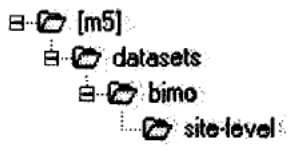
Attachment 2

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

Appendix 2
OSI Pre-NDA Request

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct the inspections (Item I and II).

The dataset that is requested as per Item III below, is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 2, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and specific Clinical Investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed Phase 2/3 clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Current Location of Principal Investigator (if no longer at Site): Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)

2. Please include the following information in a tabular format by site in the original NDA for each of the completed Phase 2/3 clinical trials:
   a. Number of subjects screened for each site by site
   b. Number of subjects randomized for each site by site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed Phase 2/3 clinical trials:
   a. Location of Trial Master File [actual physical site(s) where documents are maintained and would be available for inspection]
   b. Name, address and contact information of all CROs used in the conduct of the clinical trials
   c. The location (actual physical site where documents are maintained and would be available for inspection) for all source data generated by the CROs with respect to their roles and responsibilities in conduct of respective studies
   d. The location (actual physical site where documents are maintained and would be available for inspection) of sponsor/monitor files (e.g. monitoring master files, drug accountability files, SAE files, etc.)

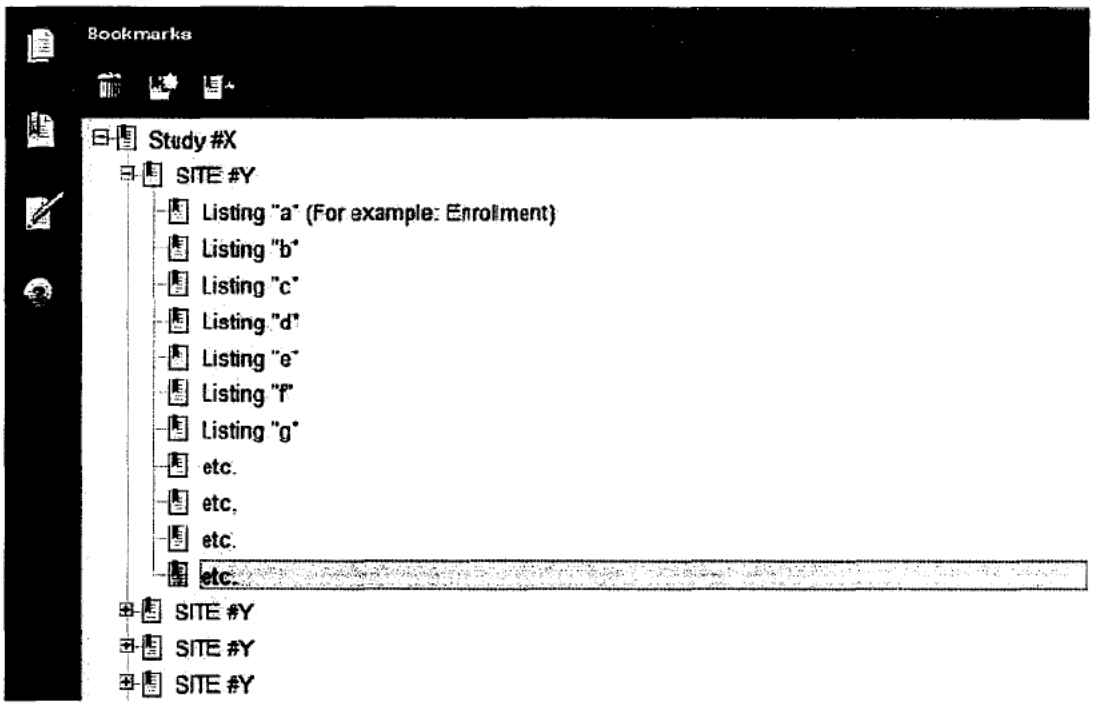
4. For each pivotal trial provide a sample annotated Case Report Form (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

5. For each pivotal trial provide original protocol and all amendments (if items are provided elsewhere in submission, please describe location or provide a link to requested information).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data ("line") listings. For each site provide line listings for:
   a. Listing for each subject/number screened and reason for subjects who did not meet eligibility requirements
   b. Subject listing for treatment assignment (randomization)
   c. Subject listing of subjects that crossed over to GSK2118436 treatment, if applicable
   d. Subject listing of drop-outs and subjects that discontinued with date and reason
   e. Evaluable subjects/ non-evaluable subjects and reason not evaluable
   f. By subject listing of eligibility determination (clinical investigator assessment of each inclusion and exclusion criterion should be included)
   g. Adverse event listings (inclusive of preferred/investigator terms, start/stop time and date, investigator assessment of relatedness to study drug, seriousness/severity, treatment for AE, action taken, and outcome):
      i. By subject listing, of AEs, SAEs, deaths and dates
      ii. By subject listing, of AEs of special interest [cutaneous squamous cell carcinoma and keratoacanthomas, actinic keratoses, other treatment emergent malignancies, renal failure, cardiac valvular abnormalities, uveitis, abnormal ejection fraction (defined as LVEF < LLN and > 10% decrease), serious non-infectious febrile syndrome (SNIFS), pyrexia, and neutropenia (defined as SAEs and grades 3/4 only).]
   h. By subject listing of protocol violations and/or deviations reported in the NDA, description of the deviation/violation
   i. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint. For example, specific data points (e.g., target/non-target lesion MRI/CT measurements, development of new lesions, non-measurable disease burden assessment, if used, etc.) used by the clinical investigator to make assessment of overall response for subjects should be included as well as the clinical investigator's overall assessment.
   j. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   k. By subject listing of treatment compliance
   l. By subject listing of 12 led ECG results
   m. By subject listing of echocardiogram/MUGA scan results
   n. By subject listing, of laboratory tests performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

Electronic submission of site level datasets will facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. Please refer to Attachment 1, "Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions" for further information. We request that you provide a dataset, as outlined, which includes requested data for each pivotal study submitted in your application.

For pivotal Dabrafenib we request that the site specific efficacy results be reported for both the PFS (progression free survival) and OS (overall survival) endpoints for studies that included these as primary and secondary endpoints.

Attachment 1

1 Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

1.1 Introduction

The purpose of this pilot for electronic submission of a single new clinical site dataset is to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process in support of the evaluation of data integrity.

1.2 Description of the Summary level clinical site dataset

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

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If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, "TRTEFFR."

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- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.

- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).

- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the "endpoint" plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

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8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not appl 1.
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applic applicable, enter -1.
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, e
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study repo characters).
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21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not ap enter -1.
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm should include multiple events per subject and all event types (i.e., not limite those that are deemed related to study drug or treatment emergent events).
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by arm. This value should include multiple events per subject.
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defin. study report. This value should include multiple violations per subject and a type (i.e., not limited to only significant deviations).
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount ($USD) by any single investigator by the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 860). If unable to obtain the information required to the corresponding stater 1.
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount ($USD) by site calculated as the sum of di the principal investigator and all sub-investigators to include all required pari the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 860). If unable to obtain the information required to the corresponding stater 1.

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.
31	MINITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US nu
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicabl
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, eac following example data set and a total of 8 rows for the entire data set.

Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	EN
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FIN
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	

Appendix 2
OSI Pre-NDA Request

MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville

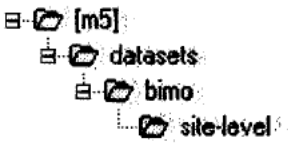
Attachment 2

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

DOP2's End-of-Phase 2
General Advice for Planned Marketing Applications

NDA and BLA applications must comply with all applicable statutes and regulations (e.g. 21 CFR 314, 21 CFR Part 201, and 21 CFR Parts 600 and 601). In addition, FDA has published many guidance documents (available at: www.fda.gov/RegulatoryInformation/Guidances/default.htm) that contain important information necessary for preparing a complete, quality application.

CDER strongly encourages IND sponsors and NDA/BLA applicants to consider the implementation and use of data standards prior to the submission of an NDA or BLA. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of the studies.

Please refer to following draft Guidance for Industry regarding the submission of standardized study data:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf.

Additionally, the **Study Data Standards Common Issues Document** can be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm. The purpose of the document is to highlight important aspects of CDISC and STDM datasets that should be addressed by the Sponsor/Applicant regarding submission of CDISC data in support of an application for registration.

In addition to the information and guidance provided in the above FDA web-links, the Division Oncology Products 2 (DOP2) has attached a separate document that details additional Oncology Specific domains and variables that we request be used for all oncology submissions.

Based on our experience with marketing applications, the following tables focus on specific areas of an application and are intended to help you plan and prepare for submitting a quality application. These comments do not include all issues you need to consider in preparing an application, but highlight areas where we have seen problems and/or issues that can delay our timely review of applications. These are general comments; if you believe some are inapplicable to your planned application we encourage you to provide justification and discuss it with us.

NDA/BLA content and format

CLINICAL

1) Original versions of all protocols, statistical analysis plans, Data Safety Monitoring Board (DSMB) and adjudication committee charters, and all amendments.

2) Minutes of all DSMB and efficacy endpoint review/adjudication committee meetings.

3) Investigator instructions that may have been produced in addition to the protocol and investigator brochure

4) All randomization lists and, if used, IVRS datasets (in SAS transport format)

5) All datasets used to track adjudications (in SAS transport format)

6) A Reviewers Guide to the data submission that includes, but is not limited to the following:

   a) description of files and documentation
   b) description of selected analysis datasets
   c) key variables of interest, including efficacy and safety variables
   d) SAS codes for sub-setting and combining datasets
   e) coding dictionary used
   f) methods of handling missing data
   g) list of variable contained in every dataset
   h) listing of raw data definitions
   i) analysis data definitions
   j) annotated CRF (the annotated CRF should contain links connecting to the document that defines the variable name and lists the data sets that contain the specific item)
   k) documentation of programs

7) Clinical study report(s) for all trials [should follow the ICH E3 Structure and Content of Clinical Study Reports guidance (www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129456.pdf)].

8) Pediatric Studies:

   All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is exempt (i.e. orphan designation), waived or deferred. We request that you submit a pediatric plan that describes development of your product to provide important information on the safe and effective use of in the pediatric population where it may be used. If the product will not be used in pediatric populations your application must include a specific waiver request with the NDA submission, including supporting data. A request for deferral, must include a pediatric plan, certification of the grounds for deferring the assessments, and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time.

9) Quantitative Safety Analysis Plan (QSAP):

   The QSAP should state the adverse events of special interest (AESI), the data to be collected to characterize AESIs, and quantitative methods for analysis, summary and data presentation. The QSAP provides the framework to ensure that the necessary data to understand the premarketing safety profile are obtained, analyzed and presented appropriately. When unanticipated safety

issues are identified the QSAP may be amended. At a minimum the Safety Analysis Plan should address the following components:

a) Study design considerations (See: FDA Guidance to Industry: Premarketing Risk Assessment, (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf).
b) Safety endpoints for Adverse Events of Special Interest (AERI)
c) Definition of Treatment Emergent Adverse Event (TEAE)
d) Expert adjudication process (Expert Clinical Committee Charter or Independent Radiology Review Charter))
e) Data/Safety Monitoring Committee (DSMC): (Attach Charter to QSAP)
f) Analytical methods (e.g., data pooling or evidence synthesis): statistical principles and sensitivity analyses considered.

10) Integrated summaries of safety and effectiveness (ISS/ISE) as required by 21 CFR 314.50 and in conformance with the following guidance documents:
   a) Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf)
   b) Cancer Drug and Biological Products-Clinical Data in Marketing Applications (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071323.pdf)

11) Perform SMQs on the ISS adverse event data that may further inform the safety profile for your investigational agent, and include the results in the ISS report

12) A statement that the manufacturing facilities are ready for inspection upon FDA receipt of the application

13) A chronology of prior substantive communications with FDA and copies of official meeting/telecom minutes.

14) References:

There should be active links from lists of references to the referenced article.

Studies, Data And Analyses

15) Provide a table listing all of the manufacturing facilities (e.g. drug product, drug substance, packaging, control/testing), including name of facility, full address including street, city, state, country, FEI number for facility (if previously registered with FDA), full name and title, telephone, fax number and email for on-site contact person, the manufacturing responsibility and function for each facility, and DMF number (if applicable).

16) Provide a table with the following columns for each of the completed Phase 3 clinical trials:
   a) Site number

b) Principle investigator
c) Location: City State, Country
d) Number of subjects screened
e) Number of subjects randomized
f) Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites for inspection)
g) Number of protocol violations (Major, minor, including definition)

17) Provide an assessment of safety as per the Guidance for Industry: Premarketing Risk Assessment (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf).

18) Provide detailed information, including a narrative (data listings are not an acceptable substitute for a narrative), for all patients who died while on study or who terminated study drug or participation in the study prematurely including those categorized as other, lost to follow up, physician decision, or subject decision. Narrative summaries should contain the following components:
a) subject age and gender
b) signs and symptoms related to the adverse event being discussed
c) an assessment of the relationship of exposure duration to the development of the adverse event
d) pertinent medical history
e) concomitant medications with start dates relative to the adverse event
f) pertinent physical exam findings
g) pertinent test results (for example: lab data, ECG data, biopsy data)
h) discussion of the diagnosis as supported by available clinical data
i) a list of the differential diagnoses, for events without a definitive diagnosis
j) treatment provided
k) re-challenge and de-challenge results (if performed)
l) outcomes and follow-up information
m) an informed discussion of the case, allowing a better understanding of what the subject experienced.

19) Provide complete case report forms (CRFs) for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events. You should be prepared to supply any additional CRFs with a rapid turnaround upon request.
20) Provide reports for any autopsies conducted on study.

21) For patients listed as discontinued to due "investigator decision," "sponsor request," "withdrew consent," or "other," the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated. In addition, the verbatim description from the CRF should be included

as a variable in the adverse event data set.

22) Regulations require that the safety and effectiveness data be presented for subgroups including "by gender, age, and racial subgroups". Therefore, as you are gathering your data and compiling your application, we request that you include this data and pertinent analysis

23) The clinical information contained in the NDA/BLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP) 6010.3 (www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm080121.pdf). To facilitate the review, we request you provide analyses and discussion, where applicable, that will address the items in the template, including:
   a) Other Relevant Background Information – important regulatory actions in other countries or important information contained in foreign labeling.
   b) Exposure-Response Relationships – important exposure-response assessments.
   c) Less common adverse events (between 0.1% and 1%).
   d) Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values.
   e) Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers.
   f) Marked outliers and dropouts for laboratory abnormalities.
   g) Analysis of vital signs focused on measures of central tendencies.
   h) Analysis of vital signs focused on outliers or shifts from normal to abnormal.
   i) Marked outliers for vital signs and dropouts for vital sign abnormalities.
   j) A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the "investigations" SOC or in a SOC pertaining to the specific abnormality. For example, all AEs coded as "hyperglycemia" (SOC metabolic) and "low blood glucose" (SOC investigations) should be tabulated. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value.
   k) Overview of ECG testing in the development program, including a brief review of the nonclinical results.
   l) Standard analyses and explorations of ECG data.
   m) Overdose experience.
   n) Analysis and summary of the reasons and patterns of discontinuation of the study drug. Identify for each patient the toxicities that result in study discontinuation or dose reduction.
   o) Explorations for:
      i) Possible factors associated with a higher likelihood of early study termination; include demographic variables, study site, region, and treatment assignment.
      ii) Dosedependency for adverse findings, which should be supported by

      summary tables of the incidence of adverse events based on the cumulative dose and the average dose administered.

iii) Time dependency for adverse finding, which should be supported by analyses

summarizing the length of time subjects experience adverse events and whether recovery occurs during treatment.

iv) Drug-demographic interactions
v) Drug-disease interactions

p) Drug-drug interactions
   i) Dosing considerations for important drug-drug interactions.
   ii) Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

24) Marketing applications must include the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Provide all appropriate data as well as a clinical study report for any study performed to evaluate QT/QTc prolongation.

Financial Disclosure Information

25) Marketing applications must include certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies, including those at foreign sites, covered by the regulation. This requires that investigators provide information to the sponsor during the course of the study and after completion. See Guidance for Industry - Financial Disclosure by Clinical Investigators (www.fda.gov/RegulatoryInformation/Guidances/ucm126832.htm).

Physician's Labeling Rule

Highlights

1) Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI. [See 21 CFR 201.57(d)(6) and Implementation Guidance]

2) The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]

3) The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product]. [See 21 CFR 201.57(a)(1)]

4) The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]

5) The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to 21 CFR 201.57(a) (4) and to

www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom).

6) For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d) (9) and Implementation Guidance]. Recent major changes apply to only 5 sections (Boxed Warning; Indications and Usage; Dosage and Administration; Contraindications; Warnings and Precautions).

7) The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:
   (a) "(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."

8) Propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.

9) Refer to 21 CFR 201.57 (a) (11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).

10) A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a) (11)].

11) Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights

12) The Patient Counseling Information statement must appear in Highlights and must read "See 17 for PATIENT COUNSELING INFORMATION." [See 21 CFR 201.57(a)(14)]

13) A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a) (15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at the time of submission and will be edited to the month/year of application or supplement approval.

14) A horizontal line must separate the Highlights, Contents, and FPI. [See 21 CFR 201.57(d)(2)]

Table of Contents

15) The headings and subheadings used in the Contents must match the headings and subheadings used in the FPI. [See 21 CFR 201.57(b)]

16) The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]

17) Create subsection headings that identify the content. Avoid using the word General, Other, or

Miscellaneous for a subsection heading.

18) Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.

19) When a subsection is omitted, the numbering does not change [see 21 CFR 201.56(d) (1)]. For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:

    8.1 Pregnancy
    8.3 Nursing Mothers *(not 8.2)*
    8.4 Pediatric Use *(not 8.3)*
    8.5 Geriatric Use *(not 8.4)*

20) When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading "Full Prescribing Information: Contents" must be followed by an asterisk and the following statement must appear at the end of the Contents:

"*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI)

22) Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).

23) Other than the required bolding [See 21 CFR 201.57(d) (1), (d) (5), and (d) (10)], use bold print sparingly. Use another method for emphasis such as italics or underline.

24) Do not refer to adverse reactions as "adverse events." Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format" (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075057.pdf).

25) The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, [see Use in Specific Populations (8.4)] not See Pediatric Use (8.4). The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print. [See Implementation Guidance, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf]

26) Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]

27) Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and

effectively. [See 21 CFR 201.57 (c)(18)]

28) The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.

29) There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.

30) The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.

31) If the "Rx only" statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.

32) Refer to www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm for fictitious examples of labeling in the new format.

33) Refer to the Institute of Safe Medication Practices' website (http://www.ismp.org/Tools/abbreviationslist.pdf) for a list of error-prone abbreviations, symbols, and dose designations.

Additional DBOP CDISC Guidance

The following two tables identify variables and domains that the division uses in conducting standardized analyses on data for marketing or licensing applications. Following the tables is a description of the Tumor Identification (TU), Tumor Results (TR), Response (RS), domains and variables therein. These are provided because DBOP uses these domains and variables in analysis tools developed by FDA. These domains and variables will be added to the CDISC implementation guide in the near future, however, we request that you implement the use of this STDM format with all your upcoming submissions.

Please use the draft CDISC *Oncology Disease-Specific Therapeutic Area Supplement to the SDTM Implementation Guide* (http://www.cdisc.org/sdtm) for submitting tumor identification, results, and response data to DBOP as soon as they become available.

Please follow the guidance as provided in the CDER Data Standards Issues Document that can be found at:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

Table 1: Variables that DBOP requires for analyses of OS, PFS, RR, Disposition, and Adverse Reactions

Domain	Variable Name	Variable Label	Required Variable Values	Currently Available	CDISC Core	CDISC Data Type	CDISC Code List
ADSL	STRATA<N>	Based on definition of strata variable	0,1	No		Num	0,1
AE	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
AE	AEBODSYS	Body System or Organ Class	--	Yes	Exp	Char	
AE	AEDECOD	Dictionary-Derived Term	--	Yes	Req	Char	
AE	AETOXGR	Standard Toxicity Grade	--	Yes	Perm	Char	
AE	AESTDTC	Start Date/Time of Adverse Event	--	Yes	Exp	Char	ISO 8601
CM	CMCAT	Category for Medication		Yes	Perm	Char	--
CM	CMDECOD	Standardized Disposition Term	--	Yes	Perm	Char	NCOMPLT (Completion/Reason for Non-Completion)

CM	CMENDTC	End Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
CM	CMSTDTC	Start Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
CM	CMSTDY	Study Day of Start of Medication	--	Yes	Perm	Num	--
CM	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
DM	AGE	Age	--	Yes	Req	Num	--
DM	AGEU	Age Units	--	Yes	Exp	Char	AGEU
DM	ARM	Description of Planned Arm	--	Yes	Req	Char	--
DM	ACTARM		--	New			--
DM	ARMCD	Planned Arm Code	--	Yes	Req	Char	--
DM	COUNTRY	Country	--	Yes	Req	Char	ISO 3166 3- char. code
DM	DTHDTC	Date of Death	--	New		Char	ISO 8601
DM	DTHFL	Subject Death Flag	Y	New		Char	--
DM	ETHNIC	Ethnicity	--	Yes	Perm	Char	--
DM	RACE	Race	--	Yes	Exp	Char	--
DM	RFPENDTC	Date/Time of End of Participation	--	New		Char	ISO 8601
DM	SEX	Sex	--	Yes	Req	Char	M, F, U
DM	SITEID	Study Site Identifier	--	Yes	Req	Char	--
DM	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
DS	DSCAT	Category for Disposition Event	PROTOCOL MILESTONE	Yes	Perm	Char	DSCAT
DS	DSDECOD	Standardized Disposition Term	DEATH, RANDOMIZED, LOST TO FOLLOW-UP, ALIVE,ADVERSE EVENT, PROGRESSIVE DISEASE	Yes	Req	Char	**NCOMPLT (Completion/Reason** for Non-Completion)
DS	DSDTC	Date/Time of Collection	--	Yes	Perm	Char	ISO 8601

	DSSCAT	Subcategory for Disposition Event	STUDY DISCONTINUATION, TREATMENT DISCONTINUATION, STUDY TERMINATION	Yes	Perm	Char	--
DS	DSSTDTC	Start Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
DS	DSSTDY	Study Day of Start of Disposition Event	--	Yes	Perm	Num	--
DS	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
EX	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
EX	EXSTDTC	Start Date/Time of Treatment	--	Yes	Exp	Char	ISO 8601
EX	EXENDTC	End Date/Time of Treatment	--	Yes	Perm	Char	ISO 8601
LB	LBBLFL	Baseline Flag	Y	Yes	Exp	Char	NY
LB	LBNRIND	Reference Range Indicator	HIGH, LOW	Yes	Exp	Char	--
LB	LBTEST	Lab Test or Examination Name	--	Yes	Req	Char	--
LB	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
MH	MHDECOD	Dictionary-Derived Term	--	Yes	Perm	Char	--
MH	MHENDTC	End Date/Time of Medical History Event	--	Yes	Perm	Char	ISO 8601
MH	MHSTDTC	Start Date/Time of Medical History Event	--	Yes	Perm	Char	ISO 8601
MH	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
RS	RSACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
RS	RSDTC	Date/Time of Response Assessment	--	Yes	Exp	Char	ISO 8601

RS	RSEVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
RS	RSSTAT	Response Assessment Status	NOT DONE	Yes	Perm	Char	ND
RS	RSSTRESC	Response Assessment Result in Std Format	CR or COMPLETE RESPONSE, PR or PARTIAL RESPONSE, SD or STABLE DISEASE, PD or PROGRESSIVE DISEASE, NE or NOT EVALUABLE	Yes	Exp	Char	--
RS	RSTESTCD	Response Assessment Short Name	OVRLRESP, looks for TGRESP, NTGRESP & BESTRESP	Yes	Req	Char	--
RS	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
RS	VISIT	Visit name	Must contain "UNSCH" for unscheduled	Yes	Perm	Char	
SV	SVSTDTC	Start Date/Time of Visit	--	Yes	Exp	Char	ISO 8601
SV	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
TA	ANCHDTC	Anchor date of assessment schedule	Variable in ADSL - no name determined	NEW		Char	
TA	MAXPRD	Maximum length of assessment schedule		NEW		Char	ISO 8601 Duration
TA	MINPRD	Minimum length of assessment schedule		NEW		Char	ISO 8601 Duration
TA	STOFFSET	Start time from anchor date		NEW		Char	ISO 8601 Duration
TA	TGTPRD	Length of assessment schedule		NEW		Char	ISO 8601 Duration
TR	TRACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
TR	TRDTC	Date/Time of Tumor Measurement	--	Yes	Exp	Char	ISO 8601
TR	TREVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL

[illegible]	TRLINKID	Link ID	--	Yes	Exp	Char	--
TR	TRLNKGRP		--	NEW		Char	--
TR	TRSTAT	Tumor Assessment Status	NOT DONE	Yes	Perm	Char	ND
TR	TRSTRESC	Character Result/Finding in Std. Format	If TRTESTCD equals "TUMSTATE" Looks for PRESENT, ABSENT, UNEQUIVOCAL PROGRESSION	Yes	Exp	Char	--
TR	TRSTRESN	Numeric Result/Finding in Std. Format	--	Yes	Exp	Num	--
TR	TRTESTCD	Tumor Assessment Short Name	LDIAM, TUMSTATE, Looks for SUMLDIAM	Yes	Exp	Char	--
TR	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--
[illegible]							
TS	DCUTDTC	Data cut off date	--	New		Char	ISO 8601
TS	TSPARMCD	Trial Summary Parameter Short Name	PSSDDUR, PSCDUR	New	Req	Char	--
TS	TSVAL	Parameter Value	ISO Duration	New	Req	Char	--
TU	TUACPTFL	Accepted Record Flag	Y	Yes	Perm	Char	Y or Null
TU	TUDTC	Date/Time of Tumor Identification	--	Yes	Exp	Char	ISO 8601
TU	TUEVAL	Evaluator	INVESTIGATOR	Yes	Exp	Char	EVAL
TU	TULINKID	Link ID	--	Yes	Exp	Char	--

TU	TULOC	Location of Tumor	--	Yes	Exp	Char	LOC
TU	TUMETHOD	Method of Identification	--	Yes	Exp	Char	
TU	TUSTRESC	Tumor Identification Result Std. Format	NEW	Yes	Exp	Char	
TU	USUBJID	Unique Subject Identifier	--	Yes	Req	Char	--

Please ensure that the following domains and variables are included in your CDISC data submissions. Although the CDISC Implementation guide lists many variables as permissible, in order for DBOP to conduct efficient and timely reviews of the clinical trial data, most permissible variables should be considered as required variables. Please consult with the division on any permissible variables that you intend not to include in your data files so we can determine the impact this will have on the review process and the acceptability of the omission.

Table 2: Additional variables in SDTM and ADaM that are necessary for efficient review

DOMAIN	VARAIBLE	DATA TYPE
ADaM		
ADSL	STUDYID	C
ADSL	USUBJID	C
ADSL	TRT01A	C
ADSL	TRT01P	C
ADSL	ARM	C
ADSL	AGE	N
ADSL	AGEGR1	C
ADSL	SEX	C
ADSL	RACE	C
ADSL	TRTEDT	N
ADSL	TRTEDTM	N
ADSL	TRTSDT	N
ADSL	TRTSDTM	N
ADSL	DEATHDSC	C
SDTM		
AE	STUDYID	C
AE	USUBJID	C
AE	AEDECOD	C
AE	AEBODSYS	C
AE	AEREL	C
AE	AESEV	C
AE	AETOXGR	C

AE	AESTDTC	C
AE	AEENDTC	C
AE	AESTDY	N
AE	AEENDY	N
AE	AEDUR	C
CM	STUDYID	C
CM	USUBJID	C
CM	CMDECOD	C
CM	CMSTDTC	C
CM	CMENDTC	C
CM	CMENDY	N
CM	CMSTDY	N
CM	CMDUR	C
DM	STUDYID	C
DM	USUBJID	C
DM	AGE	N
DM	SEX	C
DM	RACE	C
DM	ARM	C
DM	RFENDTC	C
DM	RFSTDTC	C
DS	STUDYID	C
DS	USUBJID	C
DS	DSDECOD	C
DS	DSCAT	C
DS	DSSTDTC	C
DS	DSSTDY	N
EX	STUDYID	C
EX	USUBJID	C
EX	EXTRT	C
EX	EXDOSE	N
EX	EXSTDTC	C
EX	EXENDTC	C
EX	EXSTDY	N
EX	EXENDY	N
EX	EXDUR	C
LB	STUDYID	C
LB	USUBJID	C
LB	LBTEST	C
LB	LBSTRESN	N
LB	LBSTNRHI	N
LB	LBSTNRLO	N
LB	LBDTC	C
LB	LBDY	N
MH	STUDYID	C
MH	USUBJID	C
MH	MHDECOD	C
MH	MHBODSYS	C

VS	STUDYID	C
VS	USUBJID	C
VS	VSTEST	C
VS	VSSTRESN	N
VS	VSDTC	C
VS	VSDY	N

CDISC Oncology Domains

Introduction

Assessment of the change in tumor burden is an important feature of the clinical evaluation of cancer therapeutics: both tumor shrinkage (objective response) and disease progression are useful endpoints in cancer clinical trials[1]. RECIST (Response Evaluation Criteria in Solid Tumors)[2] has been widely adopted in solid tumor clinical trials where the primary endpoints are objective response or progression and is accepted by regulatory authorities as an appropriate guideline for these assessments. The SDTM domains presented here were developed with RECIST Criteria in mind. However, the domains are intended to represent data collected in clinical trials where tumors are identified and then repeatedly measured/assessed at subsequent timepoints and used in an evaluation of response(s). As such these domains would be equally applicable for criteria other than RECIST e.g. Chesson classification[3] in the assessment lymphomas, or, MacDonald Response[4] in the assessment of malignant gliomas.

The tumor assessment package consists of three SDTM domains based on the SDTM Findings Observation Class. The three domains are related but each domain has a distinct purpose:

TU (Tumor Identification): The TU domain represents data that uniquely identifies tumors. The tumors are identified by an investigator and/or independent assessor and in RECIST terms this equates to the identification of Target, Non-Target or New tumors. A record in the TU domain contains the following information: a unique tumor ID value; anatomical location of the tumor; method used to identify the tumor; role of the individual identifying the tumor; and timing information.

TR (Tumor Results): The TR domain represents quantitative measurements and/or qualitative assessments of the tumors identified in the TU domain. These measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. A record in the TR domain contains the following information: a unique tumor ID value; test and result; method used; role of the individual assessing the tumor; and timing information.

Clinically accepted evaluation criteria expect that a tumor identified by the tumor ID is the same tumor at each subsequent assessment. The TR domain does not include anatomical location information on each measurement record because this would be a duplication of information already represented in TU. This duplication of data was a deciding factor in multi-domain approach to representing this data.

RS (Response): The RS domain represents the response evaluation determined from the data in TR. Data from other sources (in other SDTM domains) might also be used in an assessment of response for example, MacDonald Response Criteria includes a neurological aspect.

New variables:
--LINKID – The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). Therefore a new ID variable --LINKID is being proposed in order to support the linking requirements. The --LINKID variable is specifically designed to support a relrec dataset to dataset relationship. Values of LINKID could concatenate values of other variables when more than one variable are needed to do join data rows.

--ACPTFL – The Acceptance Flag identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.

--EVALID – The Evaluator Specified variable is used in conjunction with TREVAL to provide an additional level of detail. When multiple assessors play the role identified in TREVAL, values of TREVALID will attribute a row of data to a

particular assessor. For example TREVAL="INDEPENDENT ASSESSOR" and TREVALID="RADIOLOGIST 1". The --EVALID variable is not subject to Controlled Terminology. When --EVALID is populated --EVAL must also be populated.

References:

(1) E.A. Eisenhauera,*, P. Therasseb, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) *EUROPEAN JOURNAL OF CANCER 45 (2009) 228–247*

(2) RECIST Criteria - http://www.eortc.be/recist/

(3) Bruce D. Cheson, Beate Pfistner, et al. Revised Response Criteria for Malignant Lymphoma *Journal of Clinical Oncology. Vol 25 Number 5 Feb 10 2007*

(4) DR Macdonald, TL Cascino, et al. Response criteria for phase II studies of supratentorial malignant glioma *Journal of Clinical Oncology, Vol 8, 1277-1280*

1. Oncology Domains:

1.1. TUMOR IDENTIFICATION - TU

tu.xpt, Tumor Identification - Findings, Version 3..x.x ..... One record per identified tumor per visit per subject, Tabu

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.
DOMAIN	Domain Abbreviation	Char	TU	Identifier	Two-character abbreviation for the domain.
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject acr for all applications or submissions involving the
TUSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniquer dataset for a subject. May be any valid number
TUGRPID	Group ID	Char		Identifier	Used to link together a block of related records subject in a domain.
TUREFID	Reference ID	Char		Identifier	Internal or external identifier. Example:
TUSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.
TULINKID	Link ID	Char		Identifier	Identifier used to link identified tumors to the as results over the course of the study.
TUTESTCD	Tumor Identification Short Name	Char	*	Topic	Short name of the TEST in TUTEST. TUTESTC contain characters other than letters, num underscores. Examples: TUMIDENT, NEW. J Assumption 2.
TUTEST	Tumor Identification Test Name	Char	*	Synonym Qualifier	Verbatim name of the test for the tumor/lesion i The value in TUTEST cannot be longer than 40 Examples: Tumor Identification, New Tumor Ide Assumption 2.
TUCAT	Category for Tumor Identification	Char		Grouping Qualifier	Used to categorize tumors.
TUSCAT	Sub-Category for Tumor Identification	Char		Grouping Qualifier	A further classification of the TUTEST.

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes
TUORRES	Tumor Identification Result	Char	*	Result Qualifier	Result of the Tumor identification. Examples: When TUTESTCD=TUMIDENT (Tu Identification), values of TUORRES might be: T NON-TARGET. When TUTESTCD=NEWTUMOR the value of T might be: Y. When TUTESTCD=BENIGNAB the value of TU might be: BENIGN RENAL LESIONS.
TUSTRESC	Tumor Identification Result Std. Format	Char	*	Record Qualifier	Contains the result value for all findings copied TUORRES.
TUNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that perfor Tumor Identification.
TULOC	Location of the Tumor	CHAR	(LOC)	Record Qualifier	Used to specify the anatomical location of the i tumor. Example: Gastrointestinal Tract. Note: When anatomical location is broken dow collected as distinct pieces of data that when c provide the overall location information (e.g. or /location / sub-location) then the additional info added as supplemental qualifiers. See Assump
TUMETHOD	Method of Identification		*	Record Qualifier	Method used to identify the tumor. Examples: X CT-Scan.
TUEVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation INVESTIGATOR, RADIOLOGIST, ONCOLOGI This column can be left *Null* when the Investiga the complete set of data in the domain. However should contain no *Null* values when data from c independent assessors is included meaning the attributed to the Investigator rows should conta INVESTIGATOR.

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes
TUEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in con TUEVAL to provide an additional level of detail multiple assessors play the role identified in TU of TUEVALID will attribute a row of data to a pa assessor. TUEVALID should not contain the na assessors but should contain values such as R 1 or RADIOLOGIST 2. The TUEVALID variabl subject to CDISC Controlled Terminology. See Assumption 5.
TUACPTFL	Accepted Record Flag	Char	*	Record Qualifier	In cases where more than one independent ass RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments at the same timepoint this flag ide record that is considered to be the accepted as
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encou 2. May be used in addition to VISITNUM and/o
VISITDY	Planned Study Day of Visit	Num		Timing	
TUDTC	Date/Time of Tumor Identification	Char	ISO 8601	Timing	
TUDY	Study Day of Tumor Identification	Num		Timing	1. Study day of the Tumor measurement, meas integer days. 2. Algorithm for calculations must be relative to defined RFSTDTC variable in Demographics.

1.1.1. ASSUMPTIONS FOR THE TUMOR IDENTIFICATION DOMAIN MODEL

TU Definition: The TU domain represents data that uniquely identifies tumors. The tumors are identified by an investigator and/or in RECIST terms this equates to the identification of Target, Non-Target or New tumors. A record in the TU domain contains the follow ID value; anatomical location of the tumor; method used to identify the tumor; role of the individual identifying the tumor; and timing

1. The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 dc link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case beca (GRPID, REFID & SPID) are needed (see examples). The –LINKID variable is used for values that support a relrec dataset to provide a unique code for each identified tumor.

2. The values of TUTESTCD and TUTEST will be relatively simple and will either represent that the Tumor is identified and categ Tumor is identified as New (has appeared since the Screening assessment).

   Proposed TUTESTCD / TUTEST values for this domain:

TUTESTCD	TUTEST
TUMIDENT	Tumor Identification
NEWTUMOR	New Tumor Identified
BENIGNAB	Benign Abnormality
TUSPLIT	Tumor Split or Divided
TUMERGE	Tumor Merged or Coalesced

   During the course of a trial when a new Tumor (or lesion) is identified information about that new tumor may be collected to diff following three scenarios represent the most commonly seen data collection methods employed when a new Tumor (or lesion) out below are not intended to be exhaustive. The sponsor must decide the appropriate collection method based on their analys and it is possible that a sponsor's chosen method is not reflected in the scenarios presented below.

   a. The occurrence of a New Tumor is the sole piece of information that a sponsor collects because this is a sign of disease p details are required. In such cases a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y"

   b. The occurrence of a New Tumor and the anatomical location of that newly identified Tumor are the only collected pieces o expected that a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y", and the TULOC var the anatomical location information (the additional location variables may be populated depending on the level of detail coll

   c. A sponsor might record the occurrence of a New Tumor to the same level of detail as Target and Non-Target Tumors. In t new tumor and the anatomical location information, and also measure the New Tumor. In this case it is expected that a re TUTEST="New Tumor Identified" and TUORRES="Y", and the identifier, TULINKID, would all be populated. The measure Tumor would be recorded in the TR domain.

3. TUCAT and TUSCAT have been included as they are standard domain variables however these columns would generally are not included in the accompanying examples.

4. Anatomical Location information might be collected in a number of ways the simplest way is as a long text string and in these c in the TULOC variable. However, anatomical location might also be collected through a number of distinct and separate variabl subject to controlled terminology) and in such cases the additional information would be recorded in the following Supplementa

QNAM	QLABEL	Definition
TUSUBLOC	Sub-location of the Tumor	Anatomical location information with more specificity than a gross locati
TULOCDET	Detailed Location Information	Detailed anatomical location information that would include details such Posterior); relative direction (Proximal, Distal); axes (Dorsoventral, Med Coronal); and any other divisions or sub-anatomy information.
TUORGAN	Organ Affected	Actual Body Organ location of the tumor. This is more specific than Boc
TULAT	Tumor Location Laterality	Lateral location used to distinguish Right & Left sides. For example if a "Right Lung" then the TULOC and QNAM.TULAT values would be TUL QNAM.TULAT=RIGHT.

5. The Acceptance Flag variable (TUACPTFL) identifies those records that have been determined to be the accepted assessmen independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall

6. The Evaluator Specified variable (TUEVALID) is used in conjunction with TUEVAL to provide additional detail and allows for va controlled terminology expected in the TUEVAL variable. For example TUEVAL="INDEPENDENT ASSESSOR" and TUEVALI TUEVALID variable is not subject to Controlled Terminology. TUEVAL must also be populated when TUEVALID is populated.

7. The following proposed supplemental Qualifiers would be used to represent information regarding previous irradiation of a tum known:

QNAM	QLABEL	Definition
PREVIR	Previously Irradiated	Indication of previous irradiation to a tumor.
PREVIRP	Irradiated then Subsequent Progression	Indication of documented progression subsequent to irradiation.

TUMOR RESULTS - TR

tr.xpt, Tumor Results - Findings, Version 3..x.x ..... One record per tumor measurement/assessment per tumor per v

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.
DOMAIN	Domain Abbreviation	Char	TR	Identifier	Two-character abbreviation for the domain.
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject acr studies for all applications or submissions involv product.
TRSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniquene dataset for a subject. May be any valid number.
TRGRPID	Group ID	Char		Identifier	Used to link together a block of related records subject in a domain.
TRREFID	Reference ID	Char		Identifier	Internal or external identifier.
TRSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.
TRLINKID	Link ID	Char		Identifier	Identifier used to link the assessment result rec tumor identification record.
TRTESTCD	Tumor Assessment Short Name	Char	*	Topic	Short name of the TEST in TRTEST. TRTESTC contain characters other than letters, numbers, underscores. Examples: LDIAM, DIAM. See As
TRTEST	Tumor Assessment Test Name	Char	*	Synonym Qualifier	Verbatim name of the test or examination used the measurement or finding. The value in TRT belonger than 40 characters. Examples: LONG DIAMETER, LONGEST PERPENDICULAR, AX THICKNESS, VOLUME, AREA. See Assumptio
TRCAT	Category for Tumor Assessment	Char	*	Grouping Qualifier	Used to categorize assessments. Examples: Measurement Categorical.
TRSCAT	Sub-Category for Tumor Assessment	Char		Grouping Qualifier	A further classification of the TRTEST.

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes
TRORRES	Result or Finding in Original Units	Char		Result Qualifier	Result of the Tumor measurement/assessment received or collected.
TRORRESU	Original Units	Char	(UNIT)	Variable Qualifier	Original units in which the data were collected. TRORRES. Example: mm
TRSTRESC	Character Result/Finding in Std Format	Char		Record Qualifier	Contains the result value for all findings, copied from TRORRES in a standard format or standar TRSTRESC should store all results or findings i format; if results are numeric, they should also b numeric format in TRSTRESN
TRSTRESN	Numeric Result/Finding in Standard Units	Num		Result Qualifier	Used for continuous or numeric results or findin standard format; copied in numeric format from TRSTRESC. TRSTRESN should store all nume results or findings.
TRSTRESU	Standard Units	Char	(UNIT)	Variable Qualifier	Standardized unit used for TRSTRESN.
TRSTAT	Tumor Assessment Status	Char	(ND)	Result Qualifier	Used to indicate a measurement was not done, measurement was not taken. Should be Null if a exists in TRORRES.
TRREASND	Reason Tumor Measurement Not Performed	Char		Record Qualifier	Describes why a measurement or test was not p Examples: BROKEN EQUIPMENT or SUBJECT REFUSED. Used in conjunction with TRSTAT w is NOT DONE.
TRNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that p Tumor measurement or assessment.
TRMETHOD	Method used to identify the Tumor		*	Record Qualifier	Method used to measure the tumor. Examples: CT-Scan.

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes
TREVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation INVESTIGATOR, RADIOLOGIST, ONCOLOGIS This column can be left *Null* when the Investiga the complete set of data in the domain. Howeve column should contain no *Null* values when dat or more independent assessors is included mea the rows attributed to the Investigator rows shou value of INVESTIGATOR.
TREVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conj TREVAL to provide an additional level of detail. multiple assessors play the role identified in TR values of TREVALID will attribute a row of data particular assessor. TREVALID should not cont names of the assessors but should contain valu RADIOLOGIST 1 or RADIOLOGIST 2. The TRE variable would not be subject to CDISC Control Terminology. Note TREVAL must also be popul TREVALID is populated. See Assumption 4.
TRACPTFL	Accepted Record Flag	Char	*	Record Qualifier	In cases where more than one independent ass where TREVALID has values of "RADIOLOGIS "RADIOLOGIST 2") provide independent asses the same timepoint this flag identifies the record considered to be the accepted assessment.
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.
VISIT	Visit Name	Char		Timing	1. Protocol defined description of clinical encou 2. May be used in addition to VISITNUM and/or
VISITDY	Planned Study Day of Visit	Num		Timing	

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes
TRDTC	Date/Time of Tumor Measurement	Char	ISO 8601	Timing	
TRDY	Study Day of Tumor Measurement	Num		Timing	1. Study day of the Tumor measurement, meas integer days. 2. Algorithm for calculations must be relative to sponsor-defined RFSTDTC variable in Demogr

1.1.2. ASSUMPTIONS FOR THE TUMOR RESULTS DOMAIN MODEL

TR Definition: The TR domain represents quantitative measurements and/or qualitative assessments of the tumors identified in the measurements are usually taken at baseline and then at each subsequent assessment to support response evaluations. A record ir following information: a unique tumor ID value; test and result; method used; role of the individual assessing the tumor; and timing i

1. The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 dc link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case beca (GRPID, REFID & SPID) are needed (see examples). The --LINKID variable is used for values that support a relrec dataset to provide a unique code for each identified tumor. TRLINKID is a required variable as the records in the TR domain must relate b in TU.

2. TRTESTCD / TRTEST values for this domain (this is for illustration purposes these values will be published as Controlled T

TRTESTCD	TRTEST
AREA	Area
AXTHICK	Axial Thickness
DIAM	Diameter
LDIAM	Longest Diameter
LMAXSP	Major Axis Axial Plane, Long Diameter Target
LPERP	Longest Perpendicular
METVOLNO	Average Metabolic SUV
MJAX3SP	Major Axis 3D (All Planes)

MNAX3SP	Minor Axis 3D
MNAXSP	Minor Axis
MXSUVSSP	Maximum SUV (1 cm Spot)
MXSUVVSP	Maximum SUV (Single Voxel)
PCCHBL	Percent Change From Baseline
PCCHNAD	Percent Change From Nadir
PREVIR	Lesion Previously Irradiated
PREVIRP	Lesion Progressing Since Irradiated
PRODUCT	Product
RADDESP	Radio Density
SAXIS	Short Axis
SUMAREA	Sum of Area
SUMAXTHK	Sum of Axial Thickness
SUMLDIAM	Sum of Longest Diameter
SUMLPERP	Sum of Longest Perpendicular
SUMPDIAM	Sum of the product of the diameters
SUMPROD	Sum of Product
SUMVOL	Sum of Volume
VOLPETSP	Total Tumor Volume
VOLUME	Volume
XPRO3SP	Cross Product 3D
XPRODSP	Cross Product

Note: The sponsor should not derive results for any test indicated in the list above (e.g. "Percent Change From Nadir") if the re: would be included in the domain only if those data points have been collected on a CRF or have been supplied by an external a electronic data transfer. It is not intended that the sponsor would create derived records to supply those values.

3. The Acceptance Flag variable (TRACPTFL) identifies those records that have been determined to be the accepted assessmen independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall

4. The Evaluator Specified variable (TREVALID) is used in conjunction with TREVAL to provide additional detail and allows for va controlled terminology expected in the TREVAL variable. For example TREVAL="INDEPENDENT ASSESSOR" and TREVALI TREVALID variable is not subject to Controlled Terminology. TREVAL must also be populated when TREVALID is populated.

RESPONSE – RS

rs.xpt, Response - Findings, Version 3..x.x ..... One record per response assessment per visit per subject, Tabulatio

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.
DOMAIN	Domain Abbreviation	Char	RS	Identifier	Two-character abbreviation for the domain.
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject acr studies for all applications or submissions involv product.
RSSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniquene dataset for a subject. May be any valid number.
RSGRPID	Group ID	Char		Identifier	Used to link together a block of related records subject in a domain.
RSREFID	Reference ID	Char		Identifier	Internal or external identifier.
RSSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.
RSLINKID	Link ID	Char		Identifier	Used to link the response assessment to the ap measurement records (in TR) used to determin response result.
RSTESTCD	Response Assessment Short Name	Char	*	Topic	Short name of the TEST in RSTEST. RSTE contain characters other than letters, numb underscores. Examples: TRGRESP, BESTRES SYMPTPD.
RSTEST	Response Assessment Name	Char	*	Synonym Qualifier	Verbatim name of the response assessment. T RSTEST cannot be longer than 40 characters. Target Response, Best Overall Response, Sym deterioration
RSCAT	Category for Response Assessment	Char		Grouping Qualifier	Used to categorize tumors.

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes
RSSCAT	Sub-Category for Response Assessment	Char		Grouping Qualifier	A further classification of the RSTEST.
RSORRES	Response Assessment Original Result	Char		Result Qualifier	Result of the Response assessment as originall collected, or calculated.
RSSTRESC	Response Assessment Result in Std Format	Char		Record Qualifier	Contains the result value for the response asse copied or derived from RSORRES in a standarc standard units. RSSTRESC should store all res findings in character format; if results are numer should also be stored in numeric format in RSS
RSSTAT	Response Assessment Status	Char	(ND)	Result Qualifier	Used to indicate the response assessment was performed. Should be Null if a result exists in R
RSREASND	Reason Response Assessment Not Performed	Char		Record Qualifier	Describes why a response assessment was not Examples: Subject does not have target lesions conjunction with TRSTAT when value is NOT D
RSNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that perforr response assessment.
RSEVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation INVESTIGATOR, RADIOLOGIST, ONCOLOGI This column can be left *Null* when the Investiga the complete set of data in the domain. However column should contain no *Null* values when dat or more independent assessors is included mea the rows attributed to the Investigator rows shou value of INVESTIGATOR.

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes
RSEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conj RSEVAL to provide an additional level of detail. multiple assessors play the role identified in RS values of RSEVALID will attribute a row of data particular assessor. RSEVALID should not cont names of the assessors but should contain valu RADIOLOGIST 1 or RADIOLOGIST 2. The RSE variable would not be subject to CDISC Controll Terminology. See Assumption 5
RSACRTFL	Accepted Record Flag	Char		Record Qualifier	In cases where more than one independent ass independent Oncologist) provides an evaluation response this flag identifies the record that is co be the accepted evaluation.
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.
VISIT	Visit Name	Char		Timing	1. Protocol defined description of clinical encou 2. May be used in addition to VISITNUM and/or
RSDTC	Date/Time of Response Assessment	Char	ISO 8601	Timing	Date may be derived if based on multiple dates Exception: derived data in RS needed for reviev
RSDY	Study Day of Response Assessment	Num		Timing	1. Study day of the Tumor measurement, m integer days. May be from rand date not fi 2. Algorithm for calculations must be relative to sponsor-defined RFSTDTC variable in Demogra

1.1.3. ASSUMPTIONS FOR THE TUMOR RESPONSE DOMAIN MODEL

RS Definition: The RS domain represents the response evaluation determined from the data in TR. Data from other sources (in othe be used in an assessment of response for example, MacDonald Response Criteria includes a neurological aspect.

1. The RSLINKID variable is used for values that support a relrec dataset to dataset relationship. RSLINKID would be required wh relates back to an individual tumor.

2. RSTESTCD / RSTEST values for this domain(this is for illustration purposes these values will be published as Controlled Term

RSTESTCD	RSTEST	Definition
TRGRESP	Target Response	
NTRGRESP	Non-target Response	
OVRLRESP	Overall Response	
BESTRESP	Best Response	
LESNRESP	Lesion Response	
SYMPTPD	Symptomatic Deterioration	

3. When an evaluation of Symptomatic Deterioration is recorded (which is symptomatic of progressive Disease) and additional de symptoms is collected then that information would be recorded in the following Supplemental Qualifier:

QNAM	QLABEL	Definition
CLSYMP	Clinical Symptoms of PD	Textual description of clinical symptoms that led to the evaluation of Sym

4. ***TS – TSPARM/TSVAL needed to represent the Response Criteria used in the clinical trial.***

5. The Evaluator Specified variable (RSEVALID) is used in conjunction with RSEVAL to provide additional detail and allows for va the controlled terminology expected in the RSEVAL variable. For example RSEVAL="INDEPENDENT ASSESSOR" and RSEV RSEVALID variable is not subject to Controlled Terminology. RSEVAL must also be populated when RSEVALID is populated.

MEETING ATTENDANCE LIST

Meeting between GlaxoSmithKline - Joint Pre-NDA (INDs 102175 and 105032) and the Center for Drug Evaluation and Research.

DATE: May 9, 2012 TIME: 10:00-12:00 PM ROOM: WO 22/Room 1311

NAME - Please print	AFFILIATION
Norma Griffin	FDA/CDER/OND/OHOP/DOP2
Ellen Cutler	GSK
DANIELE OUELLET	GSK
Vicki Goodman	GSK
Rafael Amado	GSK
Jennifer Dudinak	GSK
Michael Streit	GSK
AMITA CHAUDHARI	GSK
ANNE-MARIE MARTIN	GSK
MARIA CHAN	FDA/CDRH/OIVD
Hong Zhao	CDER/OTS/OCP/DCP5
Robert Leung	FDA/DCP5
KUN HE	FDA/OB/DBV
Whitney Helms	FDA/CDER/DOP1
Anthony MURGO	FDA-OHOP-IO
DONNA ROSCOE	FDA-CDRH-OWD-DHAD
SACHIA KHASAR	FDA/OHOP/DHOT
Jean Mulinde	FDA/CDER/OC/OST
Amarilys Vega	FDA/CDER/OSE/DRISK
Marc Theoret	FDA/CDER/OHOP/DOP2
RICHARD PAZDUR	FDA
PATRICIA KEEGAN	FDA/CDER/OHOP/DOP2
Weishi Yuan	FDA/CDER/OTS/OB/DBV
Liliana Zhang	FDA/CDER/OTS/OCP/DP5
Jenny Zhang	FDA/CDER/OTS/OB/DB5
Eric Richards	GSK
MICHELLE CASEY	GSK

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/s/

DEANNE R VARNEY
05/23/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Memorandum

Date: May 8, 2013

From: Norma Griffin, RPM – DOP2/OHOP/CDER

Subject: NDAs 202806 and 204114 GSK – STATS Information Request During 3/8/2013 Working Session
Memo to File

During a STATS working session held at FDA on 3/8/2013, the FDA STATS reviewer requested that GSK submit the following information:

For both NDAs 204114 and 202806:

1. GSK will submit the data `ronccom` in SAS transport file formats, together with adequate documentation.

For NDA 202806:

2. GSK will submit the dataset `trt` and its documentation.

This request was made verbally during the meeting and therefore, this memo to file is being uploaded to both NDAs as record of this information request.

This memo will be uploaded into DARRTS for the NDA files – NDA 202806 and NDA 204114.

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/s/

NORMA S GRIFFIN

05/08/2013

This IR was issued on 3.8.2013 but record of the request was uploaded on 5.8.2013.

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, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 204114; GlaxoSmithKline, LLC
CMC Comments / Advice – Mekinist (trametinib) Shelf-Life

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 "Mekinist (trametinib)" received on August 3, 2012.

Our CMC Reviewers and the Review Team have the following comments for the Mekinist (trametinib) tablets:

> Based on the provided stability data, a 12-month expiration dating period is granted for the 0.5 mg and 2 mg tablets and a 9-month expiration dating period is granted for the 1 mg tablets when stored at 2° to 8°C (36°F to 46°F) and protected from moisture and light.
>
> We acknowledge your commitment provided in the submission dated April 12, 2013 to place all future commercial batches on stability to provide concurrent monitoring at 5°C and to notify us (FDA) of any changes to this protocol. Please note that a prior approval supplement will need to be submitted to revise this commitment. Refer to "Guidance for Industry, Changes to an Approved NDA or ANDA, April 2004."

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

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/s/

NORMA S GRIFFIN
05/06/2013

Team Meeting 7 – Final Issues - Summary
May 3, 2013

NDA: 204114

Product:	Mekinist (trametinib)
Submission Date:	August 2, 2012
Received Date:	August 3, 2012
Sponsor:	GlaxoSmithKline (GSK), LLC
Action Goal Date:	**Monday, June 3, 2013** ***(**possible date of May 28, 2013, per Dr. Pazdur?)***

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation as detected by an FDA approved test.

Meeting Participants

Patricia Keegan, M.D., Director DOP2
Norma Griffin., Regulatory Health Project Manager
Meredith Libeg, Regulatory Health Project Manager
Suzanne Demko, Clinical TL and CDTL
Marc Theoret, M.D., Clinical Reviewer
Huanyu (Jade) Chen, Statistics
Hong Zhao, Ph.D, Clinical Pharmacology (TL)
Whitney Helms, Nonclinical (TL)
Gabriel Sachia Khasar, Nonclinical Reviewer
Nallaperumal Chidambaram
Sue Ching Lin, Product Quality Reviewer
Jewell Martin, Product (ONDQA RPM)
Minerva Hughes, Biopharmaceutics Reviewer
Mahesh Ramanadham, OC (Facilities)
Sue Kang, OSE, Safety RPM
James Schlick, OSE Proprietary Name Reviewer
Donna Roscoe, CDRH Consultant

Discussion Items

1. Action Goal Date (10-month review): Standard 10-month review with the PDUFA

Action Goal Date of Monday, June 3. 2013 ***(**possible date of May 28, 2013, per Dr. Pazdur)***

2. Outstanding Issues:

a. CDRH need information from Clinical Summary and label. bioMerieux will be sending in dataset (investigator assessed PFS) on Monday, 5.6.2013. CDRH to verify exactly what is submitted.

b. Final EES (facilities inspection associated with blend uniformity issue) not received from Compliance/CMC. OC will recommend acceptable and documentation should be complete before 5.10.2013.

c. CMC Major Amendment (SDN 56) – new refrigerated storage temperature

   i. CMC review and decision to be complete by Friday, 5.10.2013. No CMC PMCs. Will send sponsor email (comments/advice) on Monday, 5.6.2013 regarding shelf life - 12-month expiration dating for the 0.5 mg and 2 mg tablets and 9-month expiration dating for the 1 mg tablets when stored at 2° to 8°C.

d. Need Clinical Review

   i. Requesting a few more analyses from STATS.

e. Possible PMR (ocular toxicity) – will talk with Ophthalmology consult.

   i. Need Clinical PMR template

   ii. Need to send to GSK for agreement and milestones.

f. Information for DRAFT Press Release

   i. Will provide sections from CDTL Summary by Monday, 5.6.2013.

g. Burst – DRAFT is with Clinical Reviewer and CDTL for review before going Division Director and then to OHOP.

h. FDA Proposed Labeling has not been sent to GSK. One final meeting scheduled for 5.7.2013 for one last look before sending to GSK. Current working draft (substantially complete) to be sent to OPDP and Patient Labeling.

   i. Container Labeling – DMEPA comments for new storage temperature on container labeling was sent to GSK on 5.3.2013.

i. DRAFT Approval Letter – to CPMS (Monica Hughes) on 5.6.2013 before going to the TEAM.

   i. Need to finalize Clinical PMR in the letter

   ii. Need to finalize Labeling in the letter.

j. Action Package – provide to CPMS on 5.6.2013.

k. Need Consult reviews from:

   i. OPDP

   ii. Patient Labeling

   iii. Ophthalmology review – is Dr. Chambers' edited label and information requests.

l. Janice Dutcher (sp?) is cleared as an SGE.

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/s/

NORMA S GRIFFIN
05/08/2013

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

Memorandum

Date: May 3, 2013

From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 204114; GlaxoSmithKline, LLC
Mekinist Container Labeling - Comments and Proposed Edits

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 "Mekinist (trametinib)" received on August 3, 2012.

We have the following comments for the Container labeling from our Division of Medication Error Prevention and Analysis (DMEPA) and CMC Reviewers. Please provide your response by close of business Wednesday, May 8, 2013, **or sooner if possible**.

Revise the storage statement on the side panel of the container label to read:

> **Store refrigerated at 2° to 8°C (36°F to 46°F). Do not freeze. Dispense in original bottle. Do not remove desiccant. Protect from moisture and light. Do not place medication in pill boxes.**

Bold the font and change the text color to **red** for the whole statement to increase the prominence of it.

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

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/s/

NORMA S GRIFFIN
05/03/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204114

REVIEW EXTENSION – MAJOR AMENDMENT

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

Dear Mr. Richards:

Please refer to your August 2, 2012, New Drug Application (NDA), received on August 3, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mekinist (trametinib) Tablets, 0.5 mg, 1 mg, and 2 mg.

We refer to your February 6, 2013, submission, which contained your proposal to modify the drug product storage conditions provided in your August 2, 2012, original NDA submission, [redacted] (b) (4) at the proposed new storage conditions, and a request for a meeting to discuss your proposal. We also refer to the February 26, 2013, teleconference between representatives of GlaxoSmithKline, LLC (GSK) and FDA in which we discussed your proposed plan to modify the drug product storage conditions [redacted] (b) (4) In addition, we refer to our March 1, 2013, communication in which we requested that you provide the data discussed during the teleconference in a reviewable, tabular format outlining the complete results of all stability testing performed under refrigerated conditions to support your new proposal, as discussed during the February 26, 2013, teleconference.

On April 12, 2013, we received your April 12, 2013, unsolicited major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is September 3, 2013.

In addition, in accordance with the "PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES – FISCAL YEARS 2013 THROUGH 2017," the timeline for communicating labeling changes and/or postmarketing requirements/commitments, provided in our October 14, 2012, filing communication letter, no longer applies and no new timeline will be provided.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

PATRICIA KEEGAN
04/25/2013

From: Griffin, Norma
Sent: Friday, April 12, 2013 8:09 AM
To: 'Eric Richards'
Subject: RE: NDA 204114 GSK - Question regarding Ophthalmology Information - Additional Follow Up IR

Importance: High

Eric,

Please see the following comments from our Ophthalmology Consult as a follow up to our 4.8.2013 IR Ophthalmology Information:

1) The clinical characteristics described in each of the four case histories of retinal vein occlusion is not sufficient to establish a clinical diagnosis. In all four cases, the ophthalmologist appeared to make the diagnosis of RVO based upon review of a fluorescein angiogram (FA). While this is an appropriate method of making this diagnosis, without describing the features seen on the FA or providing a copy of the FA, it is not possible to draw any conclusions about the cases. The FA should be provided.

2) Central serous retinopathy (CSR) comprises a very small subset of retinopathies. The clinical presentations listed in Safety Summary, name CSR as a diagnosis, but several of the cases do not describe the clinical features or clinical course of a CSR (e.g., Protocol MEK114267, Subject 403077). Some of the cases appear to interchange the terms macular edema, CSR and chorioretinopathy (Protocol MEK113583, Subject 109004, 202006). These terms are not interchangeable. In some cases, there are no clinical characteristics, reports of findings on Ocular Coherence Tomography (OCT) or FA, except to say that there was CSR. Without describing the features seen on the test or providing an image of the test results, it is not possible to draw any conclusions about the cases. The FA and OCT images should be provided.

3) The cases of papillary edema are more likely to be related to brain metastasis than to the study drug.

Kindly respond to confirm receipt of this email and please provide your response as soon as possible.

Thanks,

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

From: Eric Richards [mailto:eric.2.richards@gsk.com]
Sent: Monday, April 08, 2013 9:59 AM
To: Griffin, Norma
Subject: RE: NDA 204114 GSK - Question regarding Ophthalmology Information

Hi Norma – Our response follows:

GSK did not systematically collect source documentation for the ophthalmic examinations. Rather cases of CSR, RVO and Papillar Edma were reviewed by a GSK-ophthalmologist and an external consultant; [redacted] (b) (4) It would be helpful if the FDA could provide some more specifics regarding the data that is desired. We could gather this data, when feasible, and we could arrange a short TCON with our internal and external experts to discuss any questions.

Please let me know if you'd like to discuss.

Thanks,

Eric Richards
Global Regulatory Affairs
Internal phone: 8-202-6842
External: 610-917-6842
Mobile: 347-525-3231

From: Griffin, Norma [mailto:Norma.Griffin@fda.hhs.gov]
Sent: Monday, April 08, 2013 8:09 AM
To: Eric Richards
Subject: NDA 204114 GSK - Question regarding Ophthalmology Information
Importance: High

Eric,

We have consulted with one of our ophthalmology medical officers regarding the ophthalmology information for NDA 204114.

He has indicated that there is some incorrect interchange/confusion the ophthalmology terms.

Further he cannot find any of the OCTs, fluorosceins, or retinal photographs in the submission. Would you know where or could you direct me where these would be found?

Thanks,

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

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/s/

NORMA S GRIFFIN
04/12/2013

Wrap-Up Meeting Summary
April 5, 2013

NDA: 204114
Product: Mekinist (trametinib)
Submission Date: August 2, 2012
Received Date: August 3, 2012
Sponsor: GlaxoSmithKline (GSK), LLC
Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation as detected by an FDA approved test.

Review Team:
Richard Pazdur, M.D., Director, OHOP
Anthony Murgo, Associate Director of Regulatory Science, OHOP
Patricia Keegan, M.D., Director DOP2
Joseph Gootenberg, M.D., Deputy Director, DOP2
Jeffrey Summers, M.D., Depurty Director for Safety, DOP2
Karen Jones, CPMS, DOP2
Monica Hughes CPMS, DOP2
Norma Griffin, Regulatory Health Project Manager
Marc Theoret, M.D., Clinical Reviewer
Maitreyee Hazarika, Clinical Reviewer
Huanyu (Jade) Chen, Statistics
Ruby Leong, Clinical Pharmacology
Rosane Charlab-Orbach, Acting Genomics TL
Whitney Helms, Nonclinical (TL)
Gabriel Sachia Khasar, Nonclinical Reviewer
Nallaperumal Chidambaram
Zhe Jean Tang, Product Quality Reviewer
Jewell Martin, Product (ONDQA RPM)
Minerva Hughes, Biopharmaceutics Reviewer
Mahesh Ramanadham, OC (Facilities)
Donna Roscoe, CDRH Consultant
Jean Mulinde, OSI Reviewer
Frances Fahnbulleh for Sue Kang, OSE, Safety RPM
Todd Bridges for James Schlick, OSE Proprietary Name Reviewer
Katherine Coyle, DPVII
Peter Waldron, DPVII
Igor Cerny, DRISK
Nathan Caulk, Patient Labeling
Corrinne Kulick, OSE, DPVI
Melissa Tassinari, Maternal Health

Discussion Items:

1. Important Goal Dates

Milestone	6-month review	8.5-month review	10-month review	Comments
Send proposed labeling/PMR/PMC/REMS to applicant	Sunday, 1/6/ 2013 therefore **Friday, January 4, 2013**	**Monday March 18, 2013**	**Monday April 15, 2013**	
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	Sunday, 1/13/ 2013 therefore **Friday, January 11, 2013**	**Monday March 25, 2013**	**Monday April 22, 2013**	
Review Target Due Dates: ***Primary Review Due*** ***Secondary Review Due*** ***CDTL Review Due*** ***Division Director Review Due*** ***Office Director Review Due/Sign-Off***	**January 4, 2013** **January 10, 2013** **January 11, 2013** **January 24, 2013** **By February 1, 2013**	**March 18, 2013** **March 22, 2013** **March 25, 2013** **April 5, 2013** **By April 15, 2013**	**April 8, 2013** **April 15, 2013** **April 22, 2013** **May 13, 2013** **June 3, 2013**	**Monday**
FINAL Action Letter Due	Sunday, 2/3/ 2013 therefore **Friday, February 1, 2013**	**Monday April 15, 2013**	**Monday June 3, 2013**	

PDUFA Goal Date: **June 3, 2013**

2. Discipline Specific Reviews of Application

   a. Clinical: Need response to most recent Clinical IRs to complete review. Potential PMR (ocular toxicity) and PMC (skin related toxicity). Completion of labeling edits is outstanding. Goal to complete review is 4.15.2013.

      Clinical Protocol/Site inspection: Clinical Inspection Summary completed and uploaded into DARRTS as of 1.3.2013

   b. Statistics: Final analysis was submitted by GSK on 4.4.2013; STATS needs to review/QC this data. Review scheduled to be complete by 4.9.2013.

   c. Clinical Pharmacology: Review will be signed by 4.8.2013

   d. Genomics: Review is included in ClinPharm and will be signed 4.8.2013.

   e. CMC: Reviews will be ready for signature by 4.8.2013, however, scheduled to receive new storage temperature and stability data on or

before April 15, 2013 for this application. Depending on the extent of the data and review for this major amendment will determine final action date. CMC is prepared to include amended reviews.

Methods Validation Review (M.Trehy) complete and uploaded into DARRTS as of 3.20.2013 and 3.29.2013.

f. CMC (Microbiology): John Metcalfe – review in DARRTS 11.30.2012.

g. CMC (facilities): [redacted] (b) (4) issue. Communication from Compliance scheduled to be issued to Sponsor on 4.5.2013 to address and requesting ~one week turnaround for Sponsor's response.

h. Biopharmaceutics: Review will be uploaded and signed on 4.5.2013.

i. Nonclinical: Secondary review in process and will go to OHOT Division Director by early week of 4.8.2013.

j. CDRH: Sponsor for Companion diagnostic should have their requested materials. Action date will be the same as the NDA action.

3. Pending Consults

- DMEPA – Proprietary Name (MEKINIST) is acceptable –Proprietary Name Request Conditionally Acceptable letter in DARRTS on 9.20.2012. Carton and Container: No comments after company submitted 3/20 edits. Storage condition change: Once the changes in container and carton and PI are done, DMEPA will need to review and make comments, if any.
- DRISK – Review in DARRTS as of 3.14.2013 *(DRISK recommends managing the identified safety risks associated with trametinib through labeling, including a Medication Guide as part of labeling and not a REMS. The need for a REMS can be re-evaluated if new safety data becomes available that warrants more extensive risk mitigation.)*
- DSI Inspection –Clinical Inspection Summary in DARRTS on 1.3.2013
  - VAI-Foreign Inspection - Russia – in DARRTS on 3.20.2013
  - CI Foreign (NAI) – France – in DARRTS on 1.22.2013
  - SM Inspection (NAI) – Collegeville, PA – in DARRTS on 1.2.2013
- Maternal Health – scheduled to provide review on or before 4.22.2013.

4. Labeling Discussion

- Status of labeling review – need to finalize edits, provide substantially complete label, and send to Sponsor.
- Need comments from Ophthalomologic consult.

5. Discuss Postmarketing Commitments

ClinPharm requested 2 PMRs:
PMR 1 - QT/QTc Interval Prolongation Assessment
PMR 2 - Hepatic Impairment on Exposure Assessment

6. Discuss Postmarketing Safety Surveillance Plan: This will be routine safety surveillance.

6. Discussion of Proposed Action To Be Taken – As of this date, no issues (other than those that are expected to be addressed) to affect a scheduled Action.

7. Discussion of sign-off procedure and schedule – Final primary and secondary reviews need to be completed (by April 15, 2013) in order for the CDTL to review and ultimately for the DD to complete her review within the planned, 10-month review timeframe. Sign-off process will continue with labeling, PMR/PMCs, and action letter.

   All press-related documents need to be drafted and circulated. The action package and draft final action letter will be drafted and circulated for review.

   - Draft Press Release and Information Advisory – have been in contact with Stephanie Yao regarding the changed timing of Action so that this can be prepared.
   - RPM to draft ASCO Burst

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/s/

NORMA S GRIFFIN
04/17/2013

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration

CENTER FOR DRUG EVALUATION AND RESEARCH

Office of Manufacturing and Product Quality
10903 New Hampshire Avenue
Building #51, Room 4227
Silver Spring, MD 20993

TELEPHONE: (301) 796-3272
FAX: (301) 847-8742

April 9, 2013

Ms. Maria Rigotti, Site Director
GlaxoSmithKline, Manufacturing, S.p.A
Strada Asolana, 90
43056 S. Pollo Di Torille
Parma, Italy

Reference: FEI 3002807114

Dear Ms. Rigotti:

We have completed our review of response to the Request for Additional information sent on February 14, 2013. The Agency acknowledges your evaluation and response to the Request for Additional information following the 9/17/12-9/21/12 inspection of your facility in support of NDA 204114.

Your evaluation in response to Question #1 to demonstrate [redacted] (b) (4)

[redacted] (b) (4)

In response to Question #2, your clarification and evaluation of your current [redacted] (b) (4) appears adequate, however the conclusions are limited as information regarding the storage conditions of the batches used in the study are not provided. Additionally your evaluation is limited [redacted] (b) (4) The Agency has no further comment on the adequacy of your hold time study at this time. The adequacy of your hold time and supporting storage conditions may be evaluated during an on-site facility inspection.

The acceptance criteria presented in your response will not demonstrate adequacy (b) (4) for all commercial batches manufactured. The proposed acceptance criteria does not conform to the statistical requirements of Current Good Manufacturing Practices. Please revise your proposed methodology to demonstrate adequacy (b) (4) (b) (4) testing to conform to Current Good Manufacturing Practices.

Please reply to this letter by email by April 19, 2013, and include your firm's FEI number: 3002807114. Address your response to:

Mahesh.Ramanadham@fda.hhs.gov

Mahesh R. Ramanadham
CDER / Office of Compliance
Office of Manufacturing and Product Quality
WO51 RM 4227 HFD320
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

The Agency would like to ensure clarity over this matter in order to facilitate action on pending GSK applications. We propose to hold a teleconference with representatives from GSK Parma, IT and GSK Collegeville, PA so that multiple pending applications with this deficiency can be addressed. Please contact Jewell Martin, Regulatory Project Manager, at (301) 796-2072 to convey availability.

Sincerely,

Tara Gooen
Branch Chief (Acting)
New Drug Manufacturing Assessment Branch
Division of Good Manufacturing Practice Assessment
CDER / OC / OMPQ

[i] USP 35 - NF 30

From: Griffin, Norma
Sent: Monday, April 08, 2013 9:05 AM
To: 'eric.2.richards@gsk.com'
Subject: RE: NDA 204114 GSK - IR 4.8.2013 - Questions regarding Ophthalmology Information

Importance: High
Eric,

In addition to the my email below, please also provide details of the ophthalmological safety monitoring plan for protocols MEK115306, MEK116513, and MEK115532.

Thanks,

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

From: Griffin, Norma
Sent: Monday, April 08, 2013 8:09 AM
To: 'eric.2.richards@gsk.com'
Subject: NDA 204114 GSK - Question regarding Ophthalmology Information
Importance: High

Eric,

We have consulted with one of our ophthalmology medical officers regarding the ophthalmology information for NDA 204114.

He has indicated that there is some incorrect interchange/confusion the ophthalmology terms.

Further he cannot find any of the OCTs, fluorosceins, or retinal photographs in the submission. Would you know where or could you direct me where these would be found?

Thanks,

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

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/s/

NORMA S GRIFFIN
04/08/2013

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

Memorandum

Date: April 4, 2013

From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA

Subject: NDAs 202806 and 204114; GlaxoSmithKline, LLC
Clinical Comments and Information Request

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

Dear Eric/Ellen/Amita:

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.

Our Clinical Reviewer has the following comments and information request, and requests a response by **tomorrow, Friday, April 5, 2013**.

For NDAs 202806 and 204114:

1. Provide the location in the NDAs or submit the supporting datasets and summary tables (or Figures) that details the reasons for the 483 screening failures in BRF113683 and the 737 screening failures in MEK114267.

2. Please clarify the potential discrepancy in Tables 5 and 6 of the BRF113683 clinical study report in regard to the number of patients in the dabrafenib treatment arm and the trametinib treatment arm with treatment ongoing at the time of data cut-off:
   - Table 5, treatment ongoing in 107 and 17 patients in the dabrafenib and DTIC treatment arms, respectively
   - Table 6, on randomized study treatment in 106 and 14 patients in the dabrafenib and DTIC treatment arms, respectively

   A similar discrepancy was not identified within Tables 5 and 6 of the MEK114267 clinical study report.

3. Table 52 in the ISS and Table 68 in the MEK114267 study report list one chemotherapy-treated patient and four trametinib-treated patients as having an increase from baseline in QTcB ≥501 msec. The review of the ECG.xpt dataset identified four trametinib-treated patients but no chemotherapy-treated patients with a worst-case increase from baseline of QTcB to≥501 msec. Please clarify this potential discrepancy.

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

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/s/

NORMA S GRIFFIN
04/04/2013

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.

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/s/

NORMA S GRIFFIN
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 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.

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/s/

NORMA S GRIFFIN
04/02/2013

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 oncttern
   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.

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.

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/s/

NORMA S GRIFFIN
03/27/2013

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 204114; GlaxoSmithKline, LLC
Clinical Comments and Information Request

GlaxoSmithKline, LLC
Eric Richards
Amita Chaudhari
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 Clinical Reviewer has the following comments and information request and requests a response by **close of business Thursday, March 28, 2012**.

1. Please clarify the meaning of the adverse event "cytolysis" which was reported for Patient MEK114267.0402816 and provide the results from all investigation(s) or procedures performed in the evaluation of this AE (e.g., liver biopsy). In addition, clarify the timing of onset of the hepatitis AE because there is a discrepancy between the narrative and the information in the raw datasets. The narrative provided in the MEK114267 clinical study report states that the investigational product was discontinued on Day 10 for multiple adverse events, including hepatitis, but the raw data identified Day 17 as the start day of hepatitis and cytolysis, i.e., following the administration of antibiotics, paracetamol, and NSAIDS.

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

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/s/

NORMA S GRIFFIN
03/27/2013

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

Memorandum

Date: March 26, 2013

From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 204114; GlaxoSmithKline, LLC
Clinical Comments and Information Request

GlaxoSmithKline, LLC
Eric Richards
Amita Chaudhari
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 Clinical Reviewer has the following comments and information request and requests a response by Thursday, March 28, 2012, **or sooner if possible**.

1. Submit your analysis or analyses (or provide the location in the NDA) to evaluate the benefit of administering the protocol defined treatment regimen as primary prophylaxis and as treatment of patients who encountered dermatologic adverse reactions.

2. Provide an updated Table (or the location in the NDA) for the Worst-case change in Left ventricular ejection fraction based on independent review for Trial MEK114267 (i.e., updated Table 54 from the MEK114267 CSR). Provide a description of the analysis method and datasets used. For patients not included in the updated analysis, please state whether there are echocardiogram or MUGA results that are available but have not yet been submitted for independent review or that have been submitted for independent review and the data have not been provided to GSK or FDA.

Category	Trametinib(N=211)	Chemotherapy(N=99)
n (%)		
No change or any increase Any decrease 0 to <10 decrease 10 to 19 decrease ≥20 decrease ≥10 decrease and ≥LLN ≥10 decrease and below LLN ≥20 decrease and ≥ LLN ≥20 decrease and below LLN		

In addition, provide the same updated table for worst case changes in LVEF based on the Investigator assessment

3. Please submit a complete patient narrative for subject 2404 (120-Day Safety update, Section 5.2.5.4.2) which provides all relevant details of this case in regard to retinal vein occlusion. If previously submitted, please provide the location in the NDA.

4. Please submit (or provide the location in the NDA) the results of a time dependency analysis (i.e., by cycle of therapy) of the change in systolic and diastolic blood pressure over time by treatment group for MEK114267. Please provide a description of the methods used in the analysis.

5. Please submit (or provide the location in the NDA or IND) all SAE narratives and any other relevant information in regard to the following fatal SAEs (Case IDs from Table 54 in the 120-Day safety update) reported across the trametinib development program:
   a. A0952917C
   b. A0870525B
   c. A0977731A
   d. A0945891B
   e. Z0007820A
   f. Z0017092A
   g. A0959696B
   h. Z0008705C
   i. A0920728A
   j. A0887882A
   k. B0826064A

   In addition, please provide this information for the 12 Cardiovascular Deaths as assessed by the [redacted] (b) (4) review (if not included in the above list of case IDs).

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

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/s/

NORMA S GRIFFIN
03/26/2013

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

Memorandum

Date: March 20, 2013

From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 204114; GlaxoSmithKline, LLC
Mekinist Container Labeling - Comments and Proposed Edits

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 "Mekinist (trametinib)" received on August 3, 2012.

We have the following comments for the Container labeling from our Division of Medication Error Prevention and Analysis (DMEPA) Reviewer. Please provide your response by close of business Wednesday, March 27, 2012, **or sooner if possible**.

Container Labels – 30 count and 7 count physician sample

1. Relocate the net quantity statement "XX" Tablets" away from the product strength statement. Additionally, relocate the product strength in the 30 count bottles to appear just below "(trametinib) Tablets". Post-marketing data shows that confusion with the strength and bottle count can occur when they are in close proximity with each other on the principal display panel.

2. Ensure the established name is at least ½ the size of the proprietary name and has prominence commensurate with the proprietary name taking into account all pertinent factors including typography, layout, contrast and other printer features per 21 CFR 201.10(g)(2).

3. Revise the storage statement [redacted] (b) (4) to read "Dispense in original bottle. Do not remove desiccant. Protect from moisture and light. Do not place medication in pill boxes." Also, to increase the prominence of the statements, bold the font and change the text color to red.

   For example:
   Dispense in original bottle. Do not remove desiccant. Protect from moisture and light. Do not place medication in pill boxes.

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

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/s/

NORMA S GRIFFIN
03/20/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204114

REQUEST FOR METHODS VALIDATION MATERIALS

GlaxoSmithKline LLC
Attention: Eric Richards, M.S., M.P.H.
Director Global Regulatory Affairs
1250 South Collegeville Road
Collegeville, PA 19426
FAX: (919) 483-5381

Dear Eric Richards:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mekinist (trametinib) Tablets, 0.5 mg, 1 mg, and 2 mg.

We will be performing methods validation studies on Mekinist (trametinib) Tablets, 0.5 mg, 1 mg, and 2 mg, as described in NDA 204114.

In order to perform dissolution testing at 20 minutes, we request the additional samples:

Method, current version

Determination of release by dissolution of Trametinib Tablets by HPLC
Current specification for 2, 1, and 0.5 mg tablets

Samples and Reference Standards

100 2 mg tablets of trametinib
50 1 mg tablets of trametinib
50 0.5 mg tablets of trametinib

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: MVP Sample Custodian
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP coordinator
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
03/20/2013

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.

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 NDAs 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.

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/s/

NORMA S GRIFFIN
03/17/2013

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

Memorandum

Date: March 15, 2013

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:

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

Our Clinical Reviewer has the following comments and information request and requests a response by close of business, Monday, March 18, 2012, **or sooner if possible**.

1. In the summary of clinical safety for NDA 204114, the narrative summary (page 36) provided for Patient 402229 (MEK114267) stated that "On Day 105, new liver metastases were identified and trametinib was discontinued due to vomiting, liver failure and renal failure." The review of the other information submitted to NDA 204114, including the raw datasets, indicates that liver failure (Grade 5) and renal failure (Grade 5) did not start until Day 115, which is after the Day that chemotherapy was initiated (Day 109). Please clarify the potential discrepancy regarding the timing of onset of the renal and hepatic toxicities for this patient, i.e., onset before or after the start of subsequent chemotherapy.

2. For NDA 204114, please provide the location of the final report of the independent adjudication of all SAEs and cardiac SAEs with trametinib from the [redacted] (b) (4) [redacted]. In addition, please provide the location of the charter used for this independent review. If not submitted, please submit these documents to NDA 204114 by COB on March 18, 2013.

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

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/s/

NORMA S GRIFFIN
03/15/2013

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.

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/s/

NORMA S GRIFFIN
03/13/2013

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]		

Appendix 1. SAS Code for NDA 204114

```
libname der    "C:\Documents and Settings\chenhu\My Documents\NDA\NDA 204114\SAS\data\der\";
libname raw    "C:\Documents and Settings\chenhu\My Documents\NDA\NDA 204114\SAS\data\raw\";
LIBNAME MINE "C:\Documents and Settings\chenhu\My Documents\NDA\NDA 204114\SAS\data\MINE";

PROC FORMAT   ;
value trt
1='Trametinib'
0='Chemotherapy'
;
value PFSTYPE
1="Event:Death"
2="Event:PD"
3="CEN:prior anti CTX and pd"
4="CEN:DISPOSTION"
5="CEN:RANDOMIZATION"
6="CEN:CEN:prior anti CTX and non pd"
7='CEN:PRIOR CUT OFF '
8='CEN: 2 CONTINOUS MISSING'
;
run;

%macro pike(dataset, timeto, censor, cen01, rstratcd, trtcd, type=);
ods output censoredsummary=summary ;
proc lifetest data=&dataset notable;
time &timeto*&censor(&cen01);
strata &trtcd &rstratcd;
run;
ods output close;

ods output logunichisq=log;
proc sort data =&dataset;
by    &rstratcd;
run;
proc lifetest data=&dataset notable;
time &timeto*&censor(&cen01);
by &rstratcd;
test &trtcd;
run;
ods output close;
```

```
/*observed*/
data est;
set summary (rename=(failed=observe));
keep &rstratcd trtcd observe;
run;

proc sort data=est;
by &rstratcd;
run;
data lr;
set log;
keep &rstratcd statistic;
run;
proc sort data=lr;
by &rstratcd;
run;

/* Expected */
data oe;
merge est lr;
by &rstratcd;
if trtcd=1 then do;
expect=observe-statistic;
end;
else if trtcd=2 then do;
expect=statistic+observe;
end;
run;
*** now sum observed and expected values over strata ***;
*** see Armitage and Berry page 581 ***;
proc sort data=oe;
by trtcd;
run;
proc univariate data=oe noprint;
by trtcd;
var observe expect;
output out=sumoe sum=sumo sume;
run;
data sumoe1 sumoe2;
set sumoe;
dum=1;
```

```
if trtcd=1 then output sumoe1;
if trtcd=2 then output sumoe2;
run;
data pike0;
length type $20.;
merge sumoe1 (rename=(sumo=o1 sume=e1)) sumoe2 (rename=(sumo=o2 sume=e2));
by dum;
drop trtcd;
hr=(o1/e1)/(o2/e2);
lnhr=log(hr);
selnhr=sqrt((1/e1) + (1/e2));
lower=COMPRESS(PUT(exp(lnhr-1.96*(selnhr)),5.2));
upper=COMPRESS(PUT(exp(lnhr+1.96*(selnhr)),5.2));
hr round=COMPRESS(PUT(hr, 4.2));
type="&type";
PIKE=HR_round||' ('||lower||', '||upper||')';
run;
DATA pike;
length type $30.;
SET pike pike0;
RUN;
%mend;
%macro pike_us_gsk(dataset, timeto, censor, cen01, rstratcd, trtcd, type=);

DATA &DATASET;
SET &DATASET;
&rstratcd=1;
RUN;

ods output censoredsummary=summary ;
proc lifetest data=&dataset notable;
time &timeto*&censor(&cen01);
strata &trtcd &rstratcd;
run;
ods output close;

ods output logunichisq=log;
proc sort data =&dataset;
by    &rstratcd;
run;
proc lifetest data=&dataset notable;
time &timeto*&censor(&cen01);
```

```
by &rstratcd;
test &trtcd;
run;
ods output close;

/*observed*/
data est;
set summary (rename=(failed=observe));
keep &rstratcd trtcd observe;
run;

proc sort data=est;
by &rstratcd;
run;
data lr;
set log;
keep &rstratcd statistic;
run;
proc sort data=lr;
by &rstratcd;
run;

/* Expected */
data oe;
merge est lr;
by &rstratcd;
if trtcd=1 then do;
expect=observe-statistic;
end;
else if trtcd=2 then do;
expect=statistic+observe;
end;
run;
*** now sum observed and expected values over strata ***;
*** see Armitage and Berry page 581 ***;
proc sort data=oe;
by trtcd;
run;
proc univariate data=oe noprint;
by trtcd;
var observe expect;
output out=sumoe sum=sumo sume;
```

```
run;
data sumoe1 sumoe2;
set sumoe;
dum=1;
if trtcd=1 then output sumoe1;
if trtcd=2 then output sumoe2;
run;
data pike0;
length type $20.;
merge sumoe1 (rename=(sumo=o1 sume=e1)) sumoe2 (rename=(sumo=o2 sume=e2));
by dum;
drop trtcd;
hr=(o1/e1)/(o2/e2);
lnhr=log(hr);
selnhr=sqrt((1/e1) + (1/e2));
lower=COMPRESS(PUT(exp(lnhr-1.96*(selnhr)),5.2));
upper=COMPRESS(PUT(exp(lnhr+1.96*(selnhr)),5.2));
hr round=COMPRESS(PUT(hr, 4.2));
type="&type";
PIKE=HR_round||' ('||lower||', '||upper||')';
run;
DATA pike;
length type $30.;
SET pike pike0;
RUN;
%mend;

options  nodate nonumber nocenter  NOFMTERR formchar='|----|+|---+=|-/\<>*' validvarname=upcase missing=' ' formdlim=' '
orientation='LANDSCAPE' mautosource mautolocdisplay spool
sasautos=(&pgm9path, &pgm24path, sasautos)
fmtsearch=(fmteff) mlogic mprint ;

proc sort data=raw.rresp2e1(where=(progdt ne .))  out=oncpd0; by usubjid progdt; run;

data  oncpd(keep=usubjid oncpd_date);
set oncpd0;
by usubjid progdt;
format oncpd date date9.;
oncpd date=progdt;
if first.usubjid;
run;
```

```
proc sort data=raw.rlesioe1 (where=(5000<visitnum and visitnum<6000 and actdt ne .)) out= IRCpostbaselesion;
by usubjid visitnum lstypcd   lsnum;
run;

/*Split lesion assessment to three subset: target, non-target, and newl lesion*/
proc sort data=  raw.rlesioe1 out=rlesioe1; by usubjid visitnum lstypcd LSDIA; run;

data target nontarget newlesion resp;
set raw.rlesioe1;
if lstypcd='1' then output target;                          /*2490 records target lesion*/
else if lstypcd='2' then output nontarget;                  /*2476 records target lesion*/
else if lstypcd='5' then output newlesion;                  /*191 new lesion*/
else  output resp;                                          /*non value other than 1, 2, 5*/
run;

/*****************************************************************************************************************
***/
/*New leison: Keep the 1st date of new lesion as the PD date */
/*****************************************************************************************************************
***/
proc sort data=  newlesion out=newlesion; by usubjid  LSORGCD ACTDT ; run;

data NEWPDid (keep=usubjid lsorgcd);
set newlesion(where=(NEWSTSCD="U"));
by usubjid lsorgcd;
if first.lsorgcd;
run;

data NEWPDUEQid ;
merge newlesion newpdid(in=a);
by usubjid lsorgcd;
if a;
run;

proc sort data=NEWPDUEQid out=newpd0; by usubjid actdt; run;
data _NEWPD (keep=usubjid NEWPD actdt RENAME=(actdt=NEWPD_date));
set newpd0;
by usubjid ACTDT;
NEWPD=1;
if first.usubjid;
run;
```

```
/*****************************************************************************************************************
***/
/*TARGET lESION: GET SUM OF LAREST TUMOR DIAMETER PER VISIT SHOULD KEEP LESS OR EQUAL 5 ORGANS
    */
/*****************************************************************************************************************
***/
proc sort data=  target out=target; by usubjid visitnum LSORGCD lstypcd LSDIA; run;

data targetsum (KEEP=USUBJID visitnum SUMLSDIA);
set target;
by    usubjid VISITNUM ;
retain  SUMLSDIA;
IF FIRST.visitnum THEN  SUMLSDIA=0;
SUMLSDIA=SUMLSDIA+LSDIA;
IF LAST.visitnum  ;
run;

proc transpose data= targetsum out=rtarget(drop=_NAME_); by USUBJID; ID VISITNUM; var SUMLSDIA;run;

%macro pdfor(cur=, prevmin=  );
if &cur NE 0 & (&cur-&prevmin)/&cur*100>=20 & (&cur-&prevmin)>5 then do;
PD&cur=1;
PDVST= "&cur" ;
ABSCHG = &cur-&prevmin;
RELCHG = (&cur-&prevmin)/&cur*100;
end;
%mend;

data  TARGET0 TARGET6 TARGET12 TARGET21  TARGET30 ;
set rtarget;
nadir010=_10D00;
nadir011=min (nadir010,  5000D01,  5000D03,_5000D04, _5000D05 );
%pdfor(cur=_5000D01, prevmin=_10D00);
%pdfor(cur= 5000D03, prevmin= 10D00);
%pdfor(cur=_5000D04, prevmin=_10D00);
%pdfor(cur= 5000D05, prevmin= 10D00);
PD0=max(PD 5000D01, PD_5000D03,PD_5000D04, PD_5000D04);
PD0VNUM= PDVST;
IF   PD0 =1 THEN OUTPUT TARGET0  ;

nadir060=min (nadir011, _5006D00);
```

```
%pdfor(cur=_5006D00, prevmin=nadir011);

nadir061=min (nadir060,_5006D01, _5006D02,_5006D03, _5006D04, _5006D05);
%pdfor(cur=_5006D01, prevmin=nadir060);
%pdfor(cur= 5006D02, prevmin=nadir060);
%pdfor(cur=_5006D03, prevmin=nadir060);
%pdfor(cur= 5006D04, prevmin=nadir060);
%pdfor(cur=_5006D05, prevmin=nadir060);
PD6=max(PD 5006D00, PD_5006D01,PD_5006D02, PD_5006D02, PD_5006D04, PD_5006D05);
PD6VNUM= PDVST;
IF   PD0 NE 1 & PD6 =1 THEN OUTPUT TARGET6  ;
/*ALL ACCURED ON SCHEDULED VISIT 6*/

nadir120=min(nadir061, 5012D00);
%pdfor(cur=_5012D00, prevmin=nadir061);
nadir121=min(nadir120,_5012D01, _5012D02, _5012D03, _5012D04, _5012D06,
 5012D07,  5012D08 );
%pdfor(cur= 5012D01, prevmin=nadir120);
%pdfor(cur=_5012D02, prevmin=nadir120);
%pdfor(cur= 5012D03, prevmin=nadir120);
%pdfor(cur=_5012D04, prevmin=nadir120);
%pdfor(cur= 5012D06, prevmin=nadir120);
%pdfor(cur=_5012D07, prevmin=nadir120);
%pdfor(cur= 5012D08, prevmin=nadir120);
PD12=max(PD 5012D00,PD 5012D01, PD_5012D02, PD_5012D03, PD_5012D04, PD_5012D06,
PD 5012D07, PD 5012D08);
PD12VNUM= PDVST;
IF   PD0 NE 1 & PD6 NE 1 & PD12 =1 THEN OUTPUT TARGET12  ;
/*ALL ACCURED ON SCHEDULED VISIT 12 EXCEPT MEK114267.0402584 AT WEEK 12 DAY 7*/

nadir210=min (nadir121,  5021D00);
%pdfor(cur=_5021D00, prevmin=nadir121);
nadir211=min (nadir210,  5021D01,  5021D04, _5021D05, _5021D06, _5021D07);
%pdfor(cur=_5021D01, prevmin=nadir210);
%pdfor(cur= 5021D04, prevmin=nadir210);
%pdfor(cur=_5021D05, prevmin=nadir210);
%pdfor(cur= 5021D06, prevmin=nadir210);
%pdfor(cur=_5021D07, prevmin=nadir210);
PD21=max(PD 5021D00, PD_5021D01, PD_5021D04, PD_5021D05, PD_5021D06, PD_5021D07);
PD21VNUM= PDVST;
IF   PD0 NE 1 & PD6 NE 1 & PD12 NE 1 & PD21 =1 THEN OUTPUT TARGET21  ;
```

```
nadir300=min(nadir211,  5030D00);
%pdfor(cur=_5030D00, prevmin=nadir211);
nadir301=min(nadir300,  5030D05);
%pdfor(cur=_5030D05, prevmin=nadir300);
PD30=max(PD_5030D00, PD_5030D05);
PD30VNUM= PDVST;
IF   PD0 NE 1 & PD6 NE 1 & PD12 NE 1 & PD21 NE 1  & PD30 =1 THEN OUTPUT TARGET30  ;

run;
*330_00001, 345_00023, 345_00024 had nadir as 0 and no more assessment thereafter;
*349_00002 had one assessment 0 and appear again later;
DATA TARGETTEMP;
SET _NULL_;
RUN;
%MACRO TARGETTEMP(NUM=);
DATA TARGETTEMP (KEEP=USUBJID PDVIST ABSCHG RELCHG );
SET TARGET&NUM (KEEP=USUBJID PD&NUM.VNUM ABSCHG RELCHG RENAME=(PD&NUM.VNUM=PDVIST)) TARGETTEMP;
RUN;
%MEND;

%TARGETTEMP(NUM=0) ;                    /*OBS=1*/
%TARGETTEMP(NUM=6) ;                    /*OBS=24*/
%TARGETTEMP(NUM=12) ;                   /*OBS=23*/
%TARGETTEMP(NUM=21) ;                   /*OBS=16*/
%TARGETTEMP(NUM=30) ;                   /*OBS=5*/
/*transfer 50XXDXX to 50XX.XX */
DATA TARGETTEMP1(keep=usubjid  TGTPDVISIT);
SET   TARGETTEMP;
TGTPDVISIT=put(substr(PDVIST, 2, (INDEX(upcase(PDVIST),upcase('d') ) )-2) ||"."||substr(PDVIST, LENGTH(PDVIST)-1), 7.2);
RUN;
* proc contents data=    TARGETTEMP1; run;
proc sort data=TARGETTEMP1 out=TARGETTEMP2(keep=usubjid TGTPDVISIT); by usubjid TGTPDVISIT; run;
PROC SORT NODUPKEY  DATA= TARGETTEMP1 OUT=TGTPDID(KEEP=USUBJID); BY USUBJID; RUN;                    /*MAKE SURE GET 69
TARGET PD*/

PROC SORT NODUPKEY DATA=TARGET OUT=TARGET1(KEEP=USUBJID VISITNUM ACTDT); BY     USUBJID VISITNUM;
  RUN;

*proc contents data=    target1; run;
data _targetpd (KEEP=USUBJID TGTPD actdt RENAME=(actdt=TGTPD_date)) ;
```

```
MERGE target1  TARGETTEMP2(in=a);
by usubjid;
if   a;
IF abs(tgtpdvisit-visitnum)<1e-5 then tgtpd=1;
IF tgtpd=1;
RUN;
/*****************************************************************************************************************
***/
/*Non-TARGET lESION: GET SUM OF LAREST TUMOR DIAMETER PER VISIT SHOULD KEEP LESS OR EQUAL 5 ORGANS
        */
/*****************************************************************************************************************
***/
proc sort data=  nontarget out=nontarget; by usubjid visitnum LSNUM LSORGCD actdt; run;
***nontarget part with Unequivocal progression;
data  nontargetpdUPD (keep=usubjid nontgtpd actdt RENAME=(actdt=nontgpd_date));
set nontarget(where=(LSSTSCD="UPD"));
by usubjid ;
if first.usubjid;
nontgtpd=1      ;
run;
/*proc freq data=  nontarget pd; table visitnum; run;                                                          */
/*There were 83 patients has Non-target lesion UPD */

***nontarget part with new lesion;

/*keep on organ records per records (upto two records per organ)*/
data  nontarget1(keep=usubjid visitnum LSNUM LSORGCD  actdt);
set  nontarget;
by   usubjid visitnum LSNUM LSORGCD  actdt;
if first.LSNUM;
run;

/*get sum of lesion organ per patients*/
data nntgtlesion(keep=usubjid visitnum numnontgt);
set      nontarget1;
by  usubjid visitnum;
retain numnontgt;
if first.visitnum then numnontgt=0;
numnontgt+1;
if last.visitnum;
run;
```

```
proc transpose data= nntgtlesion out=TRAnntgtlesion(drop=_NAME_); by usubjid; var numnontgt;run;


data TRAnntgtlesion1;
set TRAnntgtlesion;
array x[6] col2-col7;
do i=1 to 6;
if x[i]-col1>0 then output;
end;
run;

/*****************************************************************************************************************
***/
/*Combine all the PD together
   */
/*****************************************************************************************************************
***/
proc sort data=dernew.demobase(keep=usubjid trtgrp) out=_trtgrp; by usubjid; run;
data _pdtemp(drop=newPD nontgtpd tgtpd);
merge  trtgrp _nontargetpdUPD(in=a)   _targetpd(in=b) _NEWPD(in=c)  _oncpd(in=d);
BY USUBJID;
if a or b or c or d;
format FDApd date date9. FDAPDTYPE $20. FDAONCpd_date date9. FDAONCPDTYPE $20.;
label nontgpd date="Non target PD Date"
NEWPD_date="New Lesion Date"
oncpd_date="Independent Oncologist PD";

FDAPD DATE=min(nontgpd date, NEWPD_date, TGTPD_date );
if FDAPD_DATE ne . then do;
if   FDAPD DATE=NEWPD date then   FDAPDTYPE="PD:New Lesion";
else if FDAPD DATE=TGTPD date then FDAPDTYPE="PD: Target Lesion";
else if  FDAPD_DATE=nontgpd_date then   FDAPDTYPE="PD: Non-Target Lesion";
/*there exist some type of FDA PD had the same date, I take the order of new pd, target lesion and non-target lesion*/
if FDAPD_DATE ne . then FDAPD=1;
end;

FDAONCPD_DATE=min(nontgpd_date, NEWPD_date, TGTPD_date, oncpd_date );
if FDAONCPD_DATE ne . then do;
if  FDAONCPD_DATE=NEWPD_date then   FDAONCPDTYPE="PD:New Lesion";
else if FDAONCPD DATE=TGTPD date then FDAONCPDTYPE="PD: Target Lesion";
else if  FDAONCPD DATE=nontgpd date then   FDAONCPDTYPE="PD: Non-Target Lesion";
else if FDAONCPD_DATE=oncpd_date then FDAONCPDTYPE ="PD: Ind. Oncologist";
```

```
/*there exist some type of FDA PD had the same date, I take the order of new pd, target lesion and non-target lesion*/
if FDAONCPD_DATE ne . then FDAONCPD=1;
end;
if   FDAPD_DATE ne  FDAONCPD_DATE then diff_IRC_IO=1; else   diff_IRC_IO=0;
RUN;

proc freq data=_pdtemp; table FDAONCPDTYPE* FDAPDTYPE/missing nopercent norow nocol list; where diff_IRC_IO=1;  run;

data mine.diff PD IRC IO (drop= FDAONCPD FDAPD diff_IRC_IO) ;
set _pdtemp (where=(diff_IRC_IO=1));
by usubjid;
run;
data mine.fdapd; set    _pdtemp(keep=usubjid trtgrp FDA:); by usubjid; run;

/*Make a comparison on GSK's PD dateset vs. IRC and IO+IRC PD*/
data gskpd;
set der.onctte;
where progdfcd='5' and progdt ne .;
keep usubjid progdt pfscde trtgrp;
proc sort; by usubjid;           run;

data compare;
merge mine.fdapd gskpd(in=a);
by usubjid;
if a;
if  FDAONCPD DATE ne progdt then flagIO=1;   else flagIO=0;     /*5  3:2 in kmo vs. trt arm*/
if  FDAPD Date ne progdt then flagIR=1;  else flagIR=0;        /*21 10:11 in kmo vs. trt arm*/
if FDAONCPD_DATE = progdt & FDAPD_DATE = progdt then flagnodiff=1; else flagnodiff=0;   /*overall 21 diff 10:11 in kmo
vs. trt arm*/
run;

proc freq data=compare; table flag:*trtgrp /NOPERCENT NOROW NOCOL missing; where FDAONCPD_DATE ne progdt; run;
proc freq data=compare; table flag:*trtgrp /NOPERCENT NOROW NOCOL missing; run;

proc print data=compare; var usubjid trtgrp FDAPD_Date FDAONCPD_DATE progdt flag:; where flagIO=1 or flagIR=1; run;


/*get randomization date*/
proc sort data=raw.rrand out=_rand (keep=usubjid   randdt); by usubjid;   run;
```

```
/*Get Disposition date*/
/*-------------------------add GSK's & DSSCATCD=1 inside-----------------------------------------*/
proc sort data= der.ds (where=(dsstdt^=. & dsstdt<='26OCT2011'D & pernum=1 & DSSCATCD=1))
out= disp (keep=usubjid  dsstdt TRTGRP);
by usubjid; run;
proc sort nodupkey data=_disp(keep=usubjid trtgrp) out=ndisp; by usubjid; run;
/*included 71 patients' patient disposition in the randomization phase*/

/*get date of death*/
proc sort data=DER.DEATH(  where=( dthdt<='26OCT2011'D &  pernum=1))
Out=  death (keep=usubjid TRTGRP dthdt dthcscd);
by Usubjid; run;

/*Post-treatment Anti-Cancer therapy start date*/
proc sort data=der.resp2 out=resp2; by usubjid; run;
/*only resp2 has new anti cencer therapy information*/
data _newctxdt(keep=usubjid trtgrp newctxdt newcdtfl);
set  resp2  (where=( pernum=1 & BRSPDFCD= "1" & newctxdt<='26OCT2011'D) );      /*confirmed, randomization phase, before
cut off*/
by usubjid;
format  newctxdt date9.;
if newctxdt ne .;
run;
proc freq data=  newctxdt; table  newcdtfl/missing; run;
/*only 108 patients got new anti-cancer therapy, 4 patients used imputed date (newcdtfl="D')*/

/*Using FDA's PD date: mine.fdapd to get all of the realted event dates*/

data  pddth   (KEEP=USUBJID trtgrp PDDTH DT IR DTHDT FDAPD DATE FDAONCPD DATE PFSTYPE IR PDDTH DT IRIO PFSTYPE IRIO);
merge _death (IN=A) _pdtemp (where=( FDAPD_DATE<='26OCT2011'D) keep=usubjid trtgrp FDAPD_DATE FDAONCPD_DATE IN=B) _RAND;
by USUBJID;
format  PDDTH_DT_IR PDDTH_DT_IRIO date9.;
IF A OR B;
PDDTH DT IR=MIN(FDAPD DATE, DTHDT);
IF   PDDTH DT IR=DTHDT and DTHDT ne .  THEN PFSTYPE IR=1;
ELSE if PDDTH_DT_IR=FDAPD_DATE and FDAPD_DATE ne . then PFSTYPE_IR=2;

PDDTH DT IRIO=MIN(FDAONCPD DATE, DTHDT);
IF   PDDTH DT IRIO=DTHDT and   DTHDT ne .  THEN PFSTYPE IRIO=1;
ELSE if PDDTH_DT_IRIO=FDAONCPD_DATE and FDAONCPD_DATE ne . then PFSTYPE_IRIO=2;
RUN;
```

```
PROC FREQ DATA= _pddth ; TABLE (PFSTYPE_IR PFSTYPE_IRIO)*trtgrp/nopercent norow ; RUN;

/*Count for two continous missing tumor assessment*/
DATA ASSESSDT0;
SET RAW.RLESIOE1(KEEP=USUBJID ACTDT VISITNUM where=(ACTDT<='26OCT2011'D ));
RUN;
proc sort; by usubjid visitnum;

DATA NE;
SET RAW.RRESP1E1 (KEEP=USUBJID VISITNUM RSPCD where=(RSPCD='6'));
RUN;
proc sort; by usubjid visitnum;


DATA ASSESSDT;
merge ASSESSDT0(in=a) NE(in=b);
by usubjid visitnum;
if a and not b;
run;
/*End of GSK code*/

/*dROP DUPLICATE VISIT*/
PROC SORT NODUPKEY DATA=   ASSESSDT OUT=ASSESSDT1; BY USUBJID ACTDT; RUN;

PROC SORT NODUPKEY DATA=   ASSESSDT1(KEEP=USUBJID) OUT=ASSESSid; BY USUBJID; RUN;     /*1059 OBS IN 319 PATIENTS*/


/*change data from long to wide format*/
PROC TRANSPOSE DATA=ASSESSDT1 OUT=TASSESSDT(DROP=_NAME_ _LABEL_); BY USUBJID; VAR ACTDT; RUN;

/*only one patietns has 9 records of tumor assessments*/

DATA ASSESSDIFF;
SET   TASSESSDT;
array x[8] col2-col9;
array Y[8] col1-col8;
ARRAY DIFF[8] DIFF1-DIFF8;
do i=1 to 8;
DIFF[I]=x[i]-Y[I];
END;
```

```
MAX DIFF=MAX(DIFF1, DIFF2, DIFF3, DIFF4, DIFF5,DIFF6, diff7, diff8);
MIN ASS=MIN(DIFF1, DIFF2, DIFF3, DIFF4, DIFF5,DIFF6, diff7, diff8);
DROP I;
KEEP USUBJID  DIFF: MAX_DIFF MIN_ASS;
RUN;
PROC MEANS DATA=  ASSESSDIFF; VAR MAX DIFF; RUN;     /*max gap=92 days*/
/*    DIFF PERIOD THE GAP WILL BE DIFF, FOR EXAMPLE, DURATION [0-91] THEN COUNT 2 MISSING, 91-217 AND DIFF 133 THEN YES,
>217 THEN DIFF>175 DAY
MINE IS IN THE sap PAGE 26*/

proc print data=ASSESSDIFF; where max_diff>91; run;/*max gap=92 days usubjid='MEK114267.0401271'*/
/*only one patient showed be censored due to 2 contious missing issue*/

DATA TWO2MISSING(KEEP=USUBJID max_diff);
SET  ASSESSDIFF;
BY USUBJID;
IF max_diff>91    ;
RUN;

DATA SUBASS;
MERGE ASSESSDT1 TWO2MISSING(IN=A);
BY USUBJID;
IF   A;
RUN;
PROC SORT DATA=SUBASS; BY USUBJID ACTDT; RUN;
PROC SORT DATA=_RAND; BY USUBJID; RUN;

DATA _TEMPASS (KEEP=USUBJID LASTCEN ) ;
MERGE  SUBASS(IN=A) _RAND;

BY USUBJID ;

IF A;
FORMAT   LAST LASTCEN DATE9.;
RSPDY=ACTDT-RANDDT+1;

IF FIRST.USUBJID THEN LAST=.;
LAST=LAG(ACTDT);
IF USUBJID NE LAG(USUBJID) THEN LAST=.;
DIFF=ACTDT-LAST+1;
```

```
IF DIFF=. THEN DIFF=RSPDY;

IF    RSPDY<91 AND DIFF>91 THEN   EXTENDFL=1;
ELSE IF    RSPDY<=91 AND DIFF<=91 THEN EXTENDFL=0;

ELSE IF 91<RSPDY<=217 AND DIFF >133 THEN  EXTENDFL=1;
ELSE IF 91<RSPDY<=217 AND DIFF <=133 THEN  EXTENDFL=0;

ELSE IF 217<RSPDY  AND DIFF >175 THEN  EXTENDFL=1;
ELSE IF 217<RSPDY  AND DIFF <=175 THEN  EXTENDFL=0;

IF                 EXTENDFL=1  THEN DO;
IF LAST<= RANDDT THEN LASTCEN=RANDDT;
ELSE       LASTCEN=LAST;
END;
IF         EXTENDFL=1 ;
RUN;

/*get last non pd assessment before anti-cancer therapy or 2 continous missing, disposition, or study cut off*/
/*This data does not have 2 continous missing*/

/*GET ALL THE TUMOR ASSESSMENT DATE PRIOR NEW ANTI-CACNER THERAPY*/
data _ASSPRIANTICTX (KEEP=USUBJID TRTGRP randdt  NEWCTXDT dsstdt PRICTXASSDT );
merge    RAND (in=ITT)   TASSESSDT _NEWCTXDT(in=a)   _disp(in=b)  ;
by usubjid;
format  prictxASSDT date9.;
array Y[10] RANDDT col1-col9;
ARRAY X[10] prictxASS1-prictxASS10;
/*prior anti cancer therapy*/
if itt;
IF A then do;
*from 2nd avaiable tumor assessment compare anti cancer therapy date to ass date;
*if anti ctx > ass then assign prior assess date, otherwise keep current tumor ass;
/*1st visit comparison will assign randdt*/
do i=1 to 10;
if newctxdt> y[i] then X[I]=y[i];
END;
prictxASSDT =MAX(prictxASS1, prictxASS2, prictxASS3, prictxASS4, prictxASS5, prictxASS6,
prictxASS7, prictxASS8, prictxASS9, prictxASS10);
end;

else if b & DSSTDT>randdt then do;
```

```
do i=1 to 10;
if DSSTDT> y[i] then X[I]=y[i]; /*one patient disp before randomization*/
END;
prictxASSDT =MAX(prictxASS1, prictxASS2, prictxASS3, prictxASS4, prictxASS5, prictxASS6,
prictxASS7, prictxASS8, prictxASS9, prictxASS10);
end;

/*Patient without anti-cancer therapy, get the last tumor assessment OR DATE OF RANDOMIZATION*/
else prictxASSDT =MAX(RANDDT, col1, col2, col3, col4, col5, col6, col7, col8, col9);
run;

/*MERGE ALL THE DATE TOGETHER TO DECIDE CENSORING RULES*/
DATA PFSDT (drop= trtgrp);
MERGE   RAND(in=a)  pddth(IN=B)
 DISP(in=c) ASSESSid(IN=d)   _TEMPASS  _ASSPRIANTICTX (IN=G)
;
BY USUBJID;
format pfs date IRIO date9. pfs_date_IR date9. PFSTYPE_IRIO PFSTYPE. PFSTYPE_IR PFSTYPE.;
if a; /*keep itt population*/

/*IR PD events*/
IF B & PDDTH_DT_IR ne . then   DO;
PFS DATE IR=PDDTH DT IR;
CENSOR_IR=1;              /*REAL pfs EVENT*/
PFSTYPE_IR=PFSTYPE_IR;

/*Although PFS event still need to be censored to non pd prior anti cancer therapy*/
IF  newctxdt ne . and newctxdt< PDDTH_DT_IR THEN DO;
PFS DATE IR=prictxASSDT;
CENSOR_IR=0;
PFSTYPE_IR =3; /*pfsTYPE 1 DEATH 2 pd 3 CENSORED AT NON PD PRIOR NEW ANTI CANCER THERAPY*/
END;
/*APPLY TWO CONTINOUS MISSING RULE*/
ELSE IF LASTCEN NE . AND LASTCEN<PDDTH_DT_IR THEN DO;
PFS_DATE_IR=LASTCEN;
CENSOR_IR=0;
PFSTYPE_IR =8; /*pfsTYPE 1 DEATH 2 pd 3 CENSORED AT NON PD PRIOR NEW ANTI CANCER THERAPY*/
END;

END;
```

```
/*for those without radio assessment censored at randomization date*/
ELSE IF NOT D THEN DO;
PFS_DATE_IR=RANDDT;
CENSOR IR=0;
PFSTYPE IR=5;
END;  /*CENSORED AT randoimization DATE*/
/*1 patient got PD event at randomization date and was count as PFS event*/

/*censored at disposition*/
ELSE IF C & dsstdt>randdt THEN DO;

PFS DATE IR=prictxASSDT;
CENSOR IR=0;
PFSTYPE_IR=4;  /*CENSORED AT disposition*/

END;

/*CENSORED TO NON PD PRIOR ANTI CTX*/
ELSE IF newctxdt ne . THEN DO;
PFS DATE IR=prictxASSDT;
CENSOR_IR=0;
PFSTYPE_IR =6; /*pfsTYPE 1 DEATH 2 pd 3 CENSORED AT NON PD PRIOR NEW ANTI CANCER THERAPY*/
END;

ELSE  do;
PFS DATE IR=prictxASSDT;
CENSOR_IR=0;
PFSTYPE_IR=7;  /*CENSORED AT last tumor assessment prior study cut off*/
END;


/*IRIO PD events*/
IF B & PDDTH DT IRIO ne . then   DO;
PFS DATE IRIO=PDDTH DT IRIO;
CENSOR IRIO=1;              /*REAL pfs EVENT*/
PFSTYPE_IRIO=PFSTYPE_IRIO;

/*Although PFS event still need to be censored to non pd prior anti cancer therapy*/
IF  newctxdt ne . and newctxdt<  PDDTH_DT_IRIO THEN DO;
PFS DATE IRIO=prictxASSDT;
CENSOR IRIO=0;
PFSTYPE_IRIO =3; /*pfsTYPE 1 DEATH 2 pd 3 CENSORED AT NON PD PRIOR NEW ANTI CANCER THERAPY*/
```

```
END;

        /*APPLY TWO CONTINOUS MISSING RULE*/
ELSE IF LASTCEN NE . AND LASTCEN<PDDTH_DT_IRIO THEN DO;
PFS DATE IRIO=LASTCEN;
CENSOR IRIO=0;
PFSTYPE_IRIO =8; /*pfsTYPE 1 DEATH 2 pd 3 CENSORED AT NON PD PRIOR NEW ANTI CANCER THERAPY*/
END;

END;

/*for those without radio assessment censored at randomization date*/
ELSE IF NOT D THEN DO;
PFS DATE IRIO=RANDDT;
CENSOR IRIO=0;
PFSTYPE_IRIO=5;
END;  /*CENSORED AT randoimization DATE*/
/*1 patient got PD event at randomization date and was count as PFS event*/

/*censored at disposition*/
ELSE IF C & dsstdt>randdt THEN DO;
PFS DATE IRIO=prictxASSDT;
CENSOR_IRIO=0;
PFSTYPE_IRIO=4;  /*CENSORED AT disposition*/

END;

/*CENSORED TO NON PD PRIOR ANTI CTX*/
ELSE IF newctxdt ne . THEN DO;
PFS_DATE_IRIO=prictxASSDT;
CENSOR IRIO=0;
PFSTYPE_IRIO =6; /*pfsTYPE 1 DEATH 2 pd 3 CENSORED AT NON PD PRIOR NEW ANTI CANCER THERAPY*/
END;

ELSE  do;
PFS DATE IRIO=prictxASSDT;
CENSOR IRIO=0;
PFSTYPE_IRIO=7;  /*CENSORED AT last tumor assessment prior study cut off*/
END;

PFSday IRIO= PFS DATE IRIO-randdt+1;
PFSday_IR= PFS_DATE_IR-randdt+1;
```

```
PFSMTH IRIO= (PFS DATE IRIO-randdt+1)/30.4375;
PFSMTH_IR= (PFS_DATE_IR-randdt+1)/30.4375;

run;

data mine.fdapfsdt; set pfsdt; by usubjid ;run;

/*****************************************************************************************************************
*********************************/
/*****************************************************************************************************************
*********************************/
/*Get final efficacy dataset
                                */
/*****************************************************************************************************************
*********************************/
/*****************************************************************************************************************
*********************************/
/*****************************************************************************************************************
*********************************/

proc sort data=der.oncttern out=oncttern; by usubjid; run;
*     proc contents data=dernew.oncttern; run;
proc sort data=der.demobase out=demobase; by usubjid; run;
*proc contents data=dernew.demobase; run;
proc sort nodupkey  data=der.trt out=ivrsstrata(keep=usubjid stratum); by usubjid; run;


data eff  ;
merge oncttern (in=a) demobase (DROP= sexcd racecd pathsccd chdpotcd )
ivrsstrata(rename=(STRATUM=stratIVRS)) pfsdt;
by usubjid;
if a;

*RECODE SOME VARIABLE TO BE READY FOR SUBGROUP ANALYSIS
ALL THE xCD ARE NUERICAL VAIRALBES;
region = country;
if country='Argentina' then DO;  region='L America'; regionCD=4; END;
ELSE if country='Australia' then DO;  region='Oceania'; regionCD=2; END;
ELSE if country='Austria' then DO; region='W Europe'; regionCD=3; END;
ELSE if country='Belgium' then DO; region='W Europe';regionCD=3; END;
ELSE if country='Canada' then DO; region='N America';regionCD=1; END;
```

```
ELSE if country='Czech Republic' then DO; region='E Europe';regionCD=5; END;
ELSE if country='France' then DO; region='W Europe';regionCD=3; END;
ELSE if country='Germany' then DO; region='W Europe';regionCD=3; END;
ELSE if country='Greece' then DO; region='W Europe';regionCD=3; END;
ELSE if country='Italy' then DO; region='W Europe';regionCD=3; END;
ELSE if country='New Zealand' then DO; region='Oceania';regionCD=2; END;
ELSE if country='Norway' then DO; region='W Europe';regionCD=3; END;
ELSE if country='Poland' then DO; region='E Europe';regionCD=5; END;
ELSE if country='Russian Federation' then DO; region='E Europe';regionCD=5; END;
ELSE if country='Sweden' then DO; region='W Europe';regionCD=3; END;
ELSE if country='Switzerland' then DO; region='W Europe';regionCD=3; END;
ELSE if country='UK - CMD' then DO; region='W Europe';regionCD=3; END;
ELSE if country='Ukraine' then DO; region='E Europe';regionCD=5; END;
ELSE if country='United States' then DO; region='N America';regionCD=1; END;

IF LSNT='Y' THEN LSNTCD=1; ELSE LSNTCD=2;

PRTSCCDM=PRTSCCD;
IF  PRTSCCDM='T3A' THEN PRTSCCDMCD=1;
ELSE IF  PRTSCCDM='T3B' THEN PRTSCCDMCD=2;
ELSE IF  PRTSCCDM='T4' THEN PRTSCCDMCD=3;
ELSE IF  PRTSCCDM='TIS' THEN PRTSCCDMCD=4;
ELSE IF  PRTSCCDM='TX' THEN PRTSCCDMCD=5;

if trtcd=2 then trt=0;else trt=1;
Label trt="Treatment";
format trt trt.;

if prctx ne 'Y' then do; prctxcd=2; prctx='N'; end; else prctxcd=1;

IF SEX='F' THEN SEXCD=0; ELSE SEXCD=1;

IF race='White - White/Caucasian/European Heritage' THEN do race1="white"; race1cd=1; end;
ELSE do;  race1="non-white"; race1cd=2; end;

lynsc1=lynsc;
if lynsc="N1" then lynsc1cd=1;
if lynsc="N2" then lynsc1cd=2;
if lynsc="N3" then lynsc1cd=3;
if lynsc="NX" then lynsc1cd=4;
```

```
METSC1=METSC;
if METSC="M0" then METSC1cd=1;
if METSC="M1a" then METSC1cd=2;
if METSC="M1b" then METSC1cd=3;
if METSC="M1c" then METSC1cd=4;

pathsc1=pathsc;
if pathsc="Absent" then pathsc1cd=1;
else if pathsc="Present" then pathsc1cd=2; else pathsc1cd=3;


chdpot1=chdpot ;
if chdpot="Post-menopausal" then chdpot1cd=1;
else  if chdpot="Potentially able to bear children" then chdpot1cd=2;
else if chdpot="Pre-menarcheal" then chdpot1cd=3;
else  if chdpot="Sterile (of child-bearing age)" then chdpot1cd=4;
else  chdpot1cd=5;

*GSK censoring reasons;
if PFSCFLC5=1 THEN DO;
IF pfsdt5=dthdt then  GSKIRCPFSTYPE="Death";
ELSE GSKIRCPFSTYPE="pd";
END;
ELSE GSKIRCPFSTYPE="censor";

run;
PROC PRINT DATA=EFF;
VAR USUBJID  PFSCFLC5 PFSDT5    PFS_DATE_IRIO CENSOR_IRIO PFS_DATE_IR CENSOR_IR   ;
WHERE (PFSCFLC5 NE CENSOR_IRIO  )
OR (PFSDT5 NE PFS_DATE_IRIO );
RUN;

PROC PRINT DATA=EFF;
VAR usubjid  PFSCFLC5 PFSDT5    PFS_DATE_IRIO CENSOR_IRIO PFS_DATE_IR CENSOR_IR   ;
WHERE (PFSCFLC5 NE CENSOR_IRIO OR PFSCFLC5 NE CENSOR_IR)
OR (PFSDT5 NE PFS_DATE_IRIO OR PFSDT5 NE PFS_DATE_IR);
RUN;


PROC PRINT DATA=EFF;
```

```
VAR USUBJID  PFSCFLC5 PFSDT5    PFS_DATE_IRIO CENSOR_IRIO PFS_DATE_IR CENSOR_IR   ;
WHERE (PFSCFLC5 NE CENSOR_IRIO  )
OR (PFSDT5 NE PFS_DATE_IRIO );
RUN;

data final; set  null ; run;
%efficacy(dta=eff,  trt=trt, vart2=pfsmth_IR,   varevt=censor_IR,   trtval=1 0, cen01=0, str1=RSTRATCD, title=ITT IR ex
NE);
%efficacy(dta=eff,  trt=trt, vart2=pfsmth_IRIO, varevt=censor_IRIO, trtval=1 0, cen01=0, str1=RSTRATCD, title=ITT IR IO
ex NE);
%efficacy(dta=eff,  trt=trt, vart2=srvmo,  trtval=1 0, cen01=0, varevt=srvcflcd, str1=RSTRATCD, title=ITT OS);
ods rtf file="C:\Documents and Settings\chenhu\My Documents\NDA\NDA 204114\SAS\result\PFS and OS analysis on ITT EX NE
&sysdate .rtf";
proc print data=final;
var Type TRT NUM MED_CI HR_CI_S  PV1 HR_CI_US PV2;
run;
ods rtf close;

/*
Obs    TYPE                    TRT           NUM          MED_CI

1     ITT IR ex NE       Chemotherapy     72/ 36    2.2 (1.4, 2.8)
2     ITT IR ex NE       Trametinib       96/118    4.9 (4.7, 5.1)
3     ITT IR IO ex NE    Chemotherapy     75/ 33    1.5 (1.4, 2.8)
4     ITT IR IO ex NE    Trametinib      100/114    4.9 (4.5, 5.0)


Obs         HR_CI_S            PV1        HR_CI_US            PV2

1     0.43 (0.31, 0.58)    <.0001    0.43 (0.31, 0.58)    <.0001
2
3     0.42 (0.31, 0.57)    <.0001    0.42 (0.31, 0.57)    <.0001
4                                                                    */

/*Pike estimates*/
data PIKE; set _null_; run;
%pike(dataset=eff, timeto=pfsmth_IR, censor=censor_IR, cen01=0,        rstratcd=RSTRATCD, trtcd=trtcd, type=ITT IR
Stratified);
%pike US gsk(dataset=eff, timeto=pfsmth_IR, censor=censor_IR, cen01=0, rstratcd=RSTRATCD, trtcd=trtcd, type=ITT IR
Unstratified);
%pike(dataset=eff, timeto=pfsmth_IRIO, censor=censor_IRIO, cen01=0,        rstratcd=RSTRATCD, trtcd=trtcd, type=ITT IR
IO);
```

```
%pike US gsk(dataset=eff, timeto=pfsmth_IRIO, censor=censor_IRIO, cen01=0, rstratcd=RSTRATCD, trtcd=trtcd, type=ITT IR
IO Unstratified);
ods rtf file="C:\Documents and Settings\chenhu\My Documents\NDA\NDA 204114\SAS\result\PFS and OS pike ESTIMATE IN THE
ITT Population &sysdate .rtf";
proc print data=PIKE;
VAR TYPE PIKE;
title "Pike Estiamte";
run;
ods rtf close;
/*
Pike Estiamte

Obs    TYPE                            PIKE

1     ITT IR Stratified       0.44 (0.31 , 0.62 )
2     ITT IR Unstratified     0.44 (0.31 , 0.62 )
3     ITT IR IO               0.43 (0.31 , 0.61 )
4     ITT IR IO Unstratifi    0.43 (0.31 , 0.61 )  */
```

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/s/

NORMA S GRIFFIN
03/13/2013

Team Meeting 6 Summary
March 12, 2013

NDA: 204114
Product: Mekinist (trametinib)
Submission Date: August 2, 2012
Received Date: August 3, 2012
Sponsor: GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation as detected by an FDA approved test.

Participants:
Patricia Keegan, M.D., Director DOP2
Monica Hughes, CPMS, DOP2
Norma Griffin., Regulatory Health Project Manager
Suzanne Demko, Clinical TL and CDTL
Marc Theoret, M.D., Clinical Reviewer
Kun He, Ph.D., Statistics (TL)
Huanyu (Jade) Chen, Statistics
Hong Zhao, Ph.D, Clinical Pharmacology (TL)
Ruby Leong, Clinical Pharmacology
Stacy Shord, Genomics Reviewer
Whitney Helms, Nonclinical (TL)
Gabriel Sachia Khasar, Nonclinical Reviewer
Nallaperumal Chidambaram
Liang Zhou, Ph.D., Product (TL)
Sue Ching Lin, Product Quality Reviewer
Minerva Hughes, Biopharmaceutics Reviewer
Mahesh Ramanadham, OC (Facilities)
James Schlick, OSE Proprietary Name Reviewer
Donna Roscoe, CDRH Consultant
Katherine Coyle, OSE
Peter Waldron, OSE, DPVII
Tammie Brent-Howard, Maternal Health
Nathan Caulk, Patient Labeling

1. Discussion Items:

a. Review the timing of the review for this application – Sponsor recently notified FDA (during TCON of 2.26.2013) of failed room temperature stability data and their proposal to change the drug product storage temperature from room temperature to refrigerated. Sponsor will submit complete data package supporting this change by mid-April which therefore affects the previous division goal date of April 15, 2013. Action Goal Date is now according to the 10-month review clock.

Action Goal Date	**Monday, June 3, 2013**
Wrap- Up Meeting	**Friday, April 5, 2013**
Send proposed labeling/PMR/PMC/REMS to GSK	**Monday, April 15, 2013**
Discuss the Labeling/PRM/PMC with GSK	**Monday, April 22, 2013**
Primary Review Due	**Monday, April 8, 2013**
Secondary Review Due	**Monday, April 15, 2013**
CDTL Review Due	**Monday, April 22, 2013**
Division Director Review Due	**Monday, May 13, 2013**
Office Director Review Due/Sign-Off	**Monday, June 3, 2013**

b. By Primary Discipline:

Clinical: Review is on-going.

Statistics: All day STAT working session with Sponsor on 3.8.2013. There was agreement between the Sponsor and FDA regarding the codes. Clinical and STATS to discuss further and what to put in the label. Provide the final set to Sponsor during label negotiations.

Clinical Pharmacology: Review is ready but need the final clinical data.

CMC: Sponsor proposed new storage temperature (refrigerated) and will submit complete data by mid-April (15th). Major amendment (?) and will need to see how this could potentially affect the review and Final Action date.

CMC (facilities): Issues regarding uniformity testing by the Sponsor and there is concern regarding control on uniformity. Sponso [redacted] (b) (4) than that of USP <905>. FDA to request Sponsor to follow USP <905>.

Biopharmaceutics: Agreed with DMSO content variability and uniformity. Regarding the DMSO method, Sponsor agreed to tighten the specificatios.

Nonclinical: No issues

CDRH: Need results of re-analysis and clinical scenario.

Regulatory

i. Reviews uploaded in DARRTS: Method Validation Report Summary 3.2.2013; Clinical Inspection Summary 1.3.2013; CMC Micro Review 11.30.2012

ii. Need to send DMEPA container comments to Sponsor.

c. **Sponsor Email of 3.11.2013 –** Sponsor seeks clarification on the additional analytical and clinical concordance statistical analyses to be performed. GSK's and bioMerieux's understanding is that CDRH requires the analyses for the PMA to be conducted using the final clinical dataset. This will be discussed further in TCON scheduled for 3.13.2013 with Sponsor and bioMerieux.

2. **Upcoming Meetings**:
   - **Wrap- Up Meeting**: Per 10-month clock, scheduled for April 5, 2013.
   - **Labeling Meetings:** Need to finalize Sections 2, 5, 6, and 14.
   - **Scheduled to send proposed labeling/PMR/PMC/REMS to Sponsor on Monday, April 15, 2013.**

3. **Review Status**
   - Priority Review request withdrawn on September 27, 2012.

4. **Milestone Dates / Letters**

Milestone	6-month review	8.5-month review	10-month review	Comments
Application Received	**August 3, 2012**			
Acknowledgment Letter				**Issued August 15, 2012**
Filing Action Letter	**October 2, 2012 (Tuesday)**			**GSK submitted Withdrawal of Request for Priority Review – therefore this application was 'filed' as of October 2, 2012**
Deficiencies Identified Letter (74 Day Letter)	**October 16, 2012 (Tuesday)**			**Issued October 15, 2012**
PMR/PMC Working Meetings	To be scheduled (if needed)			
Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner's Target date)	Sunday, 1/6/ 2013 therefore **Friday, January 4, 2013**	**Monday March 18, 2013**	**Monday April 15, 2013**	
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	Sunday, 1/13/ 2013 therefore **Friday, January 11, 2013**	**Monday March 25, 2013**	**Monday April 22, 2013**	
Review Target Due Dates: ***Primary Review Due*** ***Secondary Review Due*** ***CDTL Review Due*** ***Division Director Review Due*** ***Office Director Review Due/Sign-Off***	 **January 4, 2013** **January 10, 2013** **January 11, 2013** **January 24,**	 **March 18, 2013** **March 22, 2013** **March 25, 2013**	 **April 8, 2013** **April 15, 2013** **April 22, 2013** **May 13, 2013**	**Monday**

Milestone	6-month review	8.5-month review	10-month review	Comments
	2013 By February 1, 2013	April 5, 2013 By April 15, 2013	**June 3, 2013**	
Compile and circulate Action Letter and Action Package	January 11, 2013	Monday March 25, 2013	**Monday April 22, 2013**	
FINAL Action Letter Due	Sunday, 2/3/ 2013 therefore **Friday, February 1, 2013**	**Monday April 15, 2013**	**Monday June 3, 2013**	

5. **Consults/Collaborative Reviewers:**

OPDP (DDMAC)	Carole Broadnax - professional reviewer Shenee (LaToya) Toombs - consumer reviewer Olga Salis – RPM Consult request sent 9.18.2012
OSE	Sue Kang-OSE RPM Sean Bradley-OSE RPM TL DRISK assigned to review Risk Management Plan Cynthia LaCivita (TL) Igor Cerny DMEPA to review Proprietary Name Todd Bridges (TL) James Schlick DMEPA/CMC/DDMAC to review carton/container, and patient labeling DPV – Bob Pratt (TL) – invite to mid-cycle and wrap up or as requested by Team DEPI – Cunlin Wang (TL) – invite to mid-cycle and wrap up or as requested by Team
Maternal Health	Tammie Brent-Howard (optional invitees: Carrie Ceresa and Melissa Tassinari)
QT-IRT	**ClinPharm requested QT-IRT consult on 8.14.2012; per ClinPharm and QT-IRT, consult not needed at this time.
OSI	Jean Mulinde
Pediatric Page/PeRC	Full Waiver Requested

Patient Labeling Team *(Patient Information Leaflet included)*	Brantley Dorch – Project Manager Nathan Caulk – Reviewer Barbara Fuller – Team Leader
SEALD	Consult requested 9.18.2012 – as needed Ann Marie Trentacosti
CDRH	Donna Roscoe; (others Reena Philip, Yun-Fu, Hu, Maria Chan, Elizabeth Mansfield, Robert Becker) Tamika Allen (BIMO Reviewer)

6. ODAC Not Needed: the application did not raise significant safety or efficacy issues.

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/s/

NORMA S GRIFFIN
04/17/2013

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.

```
%macro pike(dataset, timeto, censor, cen01, rstratcd, trtcd, type=);
        ods output censoredsummary=summary ;
        proc lifetest data=&dataset notable;
            time &timeto*&censor(&cen01);
            strata &trtcd &rstratcd;
        run;
        ods output close;

        ods output logunichisq=log;
        proc sort data =&dataset;
            by    &rstratcd;
        run;
        proc lifetest data=&dataset notable;
            time &timeto*&censor(&cen01);
            by &rstratcd;
            test &trtcd;
        run;
        ods output close;

        data est;
            set summary (rename=(failed=observe));
            keep &rstratcd trtcd observe;
        run;

        proc sort data=est; by &rstratcd; run;
        data lr;
        set log;
        keep &rstratcd statistic;
        run;
        proc sort data=lr; by &rstratcd; run;

        /* Expected */
        data oe;
        merge est lr;
        by &rstratcd;
        if trtcd=1 then do;
        expect=observe-statistic;
        end;
        else if trtcd=2 then do;
        expect=statistic+observe;
        end;
```

```
        run;

        proc sort data=oe; by trtcd; run;
        proc univariate data=oe noprint; by trtcd;
            var observe expect;
            output out=sumoe sum=sumo sume;
        run;
        data sumoe1 sumoe2;
        set sumoe;
        dum=1;
        if trtcd=1 then output sumoe1;
        if trtcd=2 then output sumoe2;
        run;

        data pike0;
            length type $20.;
            merge sumoe1 (rename=(sumo=o1 sume=e1)) sumoe2 (rename=(sumo=o2 sume=e2));
            by dum;
            drop trtcd;
            hr=COMPRESS(PUT( ((o1/e1)/(o2/e2)),4.2));
            lnhr=log(hr);
            selnhr=sqrt((1/e1) + (1/e2));
            lower=COMPRESS(PUT(exp(lnhr-1.96*(selnhr)),5.2));
            upper=COMPRESS(PUT(exp(lnhr+1.96*(selnhr)),5.2));
            type="&type";
            PIKE=HR||' ('||lower||', '||upper||')';
        run;
            DATA pike;
            length type $30.;
                  SET pike pike0;
            RUN;
%mend;
```

```
%macro pike_US(dataset, timeto, censor, cen01, rstratcd, trtcd, type=);
        ods output censoredsummary=summary ;
        proc lifetest data=&dataset notable;
        time &timeto*&censor(&cen01);
        strata &trtcd  ;
        run;
        ods output close;

        ods output logunichisq=log;
        proc lifetest data=&dataset notable;
        time &timeto*&censor(&cen01);
            strata / group = &TRT test = (logrank);
        run;
        ods output close;

        /*observed*/
        data est;
        set summary (rename=(failed=observe));
        keep  trtcd observe;
        run;

        data lr;
        set log;
        keep   statistic;
        run;


        /* Expected */
        data oe;
        merge est lr;
        if trtcd=1 then do;
        expect=observe-statistic;
        end;
        else if trtcd=2 then do;
        expect=statistic+observe;
        end;
        run;
        *** now sum observed and expected values over strata ***;
        *** see Armitage and Berry page 581 ***;
        proc sort data=oe;
        by trtcd;
        run;
        proc univariate data=oe noprint;
```

```
        by trtcd;
        var observe expect;
        output out=sumoe sum=sumo sume;
        run;
        data sumoe1 sumoe2;
        set sumoe;
        dum=1;
        if trtcd=1 then output sumoe1;
        if trtcd=2 then output sumoe2;
        run;
        data pike0;
                  length type $20.;
                merge sumoe1 (rename=(sumo=o1 sume=e1)) sumoe2
                   (rename=(sumo=o2 sume=e2));
                by dum;
                drop trtcd;
                hr=COMPRESS(PUT( ((o1/e1)/(o2/e2)),4.2));
                lnhr=log(hr);
                selnhr=sqrt((1/e1) + (1/e2));
                lower=COMPRESS(PUT(exp(lnhr-1.96*(selnhr)),5.2));
                upper=COMPRESS(PUT(exp(lnhr+1.96*(selnhr)),5.2));
                type="&type";
                PIKE=HR||' ('||lower||', '||upper||')';
        run;
            DATA pike;
            length type $30.;
                  SET pike pike0;
            RUN;
%mend;

%pike(dataset=eff, timeto=pfsmth_IR, censor=censor_IR, cen01=0, rstratcd=RSTRATCD, trtcd=trtcd, type=ITT IR EX NE);

%pike_US(dataset=eff, timeto=pfsmth_IR, censor=censor_IR, cen01=0, rstratcd=, trtcd=trtcd, type=ITT IR EX NE strata);
```

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/s/

NORMA S GRIFFIN
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 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.

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/s/

NORMA S GRIFFIN
03/05/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204114 **INFORMATION REQUEST**

GlaxoSmithKline, LLC
Attention: Dorothea E. Roberts
Manager, Global Regulatory Affairs, CMC Pre-Approval
Five Moore Drive
Research Triangle Park, NC 27709

Dear Ms. Roberts:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for "Mekinist (trametinib)."

We refer to your February 6, 2013, submission, containing updated stability information and your proposal to modify the storage condition and your request for a meeting to discuss your proposal with us.

We also refer to the February 26, 2013, teleconference between you and representatives of GlaxoSmithKline, LLC (GSK); Nallaperumal Chidambaram, Sue Ching Lin, Minerva Hughes, and Jewell Martin of the Office of New Drug Quality Assessment; and Suzanne Demko and Norma Griffin of the Division of Oncology Products 2 in which we discussed the stability information and your proposed plan to modify the drug product storage condition that was included in your submission of February 6, 2013.

You stated during the teleconference that stability failures with additional drug product lots, i.e., not those submitted to the NDA in support of your proposed expiry dating period, were observed [redacted] (b) (4) at various time points when stored at controlled room temperature. These stability failures occurred [redacted] (b) (4). Based on your verbal report of these failures and statements made during the teleconference, there is insufficient information to establish an expiry dating period for your drug product. In order to address this deficiency, you must provide the following information:

1. Provide stability data for these [redacted] (b) (4) as an amendment to the NDA no later than March 5, 2013. We request that the data be supplied in the following tabular format specifically [redacted] (b) (4), as the data presentation by GSK for such information does not facilitate ease of review. A similar format may also be used for all attributes.

(b) (4) (% of drug substance content) for drug product stored at 25°C/60%RH

Strength	Stability Study Number	Batch Number	Fill Count	Time (Months)						
				0	3	6	9	12	18	24
0.5 mg			(b) (4)							
			30 count							
1 mg			(b) (4)							
			30 count							
2 mg			(b) (4)							
			30 count							

2. Provide the complete results of stability testing performed under refrigerated conditions to support your proposal, as communicated during the February 26, 2013, teleconference to change the proposed storage conditions. The data should be provided as a complete, stand-alone report in a single amendment to the NDA; the report should contain all information necessary to support the proposed storage condition. We acknowledge your commitment, made during the teleconference, to provide this data on or before April 15, 2013.

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

Sincerely,

{See appended electronic signature page}

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

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/s/

PATRICIA KEEGAN
03/01/2013

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.

Table 1. PFS Results per IRC assessment on the ITT Population

	TYPE	TRT	NUM	MED_CI	HR_CI_S	PV1	HR_CI_US	PV2
	ITT IRC RECIST	Chemotherapy	73/ 35	2.2 (1.4, 2.8)	0.39 (0.28, 0.53)	<.0001	0.40 (0.29, 0.55)	<.0001
	ITT IRC RECIST	Trametinib	96/118	4.8 (3.4, 4.9)				

Key variables in FDA's PFS analysis: pfsmth_hc, censor_hc

```
libname der    "C:\Documents and Settings\chenhu\My Documents\NDA\NDA 204114\SAS\data\der\";
libname raw    "C:\Documents and Settings\chenhu\My Documents\NDA\NDA 204114\SAS\data\raw\";
PROC FORMAT   ;
value trt
1='Trametinib'
0='Chemotherapy'
;
value PFSTYPE
1="Event:Death"
2="Event:PD"
3="CEN:prior anti CTX and pd"
4="CEN:DISPOSTION"
5="CEN:RANDOMIZATION"
6="CEN:CEN:prior anti CTX and non pd"
7='CEN:PRIOR CUT OFF '
;
run;

/*data source*/
/**
%msasxpt(datadir=\\Cdsesub1\evsprod\NDA204114\0009\m5\datasets\mek114267\tabulations\legacy\,
outdir=C:\Documents and Settings\chenhu\My Documents\NDA\NDA 204114\SAS\data\raw\, convert=SAS);


%msasxpt(datadir=\\Cdsesub1\evsprod\NDA204114\0009\m5\datasets\mek114267\analysis\legacy\datasets\,
outdir=C:\Documents and Settings\chenhu\My Documents\NDA\NDA 204114\SAS\data\der\, convert=SAS);
%msasxpt(datadir=\\Cdsesub1\evsprod\NDA204114\0024\m5\datasets\mek114267\analysis\legacy\datasets\,
outdir=C:\Documents and Settings\chenhu\My Documents\NDA\NDA 204114\SAS\data\dernew\, convert=SAS); */
```

```
proc sort data=raw.rlesioe1 (where=(5000<visitnum and visitnum<6000 and actdt ne .)) out= IRCpostbaselesion;
by usubjid visitnum lstypcd   lsnum;
run;
/*get target, non-target lesion, and new lesion*/
data target nontarget newlesion resp;
set raw.rlesioe1(  where=( actdt<='26OCT2011'D)) ;
if lstypcd='1' then output target;                          /*2490 records target lesion*/
else if lstypcd='2' then output nontarget;                  /*2476 records target lesion*/
else if lstypcd='5' then output newlesion;                  /*191 new lesion*/
else  output resp;                                          /*non value other than 1, 2, 5*/
run;



/*****************************************************************************************************************
***/
/*New lesion: Keep the 1st date of new lesion as the PD date */
/*****************************************************************************************************************
***/
proc sort data=  newlesion out=newlesion; by usubjid ACTDT; run;
data NEWPDid (keep=usubjid );
set   newlesion(where=(NEWSTSCD="U"));
by usubjid ;
if first.usubjid;
run;
/*156 obs to 87 obs*/
data NEWPDUEQid ;
merge newlesion newpdid(in=a);
by usubjid;
if a;
run;
/*keep 168-156=12 equivocal records*/
proc sort data=NEWPDUEQid out=newpd0; by usubjid actdt; run;
data NEWPD (keep=usubjid NEWPD actdt  RENAME=(actdt=NEWPD_date));
set   newpd0;
by usubjid ACTDT;
NEWPD=1;
if first.usubjid;
run;

/*****************************************************************************************************************
***/
```

```
/*target lesions: GET SUM OF LAREST TUMOR DIAMETER PER VISIT SHOULD KEEP LESS OR EQUAL 5 ORGANS
     */
/*****************************************************************************************************
***/
proc sort data=  target out=target; by usubjid visitnum LSORGCD lstypcd LSDIA; run;

data targetsum (KEEP=USUBJID visitnum SUMLSDIA);
set target;
by    usubjid VISITNUM ;
retain  SUMLSDIA;
IF FIRST.visitnum THEN  SUMLSDIA=0;
SUMLSDIA=SUMLSDIA+LSDIA;
IF LAST.visitnum  ;
run;

proc transpose data= targetsum out=rtarget(drop=_NAME_); by USUBJID; ID VISITNUM; var SUMLSDIA;run;

%macro pdfor(cur=, prevmin=  );
if &cur NE 0 & (&cur-&prevmin)/&cur*100>=20 & (&cur-&prevmin)>5 then do;
PD&cur=1;
PDVST= "&cur" ;
ABSCHG = &cur-&prevmin;
RELCHG = (&cur-&prevmin)/&cur*100;
end;
%mend;

/*GET MIN TUMOR LARGEST DIAMETER and at each sch or unsch visit calculate rr increase of 20% & abs increase of 5*/
data  TARGET0 TARGET6 TARGET12 TARGET21  TARGET30 ;
set rtarget;
nadir010= 10D00;
nadir011=min (nadir010, _5000D01, _5000D03,_5000D04, _5000D05 );
%pdfor(cur= 5000D01, prevmin= 10D00);
%pdfor(cur=_5000D03, prevmin=_10D00);
%pdfor(cur= 5000D04, prevmin= 10D00);
%pdfor(cur= 5000D05, prevmin= 10D00);
PD0=max(PD 5000D01, PD_5000D03,PD_5000D04, PD_5000D04);
PD0VNUM= PDVST;
IF   PD0 =1 THEN OUTPUT TARGET0  ;

nadir060=min (nadir011,  5006D00);
%pdfor(cur=_5006D00, prevmin=nadir011);
```

```
nadir061=min (nadir060, 5006D01,  5006D02,_5006D03, _5006D04, _5006D05);
%pdfor(cur=_5006D01, prevmin=nadir060);
%pdfor(cur=_5006D02, prevmin=nadir060);
%pdfor(cur= 5006D03, prevmin=nadir060);
%pdfor(cur=_5006D04, prevmin=nadir060);
%pdfor(cur= 5006D05, prevmin=nadir060);
PD6=max(PD 5006D00, PD_5006D01,PD_5006D02, PD_5006D02, PD_5006D04, PD_5006D05);
PD6VNUM= PDVST;
IF   PD0 NE 1 & PD6 =1 THEN OUTPUT TARGET6  ;
/*ALL ACCURED ON SCHEDULED VISIT 6*/

nadir120=min(nadir061, 5012D00);
%pdfor(cur= 5012D00, prevmin=nadir061);
nadir121=min(nadir120,_5012D01, _5012D02, _5012D03, _5012D04, _5012D06,
_5012D07, _5012D08 );
%pdfor(cur= 5012D01, prevmin=nadir120);
%pdfor(cur= 5012D02, prevmin=nadir120);
%pdfor(cur=_5012D03, prevmin=nadir120);
%pdfor(cur= 5012D04, prevmin=nadir120);
%pdfor(cur=_5012D06, prevmin=nadir120);
%pdfor(cur= 5012D07, prevmin=nadir120);
%pdfor(cur=_5012D08, prevmin=nadir120);
PD12=max(PD 5012D00,PD 5012D01, PD_5012D02, PD_5012D03, PD_5012D04, PD_5012D06,
PD 5012D07, PD 5012D08);
PD12VNUM= PDVST;
IF   PD0 NE 1 & PD6 NE 1 & PD12 =1 THEN OUTPUT TARGET12  ;
/*ALL ACCURED ON SCHEDULED VISIT 12 EXCEPT MEK114267.0402584 AT WEEK 12 DAY 7*/

nadir210=min (nadir121,  5021D00);
%pdfor(cur= 5021D00, prevmin=nadir121);
nadir211=min (nadir210,  5021D01,  5021D04, _5021D05, _5021D06, _5021D07);
%pdfor(cur= 5021D01, prevmin=nadir210);
%pdfor(cur=_5021D04, prevmin=nadir210);
%pdfor(cur= 5021D05, prevmin=nadir210);
%pdfor(cur=_5021D06, prevmin=nadir210);
%pdfor(cur= 5021D07, prevmin=nadir210);
PD21=max(PD 5021D00, PD_5021D01, PD_5021D04, PD_5021D05, PD_5021D06, PD_5021D07);
PD21VNUM= PDVST;
IF   PD0 NE 1 & PD6 NE 1 & PD12 NE 1 & PD21 =1 THEN OUTPUT TARGET21  ;
```

```
nadir300=min(nadir211,  5030D00);
%pdfor(cur=_5030D00, prevmin=nadir211);
nadir301=min(nadir300, _5030D05);
%pdfor(cur=_5030D05, prevmin=nadir300);
PD30=max(PD_5030D00, PD_5030D05);
PD30VNUM= PDVST;
IF   PD0 NE 1 & PD6 NE 1 & PD12 NE 1 & PD21 NE 1  & PD30 =1 THEN OUTPUT TARGET30  ;

run;
*330 00001, 345 00023, 345 00024 had nadir as 0 and no more assessment thereafter;
*349 00002 had one assessment 0 and appear again later;
DATA TARGETTEMP;
SET _NULL_;
RUN;
%MACRO TARGETTEMP(NUM=);
DATA TARGETTEMP (KEEP=USUBJID PDVIST ABSCHG RELCHG );
SET TARGET&NUM (KEEP=USUBJID PD&NUM.VNUM ABSCHG RELCHG RENAME=(PD&NUM.VNUM=PDVIST)) TARGETTEMP;
RUN;
%MEND;

%TARGETTEMP(NUM=0) ;                    /*OBS=1*/
%TARGETTEMP(NUM=6) ;                    /*OBS=24*/
%TARGETTEMP(NUM=12) ;                   /*OBS=23*/
%TARGETTEMP(NUM=21) ;                   /*OBS=16*/
%TARGETTEMP(NUM=30) ;                   /*OBS=5*/
/*transfer 50XXDXX to 50XX.XX */
DATA TARGETTEMP1(keep=usubjid  TGTPDVISIT);
SET   TARGETTEMP;
TGTPDVISIT=put(substr(PDVIST, 2, (INDEX(upcase(PDVIST),upcase('d') ) )-2) ||"."||substr(PDVIST, LENGTH(PDVIST)-1), 7.2);
RUN;
* proc contents data=    TARGETTEMP1; run;
proc sort data=TARGETTEMP1 out=TARGETTEMP2(keep=usubjid TGTPDVISIT); by usubjid TGTPDVISIT; run;
PROC SORT NODUPKEY DATA=TARGET OUT=TARGET1(KEEP=USUBJID VISITNUM ACTDT); BY     USUBJID VISITNUM;
  RUN;
     */

*proc contents data=    target1; run;
data targetpd (KEEP=USUBJID TGTPD actdt RENAME=(actdt=TGTPD_date)) ;
MERGE target1  TARGETTEMP2(in=a);
by usubjid;
if   a;
```

```
IF abs(tgtpdvisit-visitnum)<1e-5 then tgtpd=1;
IF tgtpd=1;
RUN;


/*****************************************************************************************************************
***/
/*Non-TARGET lesion: GET SUM OF LAREST TUMOR DIAMETER PER VISIT SHOULD KEEP LESS OR EQUAL 5 ORGANS
        */
/*****************************************************************************************************************
***/
proc sort data=  nontarget out=nontarget; by usubjid visitnum LSNUM LSORGCD actdt; run;
***nontarget part with Unequivocal progression;
data nontargetpdUPD (keep=usubjid nontgtpd actdt RENAME=(actdt=nontgpd_date));
set nontarget(where=(LSSTSCD="UPD"));
by usubjid ;
if first.usubjid;
nontgtpd=1      ;
run;

data  nontarget1(keep=usubjid visitnum LSNUM LSORGCD  actdt);
set  nontarget;
by   usubjid visitnum LSNUM LSORGCD  actdt;
if first.LSNUM;
run;

/*get sum of lesion organ per patients*/
data nntgtlesion(keep=usubjid visitnum numnontgt);
set      nontarget1;
by  usubjid visitnum;
retain numnontgt;
if first.visitnum then numnontgt=0;
numnontgt+1;
if last.visitnum;
run;

proc transpose data= nntgtlesion out=TRAnntgtlesion(drop=_NAME_); by usubjid; var numnontgt;run;


data TRAnntgtlesion1;
set TRAnntgtlesion;
```

```
array x[6] col2-col7;
do i=1 to 6;
if x[i]-col1>0 then output;
end;
run;
/*OBS=0*/
/*there is no new lesion in the non-target lesion */


/*****************************************************************************************************************
***/
/*Combine all the PD together
   */
/*****************************************************************************************************************
***/
proc sort data=der.demobase(keep=usubjid trtgrp) out=trtgrp; by usubjid; run;
data pdtemp;
merge  nontargetpdUPD(in=a)   targetpd(in=b) NEWPD(in=c) trtgrp;
BY USUBJID;
if a or b or c;
format FDApd date  date9. FDAPDTYPE $20.;
label nontgpd date="Non target PD Date"
NEWPD date="New Lesion Date";
FDAPD DATE =min(nontgpd date, NEWPD date, TGTPD date );
if   FDAPD_DATE  =NEWPD_date then   FDAPDTYPE ="PD:New Lesion";
else if FDAPD DATE =TGTPD date then FDAPDTYPE ="PD: Target Lesion";
else if  FDAPD DATE =nontgpd date then   FDAPDTYPE ="PD: Non-Target Lesion";
/*there exist some type of FDA PD had the same date, I take the order of new pd, target lesion and non-target lesion*/
FDAPD =1;
RUN;


/*****************************************************************************************************************
***/
/*****************************************************************************************************************
***/
/* Evaluate IRC PFS definition
        */
/*****************************************************************************************************************
***/
/*****************************************************************************************************************
```

```
***/
/*get randomization date*/
proc sort data=raw.rrand out=_rand (keep=usubjid   randdt); by usubjid;   run;


/*Get Disposition date*/
/*-----------------------------------------------------------------------------*/
proc sort data= der.ds (where=(dsstdt^=. & dsstdt<='26OCT2011'D & pernum=1))
out= disp (keep=usubjid  dsstdt TRTGRP);
by usubjid; run;

/*get date of death*/
proc sort data=DER.DEATH(  where=( dthdt<='26OCT2011'D &  pernum=1))  Out= _death (keep=usubjid TRTGRP dthdt dthcscd);
by Usubjid; run;


/*get IRC ORR results in the random phase*/
data _ircorr;
set   der.resp2ex1;
where pernum=1  & BRSPDFCD= "1" &   progdt <='26OCT2011'D;      /*exclude cross-over period and un-confirmed Best
response*/
keep   usubjid TRTGRP ontypecd brspcd BRSP progdt rspfbrdt;
run;
proc sort data=_ircorr out=ircorr; by usubjid  progdt   rspfbrdt; run;
/*Post-treatment Anti-Cancer therapy start date*/
proc sort data=der.resp2 out=resp2; by usubjid; run;
/*only resp2 has new anti cencer therapy information*/
data _newctxdt(keep=usubjid trtgrp newctxdt newcdtfl);
set  resp2  (where=( pernum=1 & BRSPDFCD= "1" & newctxdt<='26OCT2011'D) );
by usubjid;
format  newctxdt date9.;
if newctxdt ne .;
run;


data _pddth (KEEP=USUBJID PDDTH_DT_GSK DTHDT PROGDT PFSTYPE_GSK );
merge  death (IN=A) ircorr (where=( progdt ne .) IN=B) _RAND;
by USUBJID;
format  PDDTH_DT_GSK date9.;
IF A OR B;
PDDTH_DT_GSK=MIN(progdt, dthdt);
```

```
IF   PDDTH DT GSK=DTHDT THEN PFSTYPE_GSK=1;
ELSE PFSTYPE_GSK=2;
RUN;

data  pddth HC  (KEEP=USUBJID PDDTH DT hc DTHDT FDAPD DATE PFSTYPE hc );
merge  death (IN=A) pdtemp (where=( FDAPD_DATE<='26OCT2011'D) keep=usubjid trtgrp FDAPD_DATE IN=B) _RAND;
by USUBJID;
format  PDDTH_DT_HC date9.;
IF A OR B;
PDDTH DT HC=MIN(FDAPD DATE, DTHDT);
IF   PDDTH DT HC=DTHDT THEN PFSTYPE_HC=1;
ELSE PFSTYPE_HC=2;
RUN;


/*Count for two continuous missing tumor assessment*/
/* DUE TO DIFFERENT TUMOR ASSESSMENT SCHEDULE, FIRST 2 PER 6 WEEKS (91 days ) AND THEN PER 9 WEEKS*/
DATA ASSESSDT;
SET RAW.RLESIOE1(KEEP=USUBJID ACTDT where=(ACTDT<='26OCT2011'D ));
RUN;

PROC SORT NODUPKEY DATA=   ASSESSDT OUT=ASSESSDT1; BY USUBJID ACTDT; RUN;
PROC SORT NODUPKEY DATA=   ASSESSDT1(KEEP=USUBJID) OUT=NONASSESS; BY USUBJID; RUN;

proc sort data=assessdt out=assessdt; by usubjid actdt; run;
PROC TRANSPOSE DATA=ASSESSDT OUT=TASSESSDT(DROP=_NAME_ _LABEL_); BY USUBJID; VAR ACTDT; RUN;
DATA ASSESSDIFF;
SET   TASSESSDT;
array x[6] col2-col7;
array Y[6] col1-col6;
ARRAY DIFF[6] DIFF1-DIFF6;
do i=1 to 6;
DIFF[I]=x[i]-Y[I];
END;
MAX DIFF=MAX(DIFF1, DIFF2, DIFF3, DIFF4, DIFF5,DIFF6);
MIN ASS=MIN(DIFF1, DIFF2, DIFF3, DIFF4, DIFF5,DIFF6);
DROP I;
KEEP USUBJID  DIFF: MAX_DIFF MIN_ASS;
RUN;
PROC MEANS DATA=  ASSESSDIFF; VAR MAX_DIFF; RUN;     /*max gap=92 days*/
/***********************************************/
```

```
/*************************************************/
/*************************************************/
/*NONE HAS 2 COUNTINOUS MISSING TUMOR ASSESSMENT*/
/*************************************************/
/*************************************************/
/*************************************************/

PROC FREQ DATA=DERNEW.ONCTTERN; TABLE extendfl; RUN;
/*THE DERIVED DATA CONFIRMED THAT NONE WAS CENSORED DUE TO 2 CONTINOUS MISSING RULES*/

/*get last non pd assessment before anti-cancer therapy or 2 continuous missing*/
/*Mine does not have 2 continuous missing*/

/*GET ALL THE TUMOR ASSESSMENT DATE PRIOR NEW ANTI-CACNER THERAPY*/
data _ASSPRIANTICTX (KEEP=USUBJID TRTGRP randdt  NEWCTXDT dsstdt PRICTXASSDT );
merge    RAND (in=ITT)   TASSESSDT _NEWCTXDT(in=a)   _disp(in=b)  ;
by usubjid;
format  prictxASSDT date9.;
array Y[10] RANDDT col1-col9;
ARRAY X[10]   prictxASS1-prictxASS10;
/*prior anti cancer therapy*/
if itt;
IF A then do;
*from 2nd avaiable tumor assessment compare anti cancer therapy date to ass date;
*if anti ctx > ass then assign prior assess date, otherwise keep current tumor ass;
/*1st visit comparison will assign randdt*/
do i=1 to 10;
 if newctxdt> y[i]  then X[I]=y[i];
END;
prictxASSDT =MAX(prictxASS1, prictxASS2, prictxASS3, prictxASS4, prictxASS5, prictxASS6,
            prictxASS7, prictxASS8, prictxASS9, prictxASS10);

end;

else if b  & DSSTDT>randdt  then do;
do i=1 to 10;
if DSSTDT> y[i]  then X[I]=y[i];                          /*one patient disp before randomization*/
END;
prictxASSDT =MAX(prictxASS1, prictxASS2, prictxASS3, prictxASS4, prictxASS5, prictxASS6,
    prictxASS7, prictxASS8, prictxASS9, prictxASS10);
end;
/*Patient without anti-cancer therapy, get the last tumor assessment OR DATE OF RANDOMIZATION*/
```

```
else    prictxASSDT =MAX(RANDDT, col1, col2, col3, col4, col5, col6, col7, col8, col9);

run;

/*mERGE ALL THE DATE TOGETHER TO DECIDE CENSORING RULES*/
DATA PFSDT;
MERGE   RAND(in=a)  pddth(IN=B)      pddth hc(IN=B1)
 DISP(in=c) NONASSESS(IN=d)    _ASSPRIANTICTX (IN=G)   ;
BY USUBJID;
format pfs_date_GSK date9. pfs_date_hc date9. ;
if a; /*keep itt population*/

/*FOR PFS EVENTS, FLAG OUT 2 COUNTIOUS MISSING (none) AND NEW ANTI CACNER THERAPY*/
IF B THEN DO;
PFS_DATE_GSK=PDDTH_DT_GSK;
CENSOR GSK=1;              /*GSK pfs EVENT*/
PFSTYPE_GSK= PFSTYPE_GSK;

/*Although PFS event still need to be censored to non pd prior anti cancer therapy*/
IF  newctxdt ne . and newctxdt<= PDDTH_DT_GSK THEN DO;
PFS DATE GSK=prictxASSDT;
CENSOR GSK=0;
PFSTYPE_GSK =3; /*pfsTYPE 1 DEATH 2 pd 3 CENSORED AT NON PD PRIOR NEW ANTI CANCER THERAPY*/
END;
END;
/*for those without radio assessment censored at randomization date*/
ELSE IF NOT D THEN DO;
PFS DATE GSK=RANDDT;
CENSOR GSK=0;
PFSTYPE_GSK=5;
END;  /*CENSORED AT randoimization DATE*/
/*1 patient got PD event at randomization date and was count as PFS event*/

ELSE IF c & dsstdt>=randdt  THEN DO;
PFS DATE GSK=DSSTDT;
CENSOR GSK=0;
PFSTYPE_GSK=4;  /*CENSORED AT disposition*/
END;

/*CENSORED TO NON PD PRIOR ANTI CTX*/
ELSE IF newctxdt ne . THEN DO;
PFS_DATE_GSK=prictxASSDT;
```

```
CENSOR GSK=0;
PFSTYPE_GSK =6; /*pfsTYPE 1 DEATH 2 pd 3 CENSORED AT NON PD PRIOR NEW ANTI CANCER THERAPY*/
END;
/*censored at disposition*/
/*else censored at cut off date*/
ELSE  do;
PFS DATE GSK=prictxASSDT;
CENSOR GSK=0;
PFSTYPE_GSK=7;  /*CENSORED AT last tumor assessment prior study cut off*/
END;


/*************************************/
/*HC calcuated PD related PFS events*/
/*************************************/
IF B1 THEN DO;
PFS DATE HC=PDDTH DT HC;
CENSOR_HC=1;               /*REAL pfs EVENT*/
PFSTYPE_HC=PFSTYPE_HC;


/*Although PFS event still need to be censored to non pd prior anti cancer therapy*/
IF  newctxdt ne . and newctxdt<= PDDTH_DT_HC THEN DO;
PFS DATE HC=prictxASSDT;
CENSOR_HC=0;
PFSTYPE_HC =3; /*pfsTYPE 1 DEATH 2 pd 3 CENSORED AT NON PD PRIOR NEW ANTI CANCER THERAPY*/
END;
END;
/*for those without radio assessment censored at randomization date*/
ELSE IF NOT D THEN DO;
PFS DATE HC=RANDDT;
CENSOR_HC=0;
PFSTYPE HC=5;
END;  /*CENSORED AT randoimization DATE*/
/*1 patient got PD event at randomization date and was count as PFS event*/

/*censored at disposition*/
ELSE IF C & dsstdt>randdt THEN DO;
PFS DATE HC=DSSTDT;
CENSOR HC=0;
PFSTYPE_HC=4;  /*CENSORED AT disposition*/
END;
```

```
/*CENSORED TO NON PD PRIOR ANTI CTX*/
ELSE IF newctxdt ne . THEN DO;
PFS DATE HC=prictxASSDT;
CENSOR HC=0;
PFSTYPE_HC =6; /*pfsTYPE 1 DEATH 2 pd 3 CENSORED AT NON PD PRIOR NEW ANTI CANCER THERAPY*/
END;

ELSE  do;
PFS DATE HC=prictxASSDT;
CENSOR_HC=0;
PFSTYPE_HC=7;  /*CENSORED AT last tumor assessment prior study cut off*/
END;

PFSday_GSK= PFS_DATE_GSK-randdt+1;
PFSday HC= PFS DATE HC-randdt+1;
PFSMTH_GSK= (PFS_DATE_GSK-randdt+1)/30.4375;
PFSMTH_HC= (PFS_DATE_HC-randdt+1)/30.4375;

run;


proc sort data=der.oncttern out=oncttern; by usubjid; run;
*     proc contents data=dernew.oncttern; run;
proc sort data=der.demobase out=demobase; by usubjid; run;
*proc contents data=dernew.demobase; run;
proc sort nodupkey  data=der.trt out=ivrsstrata(keep=usubjid stratum); by usubjid; run;


data eff  ;
merge oncttern (in=a) demobase (DROP= sexcd racecd pathsccd chdpotcd )
ivrsstrata(rename=(STRATUM=stratIVRS))pfsdt ;
by usubjid;
if a;
if trtcd=2 then trt=0;else trt=1;
Label trt="Treatment";
format trt trt.;
run;

proc phreg data =  eff ;
model pfsmth_hc* censor_hc(0) = trt / risklimits ties=Efron;
```

```
strata RSTRATCD;
run;

proc lifetest data =eff;
time pfsmth hc * censor_hc(0);
strata TRT ;
run;
```

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/s/

NORMA S GRIFFIN
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 21, 2013

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

Subject: NDA 204114; GlaxoSmithKline, LLC
Proposed PMR Language

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

Dear Mr. Richards:

Please see FDA's post-marketing requirement proposals for the Mekinist (trametinib) NDA application 204114.

We have determined that only clinical trials (rather than a nonclinical or observational study) will be sufficient to assess a signal of the potential serious risks of QT/QTc interval prolongation related with the use of trametinib, and to determine the appropriate doses of trametinib in patients with hepatic impairment. We refer to your response submitted on October 26, 2012 with regard to the proposed milestone dates for the following studies to be conducted as postmarketing requirements.

Post Marketing Requirements (PMRs) Under 505(o)

CLINICAL PHARMACOLOGY

QT/QTc Interval Prolongation (b) (4)

1. Complete a clinical trial to evaluate the potential for trametinib to prolong the QT/QTc interval in an adequate number of patients administered repeat doses of trametinib in accordance with the principles of the FDA Guidance for Industry entitled "*E14 Clinical Evaluation of QT/QTc Interval Prolongation*" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073153.pdf. Submit the final report that includes central tendency, categorical and concentration-QT analyses, along with a thorough review of cardiac safety data.

   Final Protocol Submission: Submitted
   Trial Completion: August 2014
   Final Report Submission: April 2015

Hepatic Impairment (b) (4)

2. Conduct a pharmacokinetic trial to determine the appropriate dose of trametinib in patients with hepatic impairment in accordance with the FDA Guidance for Industry entitled "*Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf.

Final Protocol Submission: (b) (4)
Trial Completion: (b) (4)
Final Report Submission: December 2015

The FDA and Applicant must reach an agreement on the study protocol that meets the goals of the postmarketing requirement. The Division recommends that the Applicant submit the protocol at least one month prior to the final protocol submission milestone to allow adequate time for FDA review and any protocol revisions to be completed by the final protocol submission date. If the protocol is submitted on the milestone due date and upon FDA review the protocol is found to be deficient in meeting the goals of the postmarketing requirement, FDA will consider the postmarketing requirement delayed. The Applicant will then be required to provide formal justification for the delay in meeting the postmarketing requirement milestone.

We are requesting that you respond to our proposal by March 1, 2013.

To assist you in organizing the submission of final study reports, we refer you to the following resources:

- Guidance for Industry entitled, *Structure and Content of Clinical Reports* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073113.pdf
- Guidance for Industry, entitled, *Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072974.pdf
- Guidance for Industry, entitled, *Reports on the Status of Postmarketing Study Commitments – Implementation of Section 130 of the Food and Drug Administration Modernization of 1997* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080569.pdf.
- Guidance for Industry, entitled, *Postmarketing Studies and Clinical Trials — Implementation of Section 505(o) of the Food, Drug, and Cosmetic Act* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM172001.pdf >

Please note for any multi-study PMC/PMR, results from each study are to be submitted as an individual clinical study report (CSR) to the NDA or BLA as soon as possible after study completion. The cover letter for these individual CSRs should identify the submission as **PMC/PMR CORRESPONDENCE – PARTIAL RESPONSE** in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the approval letter, as well as the date of the approval letter.

The PMC/PMR final study report (FSR) submission intended to fulfill the PMC/PMR should include submission of the last remaining CSR and all previously submitted individual CSRs. The FSR should also contain an integrated analysis and thoughtful discussion across all studies regarding how these data support the fulfillment of the PMC/PMR. The cover letter should state the contents of the submission.

Furthermore, if a PMC/PMR requests, as a milestone, the submission of individual study reports as interim components of a multi-study PMC/PMR, the cover letter should identify the submission as **PMC/PMR CORRESPONDENCE – INTERIM STUDY REPORT** in bold, capital letters at the top of the letter and should identify the commitment being addressed by referring to the commitment wording and number, if any, used in the final action letter, as well as the date of the final action letter.

Please let me know if you have any questions.

Regards,

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

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/s/

NORMA S GRIFFIN
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 reivew 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)

Frequency Percent Row Pct Col Pct	Complete respons e	Non-CR/N on-PD	Not appl icable	Not eval uable	Partial response	Progress ive dise ase	Stable d isease	Total
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.

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/s/

NORMA S GRIFFIN
02/21/2013

Team Meeting 5 Summary
February 12, 2013

NDA: 204114

Product:	Mekinist (trametinib)
Submission Date:	August 2, 2012
Received Date:	August 3, 2012
Sponsor:	GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation as detected by an FDA approved test.

Participants:
Patricia Keegan, M.D., Director DOP2
Norma Griffin., Regulatory Health Project Manager
Suzanne Demko, Clinical TL and CDTL
Marc Theoret, M.D., Clinical Reviewer
Huanyu (Jade) Chen, Statistics
Hong Zhao, Ph.D, Clinical Pharmacology (TL)
Ruby Leong, Clinical Pharmacology
Rosane Charlab-Orbach, Acting Genomics TL
Stacy Shord, Genomics Reviewer
Whitney Helms, Nonclinical (TL)
Gabriel Sachia Khasar, Nonclinical Reviewer
Nallaperumal Chidambaram
Liang Zhou, Ph.D., Product (TL)
Sue Ching Lin, Product Quality Reviewer
Zhe Jean Tang, Product Quality Reviewer
Minerva Hughes, Biopharmaceutics Reviewer
Mahesh Ramanadham, OC (Facilities)
Jean Mulinde, OSI Reviewer
Sue Kang, OSE, Safety RPM
Katherine Coyle, OSE
Tammie Brent-Howard, Maternal Health

1. Discussion Items:

a. Review the timing of the review for this application - see snapshot of upcoming dates:

Division Action Goal Date	Monday, April 15, 2013
Wrap- Up Meeting	March 18, 2013
Send proposed labeling/PMR/PMC/REMS to GSK	Monday, March 18, 2013
Discuss the Labeling/PRM/PMC with GSK	Monday, March 25, 2013

Primary Review Due	Monday, March 18, 2013
Secondary Review Due	Friday, March 22, 2013
CDTL Review Due	Monday, March 25, 2013
Division Director Review Due	Friday, April 5, 2013
Office Director Review Due/Sign-Off	Monday, April 15, 2013

b. By Primary Discipline:

Clinical: No updates; comments (IR) to go out later this week. Clinical to provide suggested date for last labeling meeting.

Statistics: Discrepancies on PD dates; the criteria for PD date is wrong, based on STATS own algorithm. IR to sponsor or may need TCON for clarification.

Clinical Pharmacology: Finalizing the PMR/PMC and will provide to Deputy Safety Director for review and concurrence. ClinPharm will have revisions for labeling ready.

i. Genomics: No updates; will meet the deadlines.

CMC: couple of issues: 1) need to finalize the decision regarding shelf life stability; 2) Issue regarding [redacted] (b) (4) which is an inspection issue. CMC in discussion with Compliance.

CMC (facilities): Regarding the [redacted] (b) (4) issue – need to review the inspection report before making final decision. Plan to send IR letter to Sponsor and request 2-week turn around for response.

Biopharmaceutics: Discussion regarding the [redacted] (b) (4) limit and how low will FDA allow the limit to go. Therefore, need a decision made regarding change in the shelf-life specification.

Nonclinical: Review on-going and no issues.

Regulatory:

- Reviews uploaded in DARRTS include: Clinical Inspection Summary and CMC Micro Review
- Will not request SGE.
- Follow up on Ophthalmology Consult Request for completion date and send eye toxicities and label.
- Send DMEPA's Container labeling comments to Sponsor.
- Work with CMC to schedule TCON with Sponsor regarding shelf-life stability.

2. Upcoming Meetings:
   - **Wrap- Up Meeting**: Per 8.5-month clock, scheduled for March 18, 2013.
   - **Labeling Meetings:** Additional Labeling Meeting needs to be scheduled with Clinical input regarding timing (suggested date) – need to complete Clinical sections.
   - Scheduled to send proposed labeling/PMR/PMC/REMS to GSK by Monday, March 18, 2013.

3. Review Status
   - Priority Review request withdrawn on September 27, 2012.

4. Milestone Dates / Letters

Milestone	6-month review	Target Completion Date 4.15.2013	Comments
Application Received	**August 3, 2012**		
Acknowledgment Letter			**Issued August 15, 2012**
Filing Action Letter	**October 2, 2012 (Tuesday)**		**GSK submitted Withdrawal of Request for Priority Review – therefore this application was 'filed' as of October 2, 2012**
Deficiencies Identified Letter (74 Day Letter)	**October 16, 2012 (Tuesday)**		**Issued October 15, 2012**
Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner's Target date)	Sunday, 1/6/ 2013 therefore **Friday, January 4, 2013**	**Monday March 18, 2013**	
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	Sunday, 1/13/ 2013 therefore **Friday, January 11, 2013**	**Monday March 25, 2013**	
Review Target Due Dates: ***Primary Review Due*** ***Secondary Review Due*** ***CDTL Review Due*** ***Division Director Review Due*** ***Office Director Review Due/Sign-Off***	 **January 4, 2013** **January 10, 2013** **January 11, 2013** **January 24, 2013** **By February 1, 2013**	 **March 18, 2013** **March 22, 2013** **March 25, 2013** **April 5, 2013** **By April 15, 2013**	**Monday, March 18, 2013** **Friday, March 22, 2013** **Monday, March 25, 2013** **Friday, April 5, 2013** **Monday, April 15, 2013**
Compile and circulate Action Letter and Action Package	**January 11, 2013**	**Monday March 25, 2013**	
FINAL Action Letter Due	Sunday, 2/3/ 2013 therefore **Friday, February 1, 2013**	**Monday April 15, 2013**	

5. **Consults/Collaborative Reviewers:**

OPDP (DDMAC)	Carole Broadnax - professional reviewer Shenee (LaToya) Toombs - consumer reviewer Olga Salis – RPM Consult request sent 9.18.2012
OSE	Sue Kang-OSE RPM Sean Bradley-OSE RPM TL DRISK assigned to review Risk Management Plan Cynthia LaCivita (TL) Igor Cerny DMEPA to review Proprietary Name Todd Bridges (TL) James Schlick DMEPA/CMC/DDMAC to review carton/container, and patient labeling DPV – Bob Pratt (TL) – invite to mid-cycle and wrap up or as requested by Team DEPI – Cunlin Wang (TL) – invite to mid-cycle and wrap up or as requested by Team
Maternal Health	Tammie Brent-Howard (optional invitees: Carrie Ceresa and Melissa Tassinari)
QT-IRT	**ClinPharm requested QT-IRT consult on 8.14.2012; per ClinPharm and QT-IRT, consult not needed at this time.
OSI	Jean Mulinde
Pediatric Page/PeRC	Full Waiver Requested
Patient Labeling Team *(Patient Information Leaflet included)*	Brantley Dorch – Project Manager Nathan Caulk – Reviewer Barbara Fuller – Team Leader
SEALD	Consult requested 9.18.2012 – as needed Ann Marie Trentacosti
CDRH	Donna Roscoe; (others Reena Philip, Yun-Fu, Hu, Maria Chan, Elizabeth Mansfield, Robert Becker) Tamika Allen (BIMO Reviewer)

6. ODAC Not Needed: the application did not raise significant safety or efficacy issues

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/s/

NORMA S GRIFFIN
04/17/2013

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	PFSCTY5	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.

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/s/

NORMA S GRIFFIN
02/12/2013

Labeling Meeting #6 Summary
January 18, 2013

NDA: 204114

Product:	Mekinist (trametinib)
Submission Date:	August 2, 2012
Received Date:	August 3, 2012
Sponsor:	GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation as detected by an FDA approved test.

Meeting Participants:
Patricia Keegan, M.D., Director DOP2
Norma Griffin., Regulatory Health Project Manager
Suzanne Demko, Clinical TL and CDTL
Marc Theoret, Clinical Reviewer
Whitney Helms, Nonclinical (TL)
Sachia Khasar, Nonclinical Reviewer
Rosane Charlab-Orbach, Genomics Reviewer
Donna Roscoe, CDRH
Nathan Caulk, Patient Labeling
Carole Broadnax, OPDP
James Schlick, DMEPA
Tammie Brent-Howard, Maternal Health

1. **Labeling Sections Reviewed:** Dosage and Administration (section 2.1 and 2.2 – (b) (4) and Warnings and Precautions (5.1, 5.2, 5.3, 5.4) as needed to finalize labeling.

2. **Next Meeting:** To be determined by Clinical as data is reviewed.

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/s/

NORMA S GRIFFIN
04/17/2013

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

Memorandum

Date: December 21, 2012

From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 204114; GlaxoSmithKline, LLC
Clinical Pharmacology Comments and Information Request

GlaxoSmithKline, LLC
Eric Richards
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 Clinical Pharmacology Reviewer has the following comments and request for information.

> Please provide the relevant mRNA expression data (e.g., calculated R value, E_{max} and EC_{50} values normalized to the vehicle control) from *in vitro* studies to assess whether trametinib is an inducer of cytochrome P450 enzymes, and to determine the need to conduct pharmacokinetic drug interaction trial(s). Refer to the FDA draft Guidance for Industry entitled "*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*" found at
>
> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf.
>
> We acknowledge that E_{max} and EC_{50} values normalized to positive controls were submitted.

Please provide your response by January 3, 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.

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/s/

NORMA S GRIFFIN
12/21/2012

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

Memorandum

Date: December 19, 2012

From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 204114; GlaxoSmithKline, LLC
Biopharmaceutics Comments and Advice/Information Request

GlaxoSmithKline, LLC
Dorothea Roberts
Eric Richards
1250 South Collegeville Road
Collegeville, PA, 19426

Dear Dr. Roberts:

As discussed during the December 19, 2012, teleconference, your proposal to maintain a DMSO content lower limit of (b) (4) in response to FDA Question #3 in the November 21, 2012, information request letter is not acceptable. (b) (4) as we have communicated previously, dissolution data alone are not sufficient to support these changes. We acknowledge your plans to conduct a bioequivalence study to address the effects of DMSO content on bioavailability. In the interim, we recommend a lower limit of not less than 10.4%, which aligns with the available clinical batch data. Provide a revised drug product specification table in line with the recommendation.

In addition, we acknowledge your proposal to change the dissolution acceptance criterion from Q= (b) (4) to Q= (b) (4) at 20 minutes. Include these changes in your updated specification as well.

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.

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/s/

NORMA S GRIFFIN
12/19/2012

Team Meeting 4 Summary
December 18, 2012

NDA: 204114
Product: Mekinist (trametinib)
Submission Date: August 2, 2012
Received Date: August 3, 2012
Sponsor: GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation as detected by an FDA approved test.

Participants:
Norma Griffin., Regulatory Health Project Manager
Suzanne Demko, Clinical TL and CDTL
Jeffrey Summers, M.D., Deputy Director for Safety, DOP2
Marc Theoret, M.D., Clinical Reviewer
Huanyu (Jade) Chen, Statistics
Hong Zhao, Ph.D, Clinical Pharmacology (TL)
Ruby Leong, Clinical Pharmacology
Rosane Charlab-Orbach, Acting Genomics TL
Stacy Shord, Genomics Reviewer
Whitney Helms, Nonclinical (TL)
Gabriel Sachia Khasar, Nonclinical Reviewer
Nallaperumal Chidambaram, Acting Branch Chief
Debasis Ghosh, Acting Product Assessment Lead
Sue Ching Lin, Product Quality Reviewer
Minerva Hughes, Biopharmaceutics Reviewer
Mahesh Ramanadham, OC (Facilities)
Jean Mulinde, OSI Reviewer
James Schlick, OSE Proprietary Name Reviewer
Donna Roscoe, CDRH Consultant
Tammie Brent-Howard, Maternal Health
Igor Cerny, DRISK

Discussion Items:

1. Due to the on-going problems that exist regarding the STATS data, the Team discussed the timing of the review for this application and the Division's action goal date of Friday, February 1, 2013. New proposed Division Action Goal Date is April 15, 2013. RPM to convey to Sponsor that FDA's internal goal dates/timelines have been extended.

2. By Primary Discipline:

a. Clinical: Review is on-going

i. Clinical Protocol/Site inspection:
Domestic CI Inspection – Milhem – complete, no 483 issued.
Preliminary communication GSK sponsor inspection – no issues identified – NAI.
Update of inspection in France (Roberts) - scheduled Nov 9 - Dec 1 - NAI.

b. Update of inspection in Russia (Demidov) scheduled Nov 30 - Dec 15 – 483 issued, but minor.Statistics: Current review show limited comments for description. STATS will work with Clinical to derive own algorithms.

c. Clinical Pharmacology: No new issues. 2-3 PMRs should be communicated to Sponsor.

i. Genomics: No issues.

ii. Pharmacometrics: Review is in progress and confirming items in literature.

d. CMC: Need to schedule TCON with Sponsor regarding genotoxic impurities, acceptance criteria for proposed validation of analytical methods, and drug product lot-to-lot variability.

e. CMC (facilities): There is a very serious concern regarding commercial (b) (4) [redacted] testing. There is a discrepancy between the information given to CMC in response to an IR and the investigator. More information gathering is necessary.

f. Biopharmaceutics: There is an issue with DMSO and instability. FDA is requesting Sponsor to do a study and send the data. Currently there is some 'push back' by the Sponsor.

g. Nonclinical: Review is on-going. Nonclinical is in discussion with CMC regarding genetox impurities.

h. Regulatory

i. STATS working meeting held on November 15, 2012.

ii. Ophthalmology Consult Request submitted on 10.17.2012.

iii. Received current SGE list from Caleb Briggs 10.17.2012. Clinical to look at 3 more names to consider, but may not have one.

2. Upcoming Meetings:

- **Team Meetings**

  Team Meeting 5: January 9, 2013

  Add additional FEB Team Meeting

- **Wrap- Up Meeting**: This meeting was originally scheduled for January 3, 2013 under 6-month review clock. Per decision to have Division Target Date of April 15, 2013, and per 21st Century Review Planner, this meeting to be scheduled by March 18, 2013.

- **Labeling Meetings:** Additional Labeling Meeting – to be scheduled later in January 2013 to finalize clinical portions.

3. Review Status

- Priority Review request withdrawn on September 27, 2012.

4. Milestone Dates / Letters

Milestone	6-month review	Target Completion Date 4.15.2013	Comments
Application Received	**August 3, 2012**		
Acknowledgment Letter			**Issued August 15, 2012**
Filing Action Letter	**October 2, 2012 (Tuesday)**		**GSK submitted Withdrawal of Request for Priority Review – therefore this application was 'filed' as of October 2, 2012**
Deficiencies Identified Letter (74 Day Letter)	**October 16, 2012 (Tuesday)**		**Issued October 15, 2012**
PMR/PMC Working Meetings	To be scheduled		
Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner's Target date)	Sunday, 1/6/ 2013 therefore **Friday, January 4, 2013**		
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	Sunday, 1/13/ 2013 therefore **Friday, January 11, 2013**		
Review Target Due Dates: ***Primary Review Due*** ***Secondary Review Due*** ***CDTL Review Due*** ***Division Director Review Due*** ***Office Director Review Due/Sign-Off***	 **January 4, 2013** **January 10, 2013** **January 11, 2013** **January 24, 2013** **By February 1, 2013**	 **March 18, 2013** **March 22, 2013** **March 25, 2013** **April 5, 2013** **By April 15, 2013**	
Compile and circulate Action Letter and Action Package	**January 11, 2013**		
FINAL Action Letter Due	Sunday, 2/3/ 2013 therefore **Friday, February 1, 2013**	**April 15, 2013**	

5. **Consults/Collaborative Reviewers:**

OPDP (DDMAC)	Carole Broadnax - professional reviewer Shenee Toombs - consumer reviewer Olga Salis – RPM Consult request sent 9.18.2012
OSE	Sue Kang-OSE RPM Sean Bradley-OSE RPM TL DRISK assigned to review Risk Management Plan Igor Cerny Cynthia LaCivita (TL) DMEPA to review Proprietary Name Todd Bridges (TL) James Schlick DMEPA/CMC/DDMAC to review carton/container, and patient labeling DPV – Bob Pratt (TL) – invite to mid-cycle and wrap up or as requested by Team DEPI – Cunlin Wang (TL) – invite to mid-cycle and wrap up or as requested by Team
Maternal Health	Tammie Brent Howard (optional invitees: Carrie Ceresa and Melissa Tassinari)
QT-IRT	**ClinPharm requested QT-IRT consult on 8.14.2012; per ClinPharm and QT-IRT, consult not needed at this time.
OSI	Jean Mulinde/Paul Okwesili
Pediatric Page/PeRC	Full Waiver Requested
Patient Labeling Team *(Patient Information Leaflet included)*	Brantley Dorch – Project Manager Nathan Caulk – Reviewer Barbara Fuller – Team Leader
SEALD	Consult requested 9.18.2012 – as needed Ann Marie Trentacosti
CDRH	Donna Roscoe; (others Reena Philip, Yun-Fu, Hu, Maria Chan, Elizabeth Mansfield, Robert Becker) Tamika Allen (BIMO Reviewer)

6. ODAC Not needed: the application did not raise significant safety or efficacy issues.

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/s/

NORMA S GRIFFIN
04/17/2013

Labeling Meeting #5 Summary
December 6, 2012

NDA: 204114

Product:	Mekinist (trametinib)
Submission Date:	August 2, 2012
Received Date:	August 3, 2012
Sponsor:	GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation as detected by an FDA approved test.

Meeting Participants:
Patricia Keegan, M.D., Director DOP2
Norma Griffin., Regulatory Health Project Manager
Suzanne Demko, Clinical TL and CDTL
Marc Theoret, Clinical Reviewer
Nathan Caulk, Patient Labeling

1. **Labeling Sections Reviewed:** Adverse Reactions (6).

2. **Next Meeting (#6):** Scheduled for January 18, 2013. Sections to be reviewed: Specific Clinical and STATS section as needed to finalize labeling.

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/s/

NORMA S GRIFFIN
04/17/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204114

METHODS VALIDATION MATERIALS RECEIVED

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

Dear Eric Richards:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mekinist (trametinib) Tablets, 0.5 mg, 1mg, and 2 mg, as described in NDA 204114 and to our November 1, 2012, letter requesting sample materials for methods validation testing.

We acknowledge receipt on December 6, 2012, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (michael.trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP Coordinator
Division of Pharmaceutical Analysis
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
12/06/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204114 **INFORMATION REQUEST**

GlaxoSmithKline, LLC
Eric Richards, M.S., M.P.H.
Global Regulatory Affairs
1250 South Collegeville Road
Collegeville, PA, 19426

Dear Mr. Richards:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mekinist (trametinib) tablets, 0.5 mg, 1 mg, and 2 mg.

We also refer to your August 3, 2012, submission.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response by December 11, 2012 in order to continue our evaluation of your NDA.

Drug Substance

1. Explain the difference between [redacted] (b) (4) To allow evaluation of your control strategy, provide a complete description of the commercial scale drug substance manufacturing processes, including but not limited to details for the following manufacturing steps:

   [redacted] (b) (4)

   You can provide either a master batch record and/or a detailed manufacturing process description including equipment information as appropriate in section S.2.2 (drug

substance) of the application. The Agency recognizes that changes to non-critical process parameters can usually be managed under the firm's quality system without the need for regulatory review and approval prior to implementation. However, notification of all changes including changes to process parameters should be provided in accordance with 21CFR 314.70.

2. Clarify the procedures for "Reprocessing of Trametinib Dimethyl Sulfoxide". In the section S.2.3, the applicant states "If trametinib dimethyl sulfoxide (b) (4) does not meet the specification, it may be (b) (4). Please clarify why the (b) (4) Trametinib Dimethyl Sulfoxide. Please provide specifications for (b) (4) trametinib dimethyl sulfoxide.

3. Indicate the apparent purity of (b) (4) (b) (4)

4. Explain the inconsistent batch analysis results for (b) (4) (batch No.: MAA-PL-112002) (b) (4) (Batch No.: MGE07-O004) between Table 1 in section 2.3. "Control of Materials_Starting Materials_ Batch Analysis for (b) (4)_Trametinib Dimethyl Sulfoxide" and "Control of Materials_Starting Materials_Batch Analysis Data for (b) (4) and Figures 1 and 2 in section 2.3 "Control of Materials_Summary and List of Starting Materials, Reagents, Solvents &Auxiliary Materials_Trametinib Dimethyl Sulfoxide".

5. Revise the specifications to include the following: (a) appearance description of reagents and solvents in their specifications, (b) appearance description and apparent purity tests of all intermediates in their specifications.

6. Your justification for exclusion of potentially genotoxic impurities (b) (4) in the drug substance specification is not acceptable based on batch data provided in your submission. Include acceptance criteria for (b) (4) in the drug substance specification.

7. Provide the chromatogram for the determination of DMSO using the proposed HPLC method.

8. Specify acceptance criteria for proposed validation of analytical methods.

9. Provide justification for particle size distribution in the drug substance specification, if known, and its effect on drug product bioavailability.

10. In the drug substance specification, include test method and acceptance criteria fo (b) (4) [redacted]

11. In addition to the batch analysis data for (b) (4), please provide batch analysis data for the other [redacted] (b) (4). (Table 9 of the section S.4.5).

12. Perform heavy metal and elemental analysis testing on the Reference Standard material.

13. The (b) (4) drug substance is stored in an [redacted] (b) (4) Provide information for (b) (4) desiccant.

14. We observed that there was a [redacted] (b) (4) on stability. Please provide rationale for the observed [redacted] (b) (4) or revise your re-test period based stability data to (b) (4). The justification provided does not support a (b) (4) retest period.

Drug Product

15. Given that the finished product has a low drug load and it is manufactured (b) (4) [redacted] indicate if lot-to-lot variability in excipient properties (e.g. bulk density, particle size, surface area) would have any adverse impact on drug product quality. If there is an adverse impact, include appropriate mitigation steps within your control strategy.

16. The Agency notes that you have indicated in section P.3.3 that regulatory action for post approval changes to non-critical process parameters (NCPP) would be taken in conformance with regulations and guidance for minor changes. We would like to remind you that, if a change to an NCPP has a substantial or moderate potential impact to product quality (e.g., as might occur in the case of changes beyond ranges previously studied), you should conform to the requirements for regulatory notification as described in CFR 314.70 (b) or (c).

17. Provide justification for your proposed upper limits for [redacted] (b) (4) for 0.5 mg, 1 mg, and 2 mg tablets respectively, as specified in the master batch records).

18. Include resolution in the system suitability criteria for the analytical procedure for impurities in the drug product or provide justification for not including it.

19. The following comments pertain to the container labels:
    a. Include lot number and expiration dating period on each container label.

b. Place an asterisk next to the strength (e.g., 0.5 mg) as well as next to the equivalent statement (e.g, Each 0.5 mg tablet contains 0.5635 mg trametinib dimethyl sulfoxide equivalent to 0.5 mg of trametinib [redacted] (b) (4)).

20. Provide information in the Product Data Element section of the Structured Product Labeling (SPL).

21. Provide updated stability data for the drug product. It has been noted that only 12 months of stability data are provided for some batches (e.g., Tables 11, 15, 19, and 20 in Section 3.2.P.8.3), although Tables 3-5 of the same section indicate that 18 months of data are included in this section for all batches.

22. The following comments pertain to the information contained in Module 3 of your e-CTD submission. It is noted that the updated information was only included in Module 1 of your 11-Oct-2012 amendments but not in respective sections in Modules 3.
    a. Updated Section 3.2.P.7 with the data submitted in Section 1.11.1 of the 10/11/12 amendment for container closure system.
    b. Update Section 3.2.P.2.3 with the information contained in your response to Question #4.

If you have any questions, call Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Nallaperumal Chidambaram, PhD
Acting Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

NALLAPERUM CHIDAMBARAM
12/05/2012

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 UNSCHEDULED	QOL WEEK 11 UNSCHEDULED	QOL WEEK 12	QOL WEEK 13 UNSCHEDULED	QOL WEEK 17 UNSCHEDULED	QOL WEEK 18 UNSCHEDULED	QOL WEEK 19 UNSCHEDULED	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.

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/s/

NORMA S GRIFFIN
11/27/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204114 **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) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mekinist (trametinib) tablets, 0.5 mg, 1.0 mg, 2.0 mg.

We also refer to your August 2, 2012, submission received on August 3, 2012.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a written response by December 7, 2012, in order to continue our evaluation of your NDA.

1. Provide the complete dissolution data (individual values, means, and RSD) for all studies completed to support your proposed PAR for the 0.5 mg and 2 mg tablet [redacted] (b) (4)

2. Provide the complete dissolution data (individual values, means, and RSD) for the study evaluating the effects of the proposed changes to the 2 mg commercial tablet's dimensional attributes [redacted] (b) (4) compared with the Phase III 2 mg tablet.

3. In vitro dissolution data are not appropriate to justify your proposed DMSO content acceptance range of [redacted] (b) (4) to 12.4% given the limited discriminating power of your proposed dissolution method (500 mL pH 4.5 acetate buffer with 0.75% SDS, USP 2 at 60 rpm). In the absence of in vivo bioavailability data demonstrating acceptable drug exposure at your proposed DMSO lower limit, clinical study batch data (i.e., Table 2, Section 3.2.P.5.6) may be used to define an appropriate range. Therefore, FDA recommends that you change your DMSO content lower limit from [redacted] (b) (4) to 10.4% to align with the clinical batch data. Provide a revised specification table that includes the recommended changes.

4. In consideration of the dissolution method's robustness, sensitivity to critical quality attributes and available dissolution stability data for the clinical and registration stability data, FDA believes that an acceptance criterion of Q = [redacted] (b) (4) is more appropriate for your rapidly dissolving immediate release product. Provide a revised specification table

with the recommended changes or provide the following additional statistical data to further justify your proposed acceptance criterion of Q = [redacted] (b) (4)

a. Estimated and predicted stage 1/2/3 testing and batch failure rates at release and after 12 and 24 months long-term storage with an acceptance criterion of Q= [redacted] (b) (4) minutes compared with [redacted] (b) (4) for the pivotal clinical and primary stability lots.
b. Trend analysis of the mean dissolution stability data at the [redacted] (b) (4) and [redacted] (b) (4) (include the standard deviation) sampling times for all storage conditions.
c. Provide similar statistical data for sampling at the 20 minute time point, if these data are available.

If you have any questions, call Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Nallaperumal Chidambaram, PhD
Acting Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

NALLAPERUM CHIDAMBARAM
11/21/2012

Labeling Meeting #4 Summary
November 19, 2012

NDA: 204114

Product:	Mekinist (trametinib)
Submission Date:	August 2, 2012
Received Date:	August 3, 2012
Sponsor:	GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation as detected by an FDA approved test.

Meeting Participants:
Patricia Keegan, M.D., Director DOP2
Norma Griffin., Regulatory Health Project Manager
Suzanne Demko, Clinical TL and CDTL
Marc Theoret, Clinical Reviewer
Whitney Helms, Nonclinical (TL)
Sachia Khasar, Nonclinical Reviewer
Minerva Hughes, Biopharmaceutics
Nathan Caulk, Patient Labeling
Tammie Brent-Howard, Maternal Health
James Schlick, DMEPA
Ann Marie Trentacosti
Cathryn Lee, SRPM, DOP2

1. **Labeling Sections Reviewed:** Highlights, Indications, Warnings and Precautions (5.5), and Usage, Patient Counseling, and Maternal Health for Sections 5.4, 8.1 and 8.6 and Pregnancy part of Section 13 and 17.

2. **Next Meeting (#5):** Scheduled for December 6, 2012. Sections to be reviewed: Adverse Reactions (6)

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/s/

NORMA S GRIFFIN
04/17/2013

Labeling Meeting #3 Summary
November 14, 2012

NDA: 204114

Product:	Mekinist (trametinib)
Submission Date:	August 2, 2012
Received Date:	August 3, 2012
Sponsor:	GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation as detected by an FDA approved test.

Meeting Participants:
Patricia Keegan, M.D., Director DOP2
Norma Griffin., Regulatory Health Project Manager
Suzanne Demko, Clinical TL and CDTL
Marc Theoret, M.D., Clinical Reviewer
Kun He, Statistics (TL)
Huanyu (Jade) Chen, Statistics
Whitney Helms, Nonclinical (TL)
Carole Broadnax, OPDP
Frances Fahnbulleh, OSE
Nathan Caulk, Patient Labeling

1. **Labeling Sections Reviewed:** Indications and Usage (1), Dosage andAdministration (2.2), Drug Interactions (7), Use in Specific Populations (8.6 and 8.7), Clinical Pharmacology (12.1.and 12.2 with Nonclinical) and (12.3).

2. Maternal Health will be prepared to discuss Sections 8.1 and Pregnancy part of Section 13 for the November 19th, 2012 meeting.

3. Need ophthalmologic input from Consult.

4. **Next Meeting (#4):** Scheduled for November 14, 2012. Sections to be reviewed: Highlights, Indications, and Usage, Patient Counseling, and Maternal Health for Sections 8.1 and Pregnancy part of Section 13.

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/s/

NORMA S GRIFFIN
04/17/2013

Team Meeting 3 Summary
November 14, 2012

NDA: 204114
Product: Mekinist (trametinib)
Submission Date: August 2, 2012
Received Date: August 3, 2012
Sponsor: GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation as detected by an FDA approved test.

Participants:
Norma Griffin., Regulatory Health Project Manager
Suzanne Demko, Clinical TL and CDTL
Marc Theoret, M.D., Clinical Reviewer
Huanyu (Jade) Chen, Statistics
Hong Zhao, Ph.D, Clinical Pharmacology (TL)
Ruby Leong, Clinical Pharmacology
Rosane Charlab-Orbach, Acting Genomics TL
Stacy Shord, Genomics Reviewer
Whitney Helms, Nonclinical (TL)
Gabriel Sachia Khasar, Nonclinical Reviewer
Liang Zhou, Ph.D., Product (TL)
Sue Ching Lin, Product Quality Reviewer
Minerva Hughes, Biopharmaceutics Reviewer
James Schlick, OSE; DRISK, Proprietary Name Reviewer
Donna Roscoe, CDRH Consultant
Frances Fahnbulleh, OSE
Katherine Coyle, DPVII
Peter Waldron, DPVII
Cathryn Lee, Safety RPM, DOP2

Discussion Items:

1. By Primary Discipline:

a. Clinical: No new issues. Need the 120d update with the inclusion of SAE updates.

i. Clinical Protocol/Site inspection: Domestic CI Inspection (Milhem) complete, no 483 issued. Preliminary communication GSK sponsor inspection – no issues identified. Inspection in France (Roberts) - scheduled for Nov 9 - Dec 1. Inspection in Russia (Demidov) scheduled for Nov 30 - Dec 15.

b. Statistics: F2F STATS working meeting scheduled for Thursday, November 15, 2012. Update on newest dataset submission – data still needs corrections.

c. Clinical Pharmacology: No new review issues. Submitted proposed PMRs.

i. Genomics: No review issues.

ii. Pharmacometrics: No review issues

d. CMC: need to send IR by end of week.

e. CMC (facilities): Inspection at the finished dosage manufacturer is pending review within CDER/OC/OMPQ. Inspection at the API manufacturer started on Monday and will close on Friday.

f. Biopharmaceutics: Review is on-going.

g. Nonclinical: Review is on-going; no issues.

h. Regulatory

i. Sponsor withdrew their request for priority review on September 27, 2012. Team will continue review process under an approximate 6-month review clock.

ii. 74-.Day Deficiencies Letter issued 10.15.2012. Sponsor response received on 10.26.2012.

iii. Ophthalmology Consult Request submitted on 10.17.2012.

iv. Received current SGE list from Caleb Briggs 10.17.2012.

2. Upcoming Meetings:

- **Team Meetings**

  Team Meeting 4: December 18, 2012

  Team Meeting 5: January 9, 2013

- **Wrap- Up Meeting**: Per 6-month clock, scheduled for January 3, 2013.

- **Labeling Meetings (suggested section groupings):**

  a. Labeling Meeting 3 – 11/14/2012
  Sections to be reviewed: Clinical Sections: Dosage and Administration, Clinical Studies, Drug Interactions, Use in Specific Populations, Overdosage, Contraindications, References, Clinical Pharmacology

  b. Labeling Meeting 4 – 11/19/2012
  Sections to be reviewed: Highlights, Indications and Usage, Patient Counseling Information, Pregnancy section (with PMH reviewer)

  c. Labeling Meeting 5– December 6, 2012
  Label Sections to be reviewed: Specific sections as needed to finalize
  Disciplines: All

  d. Additional Labeling Meetings – to be scheduled after December 6th depending on STATS review of data

  Labeling included: 0.5 mg x 30 Tablets Container Label
  1 mg x 30 Tablets Container Label
  2 mg x 30 Tablets Container Label
  Draft Labeling (PI) with Patient Information Leaflet

3. Review Status

- Priority Review request withdrawn on September 27, 2012.

4. Milestone Dates / Letters

Milestone	6-month review	Comments
Application Received	**August 3, 2012**	
Acknowledgment Letter		**Issued August 15, 2012**
Filing Action Letter	**October 2, 2012 (Tuesday)**	**GSK submitted Withdrawal of Request for Priority Review – therefore this application was 'filed' as of October 2, 2012**
Deficiencies Identified Letter (74 Day Letter)	**October 16, 2012 (Tuesday)**	**Issued October 15, 2012**
PMR/PMC Working Meetings	To be scheduled	
Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner's Target date)	Sunday, 1/6/ 2013 therefore **Friday, January 4, 2013**	
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	Sunday, 1/13/ 2013 therefore **Friday, January 11, 2013**	
Review Target Due Dates: ***Primary Review Due*** ***Secondary Review Due*** ***CDTL Review Due*** ***Division Director Review Due*** ***Office Director Review Due/Sign-Off***	 **January 4, 2013** **January 10, 2013** **January 11, 2013** **January 24, 2013** **By February 1, 2013**	
Compile and circulate Action Letter and Action Package	**January 11, 2013**	
FINAL Action Letter Due	Sunday, 2/3/ 2013 therefore **Friday, February 1, 2013**	

5. Consults/Collaborative Reviewers:

OPDP (DDMAC)	Carole Broadnax - professional reviewer Karen Munoz-Nero - consumer reviewer Olga Salis – RPM Consult request sent 9.18.2012
OSE	Sue Kang-OSE RPM Sean Bradley-OSE RPM TL DRISK assigned to review Risk Management Plan Cynthia LaCivita (TL) DMEPA to review Proprietary Name Todd Bridges (TL) James Schlick DMEPA/CMC/DDMAC to review carton/container, and patient labeling

	DPV – Bob Pratt (TL) – invite to mid-cycle and wrap up or as requested by Team DEPI – Cunlin Wang (TL) – invite to mid-cycle and wrap up or as requested by Team
Maternal Health	Tammie Brent Howard (optional invitees: Carrie Ceresa and Melissa Tassinari)
QT-IRT	**ClinPharm requested QT-IRT consult on 8.14.2012; per ClinPharm and QT-IRT, consult not needed at this time.
OSI	Jean Mulinde/Paul Okwesili
Pediatric Page/PeRC	Full Waiver Requested
Patient Labeling Team *(Patient Information Leaflet included)*	Brantley Dorch – Project Manager Nathan Caulk – Reviewer Barbara Fuller – Team Leader
SEALD	Consult requested 9.18.2012 – as needed Ann Marie Trentacosti
CDRH	Donna Roscoe; (others Reena Philip, Yun-Fu, Hu, Maria Chan, Elizabeth Mansfield, Robert Becker) Tamika Allen (BIMO Reviewer)

6. ODAC not needed - the application did not raise significant safety or efficacy issues

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/s/

NORMA S GRIFFIN
04/17/2013

Labeling Meeting #2 Summary
November 13, 2012

NDA: 204114

Product:	Mekinist (trametinib)
Submission Date:	August 2, 2012
Received Date:	August 3, 2012
Sponsor:	GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation as detected by an FDA approved test.

Meeting Participants:
Patricia Keegan, M.D., Director DOP2
Norma Griffin., Regulatory Health Project Manager
Suzanne Demko, Clinical TL and CDTL
Marc Theoret, M.D., Clinical Reviewer
Huanyu (Jade) Chen, Statistics
Whitney Helms, Nonclinical (TL)
Sachia Khasar, Nonclinical Reviewer
Rosane Charlab-Orbach, Acting Genomics TL
Liang Zhou, Ph.D., Product (TL)
Sue Ching Lin, Product Quality Reviewer
Tammie Brent-Howard
James Schlick, OSE Proprietary Name Reviewer

1. **Labeling Sections Reviewed:** Dosage Forms and Strengths (Section 3), Description (Section 11), How Supplied/Storage and Handling (Section 16), and Nonclinical Sections (8.1 and 5.4).

2. Maternal Health will be prepared to discuss Sections 8.1 and Pregnancy part of Section 13 for the November 19th, 2012 meeting.

3. DMEPA discussed comments for Container label.

4. **Next Meeting (#3):** Scheduled for November 14, 2012. Sections to be reviewed: Dosage and Administration, Clinical Studies, Drug Interactions, Use in Specific Populations, Overdosage, Contraindications, Clinical Pharmacology.

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/s/

NORMA S GRIFFIN
04/17/2013

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

Memorandum

Date: November 7, 2012

From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 204114; GlaxoSmithKline, LLC
Labeling - DMEPA 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 submitted on August 3, 2012, for Mekinist (trametinib). The Division of Medication Error Prevention and Analysis (DMEPA) notes the submission of the [redacted] (b) (4) for the 2 mg strength of Mekinist in the October 26, 2012 submission. Do you intend to have a [redacted] (b) (4) for the 1 mg, and 0.5 mg strengths of Mekinist? If so, please submit the draft labels for these two strengths.

Please provide a response to this information request to me via email by Monday, November 12, 2012, or sooner if possible and follow it with a formal submission to NDA 204114. Contact me if you have any questions or concerns at (301) 796-4255 or at Norma.Griffin@fda.hhs.gov.

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/s/

NORMA S GRIFFIN
11/07/2012

Labeling Meeting #1 Summary
November 6, 2012

NDA: 204114

Product:	Mekinist (trametinib)
Submission Date:	August 2, 2012
Received Date:	August 3, 2012
Sponsor:	GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation as detected by an FDA approved test.

Meeting Participants:
Patricia Keegan, M.D., Director DOP2
Norma Griffin., Regulatory Health Project Manager
Suzanne Demko, Clinical TL and CDTL
Marc Theoret, M.D., Clinical Reviewer
Kun He, Ph.D., Statistics (TL)
Huanyu (Jade) Chen, Statistics
Whitney Helms, Nonclinical (TL)

1. **Labeling Sections Reviewed:** Indications and Usage and Adverse Reactions, and Warnings and Precautions.

2. **Next Meeting (#2):** Scheduled for November 13, 2012. Sections to be reviewed: Dosage Forms and Strengths, Description, How Supplied/Storage and Handling, Nonclinical Sections, Nonclinical Toxicology.

Note: Nonclinical will be ready for sections 8.1 and 5.4, however will not be ready for sections 13.1, 12.1, and 13.2.

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/s/

NORMA S GRIFFIN
04/17/2013

Mid-Cycle Meeting Summary
November 1, 2012

NDA: 204114

Product:	Mekinist (trametinib)
Submission Date:	August 2, 2012
Received Date:	August 3, 2012
Sponsor:	GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation as detected by an FDA approved test.

Meeting Participants:
Richard Pazdur, M.D., Director, OHOP
Anthony Murgo, Associate Director of Regulatory Science, OHOP
Gregory Reaman, Associate Director of Oncology Science, OHOP
Patricia Keegan, M.D., Director DOP2
Karen Jones CPMS, DOP2
Monica Hughes, CPMS, DOP2
Norma Griffin., Regulatory Health Project Manager
Suzanne Demko, Medical Officer (Acting TL)
Marc Theoret, M.D., Medical Officer (Efficacy Review)
Kun He, Ph.D., Statistics (TL)
Huanyu (Jade) Chen, Statistics Reviewer
Vivian Yuan, Statistics Reviewer
Hong Zhao, Ph.D, Clinical Pharmacology (TL)
Ruby Leong, Clinical Pharmacology
Rosane Charlab Orbach, Genomics (TL)
Whitney Helms, Nonclinical (TL)
Gabriel Sachia Khasar, Nonclinical Reviewer
Margaret Brower, Nonclinical Reviewer
Liang Zhou, Ph.D., Product (TL)
Sue Ching Lin, Product Quality Reviewer
Zhe Jean Tang, Product Quality Reviewer
Minerva Hughes, Biopharmaceutics Reviewer
Mahesh Ramanadham, OC (Facilities)
Derek Smith, OC (Facilities)
Jean Mulinde, OSI Reviewer
Donna Roscoe, CDRH Consultant
Robert Pratt, OSE, DRISK
Latonia Ford, Patient Labeling
Carrie Ceresa, Maternal Health
Jeffrey Summers, Deputy Director for Safety, OHOP

Discussion Items

The attached slides were presented.

- RPM Regulatory
- Clinical and Statistical, Efficacy & Safety
- Clinical Pharmacology
- CDRH
- CMC and Biopharmaceutics
- Non-Clinical

Summary (from Clinical)

- Benefit: Efficacy results (unverified due to data analysis and quality problems):
- Safety review ongoing- no REMS expected based on review at this point
- Risk: Sudden deaths (under evaluation); Cardiac, ocular, and pulmonary toxicity

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/s/

NORMA S GRIFFIN
04/17/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204114

REQUEST FOR METHODS VALIDATION MATERIALS

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

Dear Eric Richards:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Mekinist (trametinib) Tablets, 0.5 mg, 1 mg, and 2 mg.

We will be performing methods validation studies on Mekinist (trametinib) Tablets, 0.5 mg, 1 mg, and 2 mg, as described in NDA 204114.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

Determination of Trametinib Dimethyl Sulfoxide content and drug-related impurities content in Trametinib Dimethyl Sulfoxide by HPLC
Determination of Dimethyl Sulfoxide (DMSO) content of Trametinib Dimethyl Sulfoxide by HPLC
Determination of the solid state form of (b) (4) Trametinib Dimethyl Sulfoxide by X-Ray Powder Diffraction
Identification, trametinib content, uniformity, and drug-related impurities profile determination for Trametinib Tablets by HPLC
Determination of DMSO content in Trametinib Tablets by HPLC
Determination of release by dissolution of Trametinib Tablets by HPLC

Equipment

1 Zorbax Bonus-RP, 150 mm x 4.6 mm, 3.5 micron column
1 Atlantis T3, 50 mm x 3.0 mm, 3 micron column
1 Atlantis T3, 250 mm x 3.0 mm, 5 micron column
30 Acrodisc GxF/GHP 0.45 µm filters

Samples and Reference Standards

1 g trametinib dimethyl sulfoxide drug substance
1 g [redacted] (b) (4) trametinib dimethyl sulfoxide drug substance
300 mg [redacted] (b) (4) trametinib (non-solvated parent)
300 mg [redacted] (b) (4) trametinib dimethyl sulfoxide reference standard
500 mg trametinib dimethyl sulfoxide reference standard
30 mg [redacted] (b) (4)
30 mg [redacted]
30 mg [redacted]
50 0.5 mg tablets of trametinib
50 1 mg tablets of trametinib
50 2 mg tablets of trametinib
20 mg of each impurity if available
[redacted] (b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration
Division of Pharmaceutical Analysis
Attn: Sample Custodian
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

{See appended electronic signature page}

Michael L. Trehy
MVP coordinator
Division of Pharmaceutical Analysis, HFD-920
Office of Testing and Research
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

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/s/

MICHAEL L TREHY
11/01/2012

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
Nonclinical 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 submitted on August 3, 2012, for Mekinist (trametinib). Our Nonclinical Reviewer has the following comments and information request:

1. Throughout the nonclinical studies submitted to NDA 204114, it is unclear whether doses administered to animals were given based on body surface area (BSA, mg/m^2) or body weight (mg/kg). For studies G09108, G09109, G10218, and G11166, please clarify by which method (mg/kg or mg/m^2) doses administered were calculated and clarify the conversion factor used (e.g., 20 for dogs) to convert doses from mg/kg to mg/m^2 in each species.

2. For Study G10218, an embryofetal development study conducted in rats:

   a) The summary indicates that toxicokinetic samples were collected from both pregnant and non-pregnant rats. The data collected from non-pregnant rats is presented in Appendix 9. Please indicate where the data collected from pregnant rats is located.

   b) The study design (section 3.3) states that dose groups at the 2.86 mg/m^2 were included, however, there were no data included for these dose groups in the study. Please explain this discrepancy.

   c) Please provide the rationale for loading and maintenance doses in EFD studies verses all other toxicology studies.

Please provide a response to this information request to me via email by Wednesday, November 7, 2012, or sooner if possible and follow it with a formal submission to NDA 204114. Contact me if you have any questions or concerns at (301) 796-4255 or at Norma.Griffin@fda.hhs.gov.

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/s/

NORMA S GRIFFIN
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.

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NORMA S GRIFFIN
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 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 VNBTCD since the pop.ptxmet should be replaced by pop. PRCTX (On Page 133 of 528 define.pdf)

VNBTCD	Num	V600E No Brain Mets/Prior Chemo code		DERIVED DATA: POP.V600E='Y' and POP.PBMET='N' and POP.PTXMET='Y', then VNBTCD=1; else VNBTCD=0.

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."

a. Please clarify whether your stratification factors were CRF based?

b. 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)

Frequency|
Percent  |
Row Pct  |
Col Pct  |        |       0|       1|  Total
---------+--------+--------+--------+
         |      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 |      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 |      0 |      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*/
```

```
    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 baseldh=. and maxldh ne . then baseldh=maxldh;
    if baseldh>lbstnrhi then baseldh_high=1;
    else baseldh_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 baseldh1(keep=usubjid randdt maxldh maxldh_high baseldh baseldh_high);
    by usubjid;
run;

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

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

/*
     MAXLDH_ BASELDH_
Obs      USUBJID      TRTCD    TRTGRP    LDHCD LDH                   LDHBRESN LDHBULN LDHUNIT
MAXLDH BASELDH   HIGH    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.lab;
        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.

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/s/

NORMA S GRIFFIN
10/25/2012

Team Meeting 2 Summary
October 16, 2012

NDA: 204114
Product: Mekinist (trametinib)
Submission Date: August 2, 2012
Received Date: August 3, 2012
Sponsor: GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation as detected by an FDA approved test.

Participants:
Patricia Keegan, M.D., Director DOP2
Jeff Summers, M.D., Deputy Director for Safety, DOP2
Norma Griffin., Regulatory Health Project Manager
Suzanne Demko, Clinical TL and CDTL
Marc Theoret, M.D., Clinical Reviewer
Kun He, Ph.D., Statistics (TL)
Huanyu (Jade) Chen, Statistics
Hong Zhao, Ph.D, Clinical Pharmacology (TL)
Ruby Leong, Clinical Pharmacology
Rosane Charlab-Orbach, Acting Genomics TL
Stacy Shord, Genomics Reviewer
Whitney Helms, Nonclinical (TL)
Gabriel Sachia Khasar, Nonclinical Reviewer
Sue Ching Lin, Product Quality Reviewer
Minerva Hughes, Biopharmaceutics Reviewer
Mahesh Ramanadham, OC (Facilities)
Jean Mulinde, OSI Reviewer
Donna Roscoe, CDRH Consultant
Katherine Coyle, DPV

Discussion Items:

1. By Primary Discipline:
   a. Clinical: No safety issues; review is on-going
      i. Clinical Protocol/Site inspection: All inspection results pending at this point; Sponsor inspection has been pushed back to 10/29. Inspections in France (Grob and Roberts) scheduled for Nov 9 - Dec 1, inspections in Russia (Demidov) scheduled for Nov 30 - Dec 15.
   b. Statistics: Review is on-going.
   c. Clinical Pharmacology: Review is on-going and no issues. Will have 2 PMRs.
      i. Genomics: Review is on-going and no issues. Question to Clinical: will there be enough data for exposure response?
      ii. Pharmacometrics: Review is on-going and no issues.

d. CMC: Received sponsor response on 10.11.2012 to 9.27.2012 CMC IR.

e. CMC (facilities): GSK parma (finished dosage site) - inspection completed in late September with an initial acceptable recommendation. This will be reviewed by the international division. GSK Singapore - inspection scheduled for 11/12/2012 and will cover both NDA 204114 and 202806. CDER/OC and ONDQA will be participating on this inspection. GSK Zebulon - packaging - currently acceptable.

f. Biopharmaceutics: Review is on-going; no major issues; only points that require clarification.

g. Nonclinical: Review is on-going and no issues.

h. CDRH: Major deficiency letter to be issued to bioMerieux. Two inspections have been initiated; one inspection is at ResponseGenetics

i. Regulatory

   i. Sponsor withdrew their request for priority review on September 27, 2012. Team will continue review process under an approximate 6-month review clock.

      - 74-Day Deficiencies Letter signed 10.14.2012 and issued 10.15.2012 with 1 Clinical Deficiency, 2 Clinical Pharmacology Deficiencies, and RPM Labeling Comments

   ii. Need to request list from Susan Lange for screening for competing products.

2. Milestone Dates / Letters

Milestone	6-month review	Comments
Application Received	**August 3, 2012**	
Acknowledgment Letter		**Issued August 15, 2012**
Filing Action Letter	**October 2, 2012 (Tuesday)**	**GSK submitted Withdrawal of Request for Priority Review – therefore this application was 'filed' as of October 2, 2012**
Deficiencies Identified Letter (74 Day Letter)	**October 16, 2012 (Tuesday)**	**Issued October 15, 2012**
Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner's Target date)	Sunday, 1/6/ 2013 therefore **Friday, January 4, 2013**	
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	Sunday, 1/13/ 2013 therefore **Friday, January 11, 2013**	
Review Target Due Dates: ***Primary Review Due*** ***Secondary Review Due*** ***CDTL Review Due*** ***Division Director Review Due*** ***Office Director Review Due/Sign-Off***	 **January 4, 2013** **January 10, 2013** **January 11, 2013** **January 24, 2013** **By February 1, 2013**	

Milestone	6-month review	Comments
Compile and circulate Action Letter and Action Package	**January 11, 2013**	
FINAL Action Letter Due	Sunday, 2/3/ 2013 therefore **Friday, February 1, 2013**	

3. Upcoming Meetings:

- **Team Meetings**
  Team Meeting 3: November 14, 2012
  Team Meeting 4: December 18, 2012
  Team Meeting 5: January 9, 2013

- **Mid-Cycle Meeting:** Per 6-month clock, scheduled for November 1, 2012.

  Note: Need Mid-Cycle slides to CDTL by October 24, 2012

- **Wrap- Up Meeting**: Per 6-month clock, scheduled for January 3, 2013.

- **Labeling Meetings (suggested section groupings):**

  a. Labeling Meeting 1 – 11/6/2012
  Sections to be reviewed: Clinical Sections: Indications and Usage, Adverse Reactions, Warnings and Precautions

  b. Labeling Meeting 2 – 11/13/2012
  Sections to be reviewed: Dosage Forms and Strengths, Description, How Supplied/Storage and Handling, Nonclinical Sections, Nonclinical Toxicology

  **Include OSE/CMC during this labeling meeting to review carton and container.

  c. Labeling Meeting 3 – 11/14/2012
  Sections to be reviewed: Clinical Sections: Dosage and Administration, Clinical Studies, Drug Interactions, Use in Specific Populations, Overdosage, Contraindications, References, Clinical Pharmacology

  d. Labeling Meeting 4 – 11/19/2012
  Sections to be reviewed: Highlights, Indications and Usage, Patient Counseling Information

  e. Labeling Meeting 5– to be scheduled if needed

  Labeling included: 0.5 mg x 30 Tablets Container Label
  1 mg x 30 Tablets Container Label
  2 mg x 30 Tablets Container Label
  Draft Labeling (PI) with Patient Information Leaflet

- **PMR/PMC Working Meetings**: To be scheduled as needed

4. Review Status

- Priority Review request withdrawn on September 27, 2012.

5. Consults/Collaborative Reviewers:

OPDP (DDMAC)	Carole Broadnax - professional reviewer Karen Munoz-Nero - consumer reviewer Olga Salis – RPM
OSE	Sue Kang-OSE RPM Sean Bradley-OSE RPM TL DRISK assigned to review Risk Management Plan Cynthia LaCivita (TL) DMEPA to review Proprietary Name Todd Bridges (TL) James Schlick DMEPA/CMC/DDMAC to review carton/container, and patient labeling DPV – Bob Pratt (TL) – invite to mid-cycle and wrap up or as requested by Team DEPI – Cunlin Wang (TL) – invite to mid-cycle and wrap up or as requested by Team
Maternal Health	Tammie Brent Howard (optional invitees: Carrie Ceresa and Melissa Tassinari)
QT-IRT	**ClinPharm requested QT-IRT consult on 8.14.2012; per ClinPharm and QT-IRT, consult not needed at this time.
OSI	Jean Mulinde
Pediatric Page/PeRC	Full Waiver Requested
Patient Labeling Team *(Patient Information Leaflet included)*	Brantley Dorch – Project Manager Nathan Caulk – Reviewer Barbara Fuller – Team Leader
SEALD	Consult requested 9.18.2012 – as needed Ann Marie Trentacosti
CDRH	Donna Roscoe; (others Reena Philip, Yun-Fu, Hu, Maria Chan, Elizabeth Mansfield, Robert Becker) Tamika Allen (BIMO Reviewer)
SGE's or Patient Representatives	Are these needed?

- Need to request Ophthalmology consult.

6. ODAC Not needed - the application did not raise significant safety or efficacy issues

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/s/

NORMA S GRIFFIN
04/17/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204114

FILING COMMUNICATION

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

Dear Mr. Richards:

Please refer to your New Drug Application (NDA) dated August 2, 2012, received August 3, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Mekinist (trametinib) tablets, 0.5 mg, 1.0 mg, and 2.0 mg.

We also refer to your amendments dated August 7, 2012, August 15, 2012, August 16, 2012, August 17, 2012, August 31, 2012, September 17, 2012, September 18, 2012, September 21, 2012, September 25, 2012, September 27, 2012, and September 28, 2012.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is June 3, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by April 15, 2013.

During our filing review of your application, we identified the following potential review issues:

Clinical Comments

1. The raw datasets, in SAS transport file format for trial MEK111504 were not provided. Submit these datasets within 2 weeks of receipt of this letter.

Clinical Pharmacology Comments

2. During the May 9, 2012, pre-NDA meeting, you agreed to provide the milestone timelines for completion of the QTc study as a post-marketing requirement (PMR). You did not include the proposed PMR. Propose PMR language and provide milestone timelines for completion of the dedicated QTc study (MEK114655).

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

Clinical Pharmacology Comments

3. Please propose PMR language and provide milestone timelines for a hepatic impairment study.

During our preliminary review of your submitted labeling, we have identified the following labeling format issues:

4. White space must be present before each major heading in Highlights.
5. In general, in the Full Prescribing Information, there needs to be white space between sections, subsections, and paragraph text.
6. In general, in the Full Prescribing Information, the left margin of wrapped text should align with the first indented line of the paragraph.

We request that you resubmit labeling that addresses these issues by October 29, 2012. The resubmitted labeling will be used for further labeling discussions.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

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

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

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

Sincerely,

{See appended electronic signature page}

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

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/s/

PATRICIA KEEGAN
10/14/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204114 **INFORMATION REQUEST**

GlaxoSmithKline, LLC
Eric Richards, M.S., M.P.H.
Global Regulatory Affairs
1250 South Collegeville Road
Collegeville, PA, 19426

Dear Mr. Richards:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Mekinist (trametinib) tablets, 0.5 mg, 1 mg, and 2 mg.

We also refer to your August 3, 2012, submission.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a written response by October 11, 2012 in order to continue our evaluation of your NDA.

1. The following comments pertain to the container closure system (Section 3.2.P.7):
   a. Provide assurance of safety of all packaging components for the final drug product (as listed in Table 2 of Section 3.2.P.7) by reference to appropriate 21CFR food additive regulations.
   b. Provide USP <661> and <671> testing results in Section 3.2.P.7. Please note that, according to section III.G of the "Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics," the inner seals should be removed prior to USP <671> testing.
   c. Confirm that no cartons are to be used to pack the drug product.

2. In Form 356h, Establishment Information, clearly indicate in the "Function" column for the GlaxoSmithKline facility in Collegeville, PA, as well as [redacted] (b) (4) that these two sites have no responsibility for commercial batches.

3. In Section 3.2.S.2.1, indicate that the GlaxoSmithKline facility in Collegeville, PA is responsible for testing of primary NDA stability batches and that it has no testing responsibilities for commercial batches.

4. Provide stratified sampling plan in Section 3.2.P.3.3 to evaluate content uniformity to assure product quality across the entire [redacted] (b) (4)

5. Provide batch data in Section 3.2.P.5.4 for production-scale batches of 1 mg trametinib tablets that were manufactured according to the proposed commercial process at the commercial site and tested by the proposed commercial analytical methods.

If you have any questions, call Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Nallaperumal Chidambaram, PhD
Acting Branch Chief, Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

NALLAPERUM CHIDAMBARAM
09/27/2012

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

Memorandum

Date: September 21, 2012

From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 204114; GlaxoSmithKline, LLC
Division of Medication Error Prevention and Analysis (DMEPA) Comments and Information Request

---

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

Dear Mr. Richards:

For trametanib, the Division of Medication Error Prevention and Analysis (DMEPA) refers to your July 2, 2012 Request for Proprietary Name Review submission and the [redacted] (b) (4) The August 2, 2012 NDA submission contains labels and insert labeling for [redacted] (b) (4) the 30 count bottles. Please clarify if you [redacted] (b) (4) [redacted] (b) (4) [redacted]

Please provide your response to me via email by Friday, September 28, 2012, or sooner if possible and follow that with a formal submission to your NDA.

If you have any questions/concerns, please contact me at (301) 796-4255 or at Norma.Griffin@fda.hhs.gov.

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/s/

NORMA S GRIFFIN
09/21/2012

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

NDA 204114

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

GlaxoSmithKline LLC
1250 South Collegeville Road
Collegeville, PA 19426

ATTENTION: Eric Richards, M.S., M.P.H.
Director, Global Regulatory Affairs

Dear Mr. Richards:

Please refer to your New Drug Application (NDA) dated August 2, 2012, received August 3, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Trametinib Tablets, 0.5 mg, 1 mg, and 2 mg.

We also refer to your July 2, 2012, correspondence, received July 2, 2012, requesting review of your proposed proprietary name, Mekinist. We have completed our review of the proposed proprietary name, Mekinist and have concluded that it is acceptable.

The proposed proprietary name, Mekinist, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your July 2, 2012, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Norma Griffin at (301) 796-4255.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
09/20/2012

Team Meeting 1 Summary
September 19, 2012

NDA: 204114

Product:	Mekinist (trametinib)
Submission Date:	August 2, 2012
Received Date:	August 3, 2012
Sponsor:	GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation as detected by an FDA approved test.

Participants:
Patricia Keegan, M.D., Director DOP2
Anthony Murgo, M.D., Associate Director for Regulatory Science, OHOP
Jeffrey Summers, M.D., Deputy Director for Safety, DOP2
Cathryn Lee, Safety RPM, DOP2
Norma Griffin., Regulatory Health Project Manager
Marc Theoret, M.D., Clinical Reviewer
Kun He, Ph.D., Statistics (TL)
Huanyu (Jade) Chen, Statistics
Hong Zhao, Ph.D, Clinical Pharmacology (TL)
Ruby Leong, Clinical Pharmacology
Stacy Shord, Genomics Reviewer
Nitin Mehrotra, Pharmacometrics (TL)
Jingyu (Jerry) Yu, Pharmacometrics Reviewer
Whitney Helms, Nonclinical (TL)
Gabriel Sachia Khasar, Nonclinical Reviewer
Liang Zhou, Ph.D., Product (TL)
Sue Ching Lin, Product Quality Reviewer
Zhe Jean Tang, Product Quality Reviewer
Jewell Martin, Product (ONDQA RPM)
Minerva Hughes, Biopharmaceutics Reviewer
Derek Smith, OC (Facilities)
Jean Mulinde, OSI Reviewer
Donna Roscoe, CDRH Consultant
Ranjit Thomas, Panorama

Discussion Items:

1. Panorama (Ranjit Thomas): brief introduction/overview
2. By Primary Discipline:
   a. Clinical: Need to submit IR to include another variable.
      i. Clinical Protocol/Site inspection sites selected: Sites 86614, 86717, 84362.
   b. Statistics: Working (hands-on) meeting held 9.19.2012 with GSK STATS. Requesting raw datasets and response by 9.21.2012.
   c. Clinical Pharmacology: issuing IR for hepatic study.
      i. Genomics: no issues
      ii. Pharmacometrics: issuing IR for organ impairment.
   d. CMC: IR issued by ONDQA RPM.
   e. CMC (facilities): Finished Dosage facility being inspected now. Singapore facility to be inspected ~November 12, 2012.
   f. Biopharmaceutics: Review is on-going and no issues thus far.
   g. Nonclinical: Review is on-going and no issues thus far.
   h. Regulatory
      i. Per ClinPharm, QT-IRT Consult Request cancelled.
      ii. Confirmed that GSK will not be submitting carton labeling.
      iii. Filing Letter drafted – 9.19.2012
3. Review Status
   - Priority Review requested, team agreed to a 6-month clock
4. Milestone Dates Letters

Milestone	6-month review	Comments
Application Received	**August 3, 2012**	
Acknowledgment Letter		**Issued August 15, 2012**
Filing Action Letter •If the filing issues are not identified, we will need to send a "Notification of Review Status" letter.	**October 2, 2012 (Tuesday)**	
Deficiencies Identified Letter (74 Day Letter)	**October 16, 2012 (Tuesday)**	
Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner's Target date)	Sunday, 1/6/ 2013 therefore **Friday, January 4, 2013**	
Week after the proposed labeling has been sent, discuss the	Sunday, 1/13/ 2013 therefore	

Milestone	6-month review	Comments
Labeling/PRM/PMC with Applicant	**Friday, January 11, 2013**	
Review Target Due Dates: ***Primary Review Due*** ***Secondary Review Due*** ***CDTL Review Due*** ***Division Director Review Due*** ***Office Director Review Due/Sign-Off***	 **January 4, 2013** **January 10, 2013** **January 11, 2013** **January 24, 2013** **By February 1, 2013**	
Compile and circulate Action Letter and Action Package	**January 11, 2013**	
FINAL Action Letter Due	Sunday, 2/3/ 2013 therefore **Friday, February 1, 2013**	

5. Consults/Collaborative Reviewers:

OPDP	????- professional reviewer ????- consumer reviewer Olga Salis – RPM Consult request sent 9.18.2012
OSE	Sue Kang-OSE RPM Sean Bradley-OSE RPM TL DRISK assigned to review Risk Management Plan Cynthia LaCivita (TL) DMEPA to review Proprietary Name Todd Bridges (TL) James Schlick DMEPA/CMC/DDMAC to review carton/container, and patient labeling DPV – Bob Pratt (TL) – invite to mid-cycle and wrap up or as requested by Team DEPI – Cunlin Wang (TL) – invite to mid-cycle and wrap up or as requested by Team
Maternal Health	Consult request sent 9.18.2012
QT-IRT	**ClinPharm requested QT-IRT consult on 8.14.2012; per ClinPharm and QT-IRT, consult not needed at this time.
OSI	Jean Mulinde
Pediatric Page/PeRC	Full Waiver Requested
Patient Labeling Team	Patient Information Leaflet included
SEALD	Consult requested 9.18.2012 – as needed

	Ann Marie Trentacosti
CDRH	Donna Roscoe; (others Reena Philip, Yun-Fu, Hu, Maria Chan, Elizabeth Mansfield, Robert Becker) Tamika Allen (BIMO Reviewer)
SGE's or Patient Representatives	Are these needed?

6. Upcoming Meetings:

- **Team Meetings**

  Team Meeting 2: October 16, 2012

  Team Meeting 3: November 14, 2012

  Team Meeting 4: December 18, 2012

  Team Meeting 5: January 9, 2013

- **Mid-Cycle Meeting:** Per 6-month clock, scheduled for November 1, 2012.
  Note: Need Mid-Cycle slides to CDTL by October 24, 2012
- **Wrap- Up Meeting**: Per 6-month clock, scheduled for January 3, 2013.
- **Labeling Meetings (with suggested section groupings):** Scheduled approximately after mid-cyclewith ~2 labeling meetings per week.
  a. Labeling Meeting 1 – tentatively 11/6/2012
     Sections to be reviewed: Clinical Sections: Indications and Usage, Adverse Reactions, Warnings and Precautions
  b. Labeling Meeting 2 – tentatively 11/13/2012
     Sections to be reviewed: Dosage Forms and Strengths, Description, How Supplied/Storage and Handling, Nonclinical Sections, Nonclinical Toxicology

     **Include OSE/CMC during this labeling meeting to review carton and container.
  c. Labeling Meeting 3– tentatively 11/14/2012
     Sections to be reviewed: Clinical Sections: Dosage and Administration, Clinical Studies, Drug Interactions, Use in Specific Populations, Overdosage, Contraindications, References, Clinical Pharmacology
  d. Labeling Meeting 4 – to be scheduled
     Sections to be reviewed: Highlights, Indications and Usage, Patient Counseling Information
  e. Labeling Meeting 5– to be scheduled
     If needed
     Labeling included: 0.5 mg x 30 Tablets Container Label
     1 mg x 30 Tablets Container Label
     2 mg x 30 Tablets Container Label
     Draft Labeling (PI) with Patient Information Leaflet
- **Team Meetings**

  Team Meeting 2: October 16, 2012

  Team Meeting 3: November 14, 2012

  Team Meeting 4: December 18, 2012

  Team Meeting 5: January 9, 2013

- **PMR/PMC Working Meetings**: To be scheduled as needed
- **ODAC Needed/Not Needed:** Not needed – reason to be drafted for filing memo.

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/s/

NORMA S GRIFFIN
04/17/2013

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

Memorandum

Date: September 19, 2012

From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 204114; GlaxoSmithKline, LLC
CMC Microbiology 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, our CMC Microbiology Reviewer has the following comments and information request:

> Your proposal to forgo performance of microbial limits testing on the finished drug product is acceptable based on the drug substance and drug product manufacturing processes, (b) (4) of the drug product. However, we suggest that microbial limits testing should be performed at the initial time point (at a minimum) on stability samples as a periodic measure of the microbiological quality of the drug product.
>
> > Provide a commitment to amend the drug product stability testing protocol with test methods and acceptance criteria for microbial limits testing.

Please provide your response to me via email as soon as possible and follow that with a formal submission to your NDA.

If you have any questions/concerns, please contact me at (301) 796-4255 or at Norma.Griffin@fda.hhs.gov.

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/s/

NORMA S GRIFFIN
09/19/2012

From: Griffin, Norma
Sent: Monday, September 17, 2012 12:52 PM
To: 'Eric Richards'; Ellen Cutler
Subject: NDAs 204114 and 202806 GSK- Package Insert - SPL Format

Importance: High
For both NDAs, was SPL format labeling submitted for the Prescribing Information (PI)?

Please submit.
Thanks,

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

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/s/

NORMA S GRIFFIN
05/08/2013

From: Griffin, Norma
Sent: Monday, September 17, 2012 9:35 AM
To: 'eric.2.richards@gsk.com'; 'ellen.s.cutler@gsk.com'
Subject: NDAs 202806 and 204114 GSK - Questions from CDRH and BIOMO

Importance: High

Good Morning Ellen/Eric,

I thought I'd start here with you first:

(1) Does GSK have a contract with Response Genetics Institute? CDRH BIMO is trying to determine who would get a letter if FDA inspected RGI.

(2) CDRH has an inspection assignment going to Singapore for the PMA associated with these NDAs. We (CDER) is also sending someone to a drug manufacturing site in Singapore. Can you provide a contact name for someone there that we can speak to?

Thanks 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

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/s/

NORMA S GRIFFIN
05/08/2013

From: Mulinde, Jean
Sent: Friday, September 14, 2012 11:59 AM
To: Griffin, Norma
Cc: Theoret, Marc; Demko, Suzanne
Subject: FW: NDA 202806 IRC charters

Attachments: 201810_Charter_v2.0 (signed) full charter.doc.pdf; 201810 Charter_v1.0_20Jan2011.pdf; 202031_Charter_v2.0.FINAL.PDF; 202031_Charter_v1.0.pdf; 202050_Charter_v1.0_w signature page.pdf

Norma,
In preparing the sponsor assignments for the applications (202806 and 204114) I came across some conflicting information in BIMO info submission and study reports as to location of sponsor's trial related documnents so had called to clarify with the reg contacts. At same time asked if they could direct me to the independent review committee charters referenced in study reports (need them for background package sending to field investigators) -- they were not submitted. They will also be sending the attached into NDA 202806.

(I am waiting to here back from Eric as to my questions on document locations and IRC charters for NDA 204114).
Jean

From: Ellen Cutler [mailto:ellen.s.cutler@gsk.com]
Sent: Friday, September 14, 2012 11:33 AM
To: Mulinde, Jean
Cc: Griffin, Norma; Libeg, Meredith
Subject: NDA 202806 IRC charters

Dr. Mulinde,
Attached are the IRC documents for the radiologic review for studies BRF113683, BRF113929, BRF113710.
(b) (4) BRF113683 Independent Review Charter
BRF113929 Independent Review Charter
BRF113710 Independent Review Charter
These will be submitted to the NDA.

Please let me know if you want the documentation for the independent review of all ECHOs on BRF113710 and select ECHOs on BRF113929 and BRF113683.

Kind regards,
Ellen

Ellen Cutler
Senior Director
Global Regulatory Affairs
GlaxoSmithKline
610-917-6823

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/s/

NORMA S GRIFFIN
05/08/2013

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 [redacted] (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:

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

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.

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 **NDAs** (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)

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/s/

MEREDITH LIBEG
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 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

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 (b) (4)" 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.

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/s/

NORMA S GRIFFIN
09/06/2012

From: Griffin, Norma
Sent: Tuesday, September 04, 2012 3:58 PM
To: 'Ellen Cutler'; Eric Richards
Subject: Question for NDAs 204114 and 202806 - Carton Labeling

Importance: High

Eric/Ellen,

We notice that a carton label has not been submitted for either NDAs (202806 and 204114). Kindly respond to confirm whether a carton label should or should not be included in the NDA submissions.

Regards,

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

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/s/

NORMA S GRIFFIN
09/04/2012

Filing Meeting Summary
August 31, 2012

NDA: 204114

Product:	Mekinist (trametinib)
Submission Date:	August 2, 2012
Received Date:	August 3, 2012
Sponsor:	GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation as detected by an FDA approved test.

Meeting Participants:
Richard Pazdur, M.D., Director, OHOP
Joseph Gootenberg, M.D., Deputy Director, DOP2
Jeff Summers, DOP2 Deputy Director for Safety
Norma Griffin., Regulatory Health Project Manager
Suzanne Demko, Clinical TL and CDTL
Marc Theoret, M.D., Clinical Reviewer
Kun He, Ph.D., Statistics (TL)
Huanyu (Jade) Chen, Statistics
Hong Zhao, Ph.D, Clinical Pharmacology (TL)
Ruby Leong, Clinical Pharmacology
Rosane Charlab-Orbach, Genomics Reviewer
Whitney Helms, Nonclinical (TL)
Gabriel Sachia Khasar, Nonclinical Reviewer
Nallaperumal Chidambaram, Acting Branch Chief
Liang Zhou, Ph.D., Product (TL)
Sue Ching Lin, Product Quality Reviewer
Zhe Jean Tang, Product Quality Reviewer
Jewell Martin, Product (ONDQA RPM)
Minerva Hughes, Biopharmaceutics Reviewer
Mahesh Ramanadham, OC (Facilities)
Derek Smith, OC (Facilities)
Jean Mulinde, OSI Reviewer
Sue Kang, OSE, Safety RPM
James Schlick, OSE Proprietary Name Reviewer
Donna Roscoe, CDRH Consultant
Cathryn Lee, DOP2 Safety RPM

Discussion Items

1. The review team agreed to review this submission as a priority review.
2. A mid-cycle meeting is scheduled for November 1, 2012 (based on a 6-month review clock). Mid-cycle slides are due to CDTL by October 24, 2012.
3. Standing monthly meetings were scheduled for September 2012 – January 2013.
4. Labeling meetings need to be scheduled.
5. Clinical sites have been selected for inspections, inspections are being scheduled.
6. Facility manufacturing site inspections are being scheduled.
7. Possible PMRs: disciplines will determine and may go in the 74-day letter.
8. Disciplines determined application is fileable, however Division Director and CDTL requested that all deficiencies be identified and included in the 74-day letter.
   - Clinical – still need some raw datasets; will request more narratives.
   - STATS – still some issures/concerns
   - ClinPharm – potential PMRs
   - CMC – solubility issue and DMSO
9. Priority Review requested, team agreed to a 6-month clock.
10. Milestone Dates Letters

Milestone	6-month review	Comments
Application Received	**August 3, 2012**	
Acknowledgment Letter		**Issued August 15, 2012**
Filing Action Letter •If the filing issues are not identified, we will need to send a "Notification of Review Status" letter.	**October 2, 2012 (Tuesday)**	
Deficiencies Identified Letter (74 Day Letter)	**October 16, 2012 (Tuesday)**	
Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner's Target date)	Sunday, 1/6/ 2013 therefore **Friday, January 4, 2013**	
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	Sunday, 1/13/ 2013 therefore **Friday, January 11, 2013**	
Review Target Due Dates: ***Primary Review Due*** ***Secondary Review Due*** ***CDTL Review Due*** ***Division Director Review Due*** ***Office Director Review Due/Sign-Off***	 **January 4, 2013** **January 10, 2013** **January 11, 2013** **January 24, 2013** **By February 1, 2013**	
Compile and circulate Action Letter and Action Package	**January 11, 2013**	

Milestone	6-month review	Comments
FINAL Action Letter Due	Sunday, 2/3/ 2013 therefore **Friday, February 1, 2013**	

11. Upcoming Meetings:

- **Applicant Orientation Presentation:** scheduled for Friday, September 7, 2012. Joint meeting with NDA 202806
- **Mid-Cycle Meeting:** per 6-month clock, scheduled for November 1, 2012.
- **Labeling Meetings:** to schedule after mid-cycle; ~2 labeling meetings per week.

  Labeling included: 0.5 mg x 30 Tablets Container Label
  1 mg x 30 Tablets Container Label
  2 mg x 30 Tablets Container Label
  Draft Labeling (PI) with Patient Information Leaflet

- **Team Meetings Scheduled:**

  Team Meeting 1: September 19, 2012
  Team Meeting 2: October 16, 2012
  Team Meeting 3: November 14, 2012
  Team Meeting 4: December 18, 2012
  Team Meeting 5: January 9, 2013

- **PMR/PMC Working Meetings**: To be scheduled as needed
- **Wrap- Up Meeting**: Per 6-month clock, scheduled for January 3, 2013.
- **ODAC Needed/Not Needed:** Not needed - the application did not raise significant safety or efficacy issues.

12. Miscellaneous
- Possible – need input from patient expert.
- Verify if there is a carton label
- No REMS
- Ophthalmology consult request

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/s/

NORMA S GRIFFIN
04/17/2013

Filing Meeting Minutes
August 31, 2012

NDA: 204114

Product:	Mekinist (trametinib)
Submission Date:	August 2, 2012
Received Date:	August 3, 2012
Sponsor:	GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation as detected by an FDA approved test.

Meeting Participants:
Richard Pazdur, M.D., Director, OHOP
Patricia Keegan, M.D., Director, DOP2
Joseph Gootenberg, M.D., Deputy Director, DOP2
Norma Griffin., Regulatory Health Project Manager
Suzanne Demko, Clinical TL and CDTL
Marc Theoret, M.D., Clinical Reviewer
Kun He, Ph.D., Statistics (TL)
Huanyu (Jade) Chen, Statistics
Hong Zhao, Ph.D, Clinical Pharmacology (TL)
Ruby Leong, Clinical Pharmacology
Rosane Charlab-Orbach, Genomics Reviewer
Whitney Helms, Nonclinical (TL)
Gabriel Sachia Khasar, Nonclinical Reviewer
Nallaperum Chidambaram, Acting Branch Chief
Liang Zhou, Ph.D., Product (TL)
Sue Ching Lin, Product Quality Reviewer
Zhe Jean Tang, Product Quality Reviewer
Jewell Martin, Product (ONDQA RPM)
Minerva Hughes, Biopharmaceutics Reviewer
Mahesh Ramanadham, OC (Facilities)
Derek Smith, OC (Facilities)
Jean Mulinde, OSI Reviewer
Sue Kang, OSE, Safety RPM
James Schlick, OSE Proprietary Name Reviewer
Donna Roscoe, CDRH Consultant
Jeff Summers, DOP2 Deputy Director for Safety
Cathryn Lee, DOP2 Safety RPM

Discussion Items

1. **Reminder** - all team members should notify the RPM, the CDTL, their team leader and other team members as soon as issues arise during the review process, instead of waiting until the next scheduled meeting to discuss.
2. The review team agreed to review this submission as a priority review.
3. A mid-cycle meeting was scheduled for November 1, 2012 (based on a 6-month review clock). Mid-cycle slides are due to CDTL by October 24, 2012
4. Standing monthly meetings were set up from September 2012 – January 2013.
5. Labeling meetings need to be scheduled.
6. Clinical sites have been selected for inspections, inspections are being scheduled.
7. Facility manufacturing site inspections are being scheduled.
8. Possible PMRs: disciplines will determine and may go in the 74-day letter.
9. Disciplines determined application is fileable, however Division Director and CDTL requested that all deficiencies be identified and included in the 74-day letter.

Review Status

- Priority Review requested, team agreed to a 6-month clock
- Orphan Drug Exclusivity – December 20, 2010
- Fast Track Designation granted – June 29 2012
- 5-Year (New Chemical Entity) Exclusivity
- Requested full waiver of pediatric studies
- Proprietary Name Request – submitted in first part of rolling submission of July 2, 2012 – DMEPA requesting comments/concerns
- BioMerieux Letter of Authorization to cross reference IDE G120011 for the THxID BRAF assay – letter dated June 29, 2012 submitted in Part 1 of rolling submission of July 2, 2012.
- Received (on 8.29.2012) Letter of Authorization to cross reference PMA of the companion diagnostic to NDAs 204114, 202806, (b) (4).
- Categorical Exclusion requested July 2, 2012 in the Part 1 submission
- Risk Management Plan
- The clinical development of trametinib has been conducted under IND 102175.

Milestone Dates Letters

Milestone	6-month review	Comments
Application Received	**August 3, 2012**	
Acknowledgment Letter		**Issued August 15, 2012**
Filing Action Letter •If the filing issues are not identified, we will need to send a "Notification of Review Status" letter.	**October 2, 2012** **(Tuesday)**	
Deficiencies Identified Letter (74 Day Letter)	**October 16, 2012** **(Tuesday)**	
Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner's Target date)	Sunday, 1/6/ 2013 therefore **Friday, January 4, 2013**	
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	Sunday, 1/13/ 2013 therefore **Friday, January 11, 2013**	
Review Target Due Dates: ***Primary Review Due*** ***Secondary Review Due*** ***CDTL Review Due*** ***Division Director Review Due*** ***Office Director Review Due/Sign-Off***	 **January 4, 2013** **January 10, 2013** **January 11, 2013** **January 24, 2013** **By February 1, 2013**	
Compile and circulate Action Letter and Action Package	**January 11, 2013**	
FINAL Action Letter Due	Sunday, 2/3/ 2013 therefore **Friday, February 1, 2013**	

Upcoming Meetings:

- **Applicant Orientation Presentation:** Scheduled for Friday, September 7, 2012. Joint meeting with NDA 202806

- **Mid-Cycle Meeting:** Per 6-month clock, scheduled for November 1, 2012.

  Note: Need Mid-Cycle slides to CDTL by October 24, 2012

- **Labeling Meetings (suggested section groupings): When should we begin labeling meetings?** After mid-cycle; plan to have ~2 labeling meetings per week.

  a. _____TBD__ (Clinical Sections: Indications and Usage, Adverse Reactions, Warnings and Precautions)
  b. _____TBD__ (Clinical Sections: Dosage and Administration, Clinical Studies, Drug Interactions, Use in Specific Populations, Overdosage, Contraindications, References)

  c. _____TBD__ (Dosage Forms and Strengths, Description, How Supplied/Storage and Handling, Nonclinical Sections, Clinical Pharmacology, Nonclinical Toxicology)

  **Include OSE/CMC during this labeling meeting to review carton and container.

  d. _____TBD__ (Highlights, Indications and Usage, Patient Counseling Information)
  e.

  Labeling included: 0.5 mg x 30 Tablets Container Label
  1 mg x 30 Tablets Container Label
  2 mg x 30 Tablets Container Label
  Draft Labeling (PI) with Patient Information Leaflet

- **Team Meetings**

  Team Meeting 1: September 19, 2012
  Team Meeting 2: October 16, 2012
  Team Meeting 3: November 14, 2012
  Team Meeting 4: December 18, 2012
  Team Meeting 5: January 9, 2013

- **PMR/PMC Working Meetings**: To be scheduled

- **Wrap- Up Meeting**: Per 6-month clock, scheduled for January 3, 2013.

ODAC Needed/Not Needed: Not needed

If not needed, for an original NME or BLA application, include the reason in the RPM filing review memo. For example:

- ***this drug/biologic is not the first in its class***
- ***the clinical study design was acceptable***
- ***the application did not raise significant safety or efficacy issues***
- ***the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease***

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/s/

NORMA S GRIFFIN
10/02/2012

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

Memorandum

Date: August 29, 2012

From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA

Subject: NDA 204114; GlaxoSmithKline, LLC
Information Request

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

Dear Eric:

Please refer to your New Drug Application (NDA) NDA 204114 for Mekinist (trametinib)."

We are reviewing your NDA 204114 submission and our Pharmacometrics Reviewer has the following comments and request for information. Please provide a response by close of business, Friday, August 31, 2012.

1. For your report named "POPULATION PHARMACOKINETICS OF TRAMETINIB IN SUBJECTS WITH CANCER (PROTOCOLS MEK111054, MEK113583, AND MEK114267)", the data items in NMGSK.XPT (NONMEM data file included in submission) are not consistent with those specified in the NONMEM control stream included in your report (PDF format). Please submit NONMEM dataset, control stream and scripts of exploration/diagnostics for base and final popPK model as TXT format.

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

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/s/

NORMA S GRIFFIN
08/29/2012

Initial Planning Meeting Summary
August 15, 2012

NDA: 204114

Product: Mekinist (trametinib)
Submission Date: August 2, 2012
Received Date: August 3, 2012
Sponsor: GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation as detected by an FDA approved test.

Meeting Participants:
Patricia Keegan, M.D., Director DOP2
Karen Jones (CPMS), DOP2
Norma Griffin., Regulatory Health Project Manager
Suzanne Demko, Medical Officer (Acting TL)
Marc Theoret, M.D., Medical Officer (Efficacy Review)
Kun He, Ph.D., Statistics (TL)
Hong Zhao, Ph.D, Clinical Pharmacology (TL)
Whitney Helms, Non-Clinical (TL)
Gabriel Sachia Khasar, Non-Clinical
Nallaperum Chidambaram, Acting Branch Chief
Liang Zhou, Ph.D., Product (TL)
Jewell Martin, Product (ONDQA RPM)
Minerva Hughes, Biopharmaceutics Reviewer
Mahesh Ramanadham, OC (Facilities)
Sue Kang, OSE, Safety RPM
Jeff Summers, Deputy Director for Safety, DOP2
Anthony Murgo, Associate Director for Regulatory Science, OHOP

Discussion Items:

1. The following review status items were discussed:
   - Priority Review requested - discussion for expedite review clock with action goal date of February 3, 2013 – to be discussed further.
   - Orphan Drug Exclusivity – January 12, 2011
   - Fast Track Designation granted – February 11, 2011
   - 5-Year (New Chemical Entity) Exclusivity
   - Requested full waiver of pediatric studies
   - Proprietary Name Request – April 13, 2012 conditional acceptance of proposed proprietary name (b) (4) Request also included in the July 30, 2012 submission.
   - BioMerieux Letter of Authorization to cross reference IDE G120011 for the THxID BRAF assay – June 29, 2012
   - Categorical Exclusion requested July 12, 2012
   - Risk Management Plan
   - The clinical development of dabrafenib has been conducted under IND 105025.

2. Milestone Dates for 6-month priority review clock:

Milestone	6-month review
Application Received	**August 3, 2012**
Acknowledgment Letter	**Issued August 15, 2012**
Filing Action Letter •Do we have any filing issues that we should discuss today? •Do we need to have teleconference with the Applicant before the filing meeting? •If the filing issues are not identified, we will need to send a "Notification of Review Status" letter.	**October 2, 2012 (Tuesday)**
Deficiencies Identified Letter (74 Day Letter)	**October 16, 2012 (Tuesday)**
Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner's Target date)	**January 6, 2013 (Sunday)**
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	**January 13, 2013 (Sunday)**
Review Target Due Dates: ***Primary Review Due*** ***Secondary Review Due*** ***CDTL Review Due*** ***Division Director Review Due*** ***Office Director Review Due/Sign-Off***	 **January 6, 2013** **January 10, 2013** **January 13, 2013** **January 24, 2013** **By February 3, 2013**
Compile and circulate Action Letter and Action Package	**January 13, 2013 (Sunday)**
FINAL Action Letter Due	**February 3, 2013 (Sunday)**

3. Potential Consults/Collaborative Reviewers:

OPDP	????- professional reviewer ????- consumer reviewer Olga Salis – RPM Consult to be sent -
OSE	Sue Kang-OSE RPM Sean Bradley-OSE RPM TL DRISK assigned to review Risk Management Plan Cynthia LaCivita (TL) DMEPA to review Proprietary Name Todd Bridges (TL) James Schlick DMEPA/CMC/DDMAC to review carton/container, and patient labeling DPV – Bob Pratt (TL) – invite to mid-cycle and wrap up or as requested by Team DEPI – Cunlin Wang (TL) – invite to mid-cycle and wrap up or as requested by Team

Maternal Health	Consult to be sent -
QT-IRT	**ClinPharm requested QT-IRT consult on 8.14.2012
OSI	Jean Mulinde/Paul Okwesili
Pediatric Page/PeRC	Full Waiver Requested
Patient Labeling Team	Patient Information Leaflet included
SEALD	Consult to be sent -
CDRH	Donna Roscoe; (others Reena Philip, Yun-Fu, Hu, Maria Chan, Elizabeth Mansfield, Robert Becker) Tamika Allen (BIMO Reviewer)
SGE's or Patient Representatives	Consult to be sent if needed

4. Upcoming/TBD Internal Team Meetings:

- **Filing Meeting:** August 31, 2012.
- **Mid-Cycle Meeting:** Per 6-month clock, November 1, 2012.
- **Labeling Meetings** to be scheduled soon after mid-cycle (mid-November). Suggested section groupings:
  a. Labeling Mtg 1 - (Clinical Sections: Indications and Usage, Adverse Reactions, Warnings and Precautions)
  b. Labeling Mtg 2 - (Clinical Sections: Dosage and Administration, Clinical Studies, Drug Interactions, Use in Specific Populations, Overdosage, Contraindications, References)
  c. Labeling Mtg 3 - (Dosage Forms and Strengths, Description, How Supplied/Storage and Handling, Nonclinical Sections, Clinical Pharmacology, Nonclinical Toxicology)
  **Include OSE/CMC during this labeling meeting to review carton and container.
  d. Labeling Mtg 4 - (Highlights, Indications and Usage, Patient Counseling Information)
  e. Labeling Mtg 5 – as needed

  Labeling included: 0.5 mg x 30 Tablets Container Label
  1 mg x 30 Tablets Container Label
  2 mg x 30 Tablets Container Label
  Draft Labeling with Patient Information Leaflet

- **Team Meetings** scheduled monthly.
- **PMR/PMC Working Meetings** scheduled as needed.
- **Wrap- Up Meeting**: Per 6-month clock, January 3, 2013.
- **Applicant Orientation Presentation:** Scheduled for Friday, September 7, 2012.
- **ODAC Needed/Not Needed?**
  If needed, target AC date: December 2012-January 2013 (month 4-5)

5. Miscellaneous Items:

a. OSI inspections are needed. OSI held an initial meeting with clinical/stats reviewers on Thursday, August 8, 2012 for discussion to pick the sites that will be inspected.

*No preclinical study site Audits are needed.

b. CMC/Jewell Martin will assist with the following consults:
- Establishment (EES)/Coordinate Inspections
- Environmental Analysis: Request for Categorical Exclusion
- Labeling

c. August 13, 2012 teleconference with GSK to discuss clinical and statistical concerns regarding the submission. GSK agreed to provide updated information including commitment plan regarding datasets, statistical codes, etc. The plan is expected to be submitted by August 15, 2012 with the remainder of the information within 3 weeks (by September 3, 2012).

d. Meeting between CDRH and Sponsor regarding the PMA associated with this application - it was learned that GSK did not provide CDRH with the raw data for the PMA, but when asked about it, the data was provided.

e. Cross reference letters to the NDA submitted in the PMA to reference **NDA 204114** on behalf of a Pre-Market Application (PMA) to be submitted by bioMerieux for the THxID-BRAFkit.

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/s/

NORMA S GRIFFIN
04/17/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204114

NDA ACKNOWLEDGMENT

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

Dear Mr. Richards:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Mekinist (trametinib) tablets, 0.5 mg, 1.0 mg, 2.0 mg

Date of Application: August 2, 2012

Date of Receipt: August 3, 2012

Our Reference Number: NDA 204114

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 2, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

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

Sincerely,

{See appended electronic signature page}

Karen D. Jones
Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

KAREN D JONES
08/15/2012

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: Norma 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.

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/s/

NORMA S GRIFFIN
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 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" [redacted] (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.

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/s/

NORMA S GRIFFIN
08/13/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 204114

NDA PRESUBMISSION ACKNOWLEDGEMENT

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

Dear Mr. Richards:

We have received the first section of your New Drug Application (NDA) under the program for step-wise submission of sections of an NDA (section 506 of the Federal Food, Drug, and Cosmetic Act) for the following:

Name of Drug Product: trametinib tablet; 0.5 mg, 1 mg, and 2 mg

Date of Submission: July 2, 2012

Date of Receipt: July 2, 2012

Our Reference Number: NDA 204114

We will review this presubmission as resources permit. Presubmissions are not subject to a review clock or to a filing decision by FDA until the application is complete.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

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

Sincerely,

{See appended electronic signature page}

Karen D. Jones
Chief, Project Management Staff
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

KAREN D JONES
07/20/2012

From: Griffin, Norma
Sent: Thursday, July 19, 2012 4:04 PM
To: 'eric.2.richards@gsk.com'
Cc: 'ellen.s.cutler@gsk.com'
Subject: NDA 204114 GSK for "Trametinib" - Request for Establishment Information

Importance: High

Attachments: Dabrafenib establishment-info.pdf

Good Afternoon Eric,

For the Dabrafenib NDA (202806), the attached Establishment Information was submitted in the first part of the rolling submission.

Dabrafenib
establishment-info...

Was the same submitted for the Trametinib? Did I overlook it? If it was not included, could you please provide the same for the Trametinib NDA?

PS - Did you receive my email regarding OSI comments and the revised datasets?

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

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/s/

NORMA S GRIFFIN
07/19/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102175

MEETING MINUTES

GlaxoSmithKline LLC
Attention: Dorothea Roberts, Assistant Director
Global Pre-Approval, CMC Regulatory Affairs
PO Box 13398, Bldg 14.1130F
5 Moore Drive
Research Triangle Park, NC 27709

Dear Ms. Roberts:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GSK1120212 MEK1/2 Inhibitor.

We also refer to the teleconference between representatives of your firm and the FDA on Wednesday, February 15, 2012. The purpose of the meeting was to discuss the chemistry, manufacturing, and controls for GSK1120212.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Senior Regulatory Health Project Manager for
Product Quality
Center for Drug Evaluation and Research
Office of New Drug Quality Assessment
Food and Drug Administration

ENCLOSURE: Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA Chemistry, Manufacturing, and Controls (CMC) Guidance Meeting
Meeting Date and Time:	Wednesday, February 15, 2012, 1100 – 1200 ET
Meeting Location:	Teleconference
Application Number:	IND 102175
Product Name:	GSK1120212 MEK1/2 Inhibitor
Indication:	Treatment of Subjects with Solid Tumors or Lymphoma
Sponsor/Applicant Name:	GlaxoSmithKline LLC (GSK)
Meeting Chair:	Richard T Lostritto, Ph.D.
Meeting Recorder:	Scott N. Goldie, Ph.D.

FDA ATTENDEES

Janice Brown, Ph.D.	CMC Lead, Branch II
Debasis Ghosh Ph.D.	Quality Reviewer, Branch II
Scott N. Goldie, Ph.D.	Senior Regulatory Health Project Manager for Product Quality
Richard T Lostritto, Ph.D.	Director, Division I
Jewell D. Martin, MA, MBA, PMP	Product Quality Regulatory Project Manager
Minerva Hughes, Ph.D.	Biopharmaceutics Reviewer
Liang Zhou, Ph.D.	CMC Lead, Branch II

SPONSOR ATTENDEES

Richard Ward, Ph.D.	Director, API Chemistry and Analysis
Al Kearney, Ph.D.	Vice President, Product Development
Choon Oh, Ph.D.	Director, Product Development
Francisco Henriquez	Senior Scientific Investigator, Product Development
Lihong Wang	Investigator, Product Development
Manish Gupta, Ph.D.	Quality by Design Lead, Product Development
Jeff Brum, Ph.D.	Manager, Physical Properties
Sander van den Ban, MSc.	Dose Form Leader, Global Manufacturing and Supply
Kevin Miller Director	Global Regulatory Affairs, CMC Pre-Approval
Dorothea Roberts	Assistant Director, Global Regulatory Affairs, CMC Pre-Approval

1.0 BACKGROUND

GSK1120212, a potent and selective inhibitor of MEK1 and MEK2 activation and kinase activity, is under development for the treatment of patients with BRAF V600E/K [redacted] (b) (4) metastatic melanoma. Reference is made to the Pre-NDA meeting request submitted on November 17, 2011 (Serial No. 0241, Sequence No. 0240). Reference is also made to the EOP1/Pre-Phase 3 Briefing Document (IND 102,175 Serial No. 0130) and subsequent teleconference on November 9, 2010, and the advice provided during those discussions. Preliminary responses to the questions contained in the briefing package were sent to GSK on February 10, 2012. The meeting discussion and the slides submitted by GSK to facilitate the discussion are recorded below.

2.0 DISCUSSION

2.1. Drug Substance Questions:

Question 1: GSK proposes to include proven acceptable ranges (PAR) for critical process parameters (CPP) and other relevant process parameters for completeness in the registered process description in m3.2.S.2.2 of the NDA. Information and data to justify these designations will be provided in m3.2.S.2.6. Future changes to PARs for CPPs will be filed in conformance with post-approval regulations and guidance. Future changes to the values or ranges of the other relevant process parameters are considered minor change and will be filed via the Annual Report. Does the Agency agree with this approach?

FDA Response to Question 1: **Your approach to drug substance process development is reasonable. Use ICHQ8, Q9 and Q10 principles to describe the process understanding in Section 3.2.S.2.6. Include a detailed regulatory process description in Section 3.2.S.2.2 including operating ranges for all process variables including non-critical process parameters. Please note that the reporting mechanism for future changes of process variables will be determined at the time of NDA review.**

Discussion: GSK acknowledged receipt of FDA's response. No further discussion occurred during the teleconference.

Question 2: GSK propose [redacted] (b) (4) as a registered starting material for the manufacture of trametinib dimethyl sulfoxide. Does the Agency agree with this proposal?

FDA Response to Question 2: **Your proposal appears reasonable.** [redacted] (b) (4) **may be acceptable as a starting material. However, the adequacy of the information required for a regulatory starting material will be determined at the time of NDA review.**

Discussion: GSK acknowledged receipt of FDA's response. No further discussion occurred during the teleconference.

FDA Additional Comments:
In the NDA provide the following information for any proposed starting materials:

- Impurity profile
- In-house acceptance criteria and Vendor's Certificate of Analysis
- Brief description of synthetic strategies and methods to manufacture
- Detailed discussion on carry-forward impurities
- Controls and Analytical methods to separate and measure appropriate impurities
- Supplier information for the starting materials used to manufacture
- Detailed discussion on purging studies using impurities to demonstrate the ability of the manufacturing process to remove and control the impurities to the desired levels
- Change of control strategies for any potential revisions to the manufacture of proposed starting materials including the vendor's reporting of any changes in starting material specification or controls
- Supportive literature data if available

Discussion: GSK acknowledged receipt of FDA's response. No further discussion occurred during the teleconference.

Question 3: Does the Agency agree that the testing proposed will suitably control the quality of the starting material [redacted] (b) (4) and support an appropriate control strategy for the NDA?

***FDA Response to Question 3*:** **Your plan appears reasonable. However, the adequacy of the plan will be determined at the time of NDA review.**

Discussion: GSK acknowledged receipt of FDA's response. No further discussion occurred during the teleconference.

FDA Additional Comments: Since [redacted] (b) (4) was used as one of the solvents in the preparation of the starting material [redacted] (b) (4) provide residual amount of [redacted] (b) (4) as one of the quality attributes in the acceptance criteria of [redacted] (b) (4) or justify.

Discussion: GSK acknowledged receipt of FDA's response. No further discussion occurred during the teleconference.

Question 4: The potential genotoxin [redacted] (b) (4) has been demonstrated to be controlled in the synthetic process to levels well below the TTC in batches of the intermediate grade drug substance. Control of this impurity has additionally been demonstrated for the process operated at the extremes of the [redacted] (b) (4) operating spaces, and in batches spiked with the impurity at elevated levels. GSK therefore propose not to specify [redacted] (b) (4) in either the intermediate grade or final drug substance specifications.

Furthermore, given the control outlined for the [redacted] (b) (4) specified impurities [redacted] (b) (4), the consideration given to potential for their formation in the synthetic process and demonstration [redacted] (b) (4) to below the TTC, GSK propose not to include any additional downstream controls for these impurities in the synthetic route.

Does the Agency agree with these proposals?

***FDA Response to Question 4*:** **Your approach is reasonable based on the information you have included in the briefing package. However, the final determination will be made at the time of NDA review based on the data submitted.**

Discussion: GSK acknowledged receipt of FDA's response. No further discussion occurred during the teleconference.

Question 5: Does the Agency agree that the primary NDA stability package for trametinib dimethyl sulfoxide described in the briefing document will support filing of the NDA?

***FDA Response to Question 5*:** **Your plan appears reasonable. A filing decision will be made at the time of NDA receipt. If the stability data from three production batches are not available at the time of NDA submission, provide a post approval stability commitment as per ICHQ1A(R2).**

Discussion: GSK acknowledged receipt of FDA's response. No further discussion occurred during the teleconference.

2.2. Drug Product:

Question 6: Does the Agency agree that the proposed dissolution method and specification is suitable for controlling the quality of commercial Trametinib Tablets?

***FDA Response to Question 6*:** **The information provided in your briefing package suggests that the proposed dissolution method may provide a reasonable approach for product quality control. However, to complete the evaluation of your proposed method under the IND, provide complete details for each condition tested (method, sample size, individuals, mean, min, max, and RSD) in your development report to allow for a meaningful interpretation of the results, and provide the analytical method validation report. Note that the final determination on the acceptability of your proposed dissolution specification will be made during the NDA review and it will be based on the overall dissolution profile data from the bio-batches (clinical/PK) and primary stability batches.**

In addition, your report indicates that [redacted] (b) (4) for product dissolution. Therefore, to justify the proposed DMSO ranges and support setting a clinically relevant specification, provide in vivo bioavailability data on the effects of drug-DMSO desolvation within the proposed ranges.

Discussion: GSK acknowledged receipt of FDA's response and referred to slides 9–11 in Section 6.0 to facilitate the discussion. FDA stated that the dissolution specification is a review issue based on data included in the NDA, and referred to the preliminary response comments regarding additional information requested for inclusion in the dissolution method development report. GSK proposed submission of updated dissolution development report to the NDA. FDA acknowledged the NDA submission time line as reflected in slide 12 and agreed with the approach to include the revised method development report in the NDA submission for review and evaluation.

Question 7: Does the Agency agree with GSK's proposed acceptance criteria for DMSO content in Trametinib Tablets?

***FDA Response to Question 7*:** **Provide a justification for the proposed acceptance criteria for DMSO content in drug product in the NDA. Your justification should provide a detailed safety assessment based on the proposed maximum daily dose and an evaluation of any known or expected drug bioavailability issues within the proposed content limits.**

Discussion: GSK acknowledged receipt of FDA's response and referred to slides 3-8 (Section 6.0) to facilitate the discussion. GSK acknowledged that [redacted] (b) (4) [redacted] (b) (4) for drug product dissolution. Based on FDA's preliminary feedback, GSK proposed to change the lower limit of DMSO content from [redacted] (b) (4) which provided for a new acceptance range of [redacted] (b) (4) to 12.5%. The justification for the new specification was based on comparative dissolution data of samples from a single clinical batch with DMSO content ranging from [redacted] (b) (4) a drug product designation of Class 1 (highly soluble, highly permeability) using the Developability Classification System (DCS), and bioavailability and pharmacokinetic data to be provided in the NDA. GSK further clarified that bioequivalence studies were not performed to qualify the proposed DMSO content ranges.

FDA noted that the Biopharmaceutics Classification System (BCS) is the current standard for granting a Class 1 designation of highly soluble and highly permeable. GSK stated that they do not plan to seek a BCS Class 1 designation. However, the DCS Class 1 information was included as supportive data for the proposed DMSO content specification. FDA acknowledged that GSK's rationale provided some support for the proposed specification, the adequacy of which will be determined during the NDA review. FDA expressed concern about the impact of DMSO desolvation on bioavailability and product quality, and recommended the following additional information in the NDA to support setting an appropriate specification:

- DMSO content for clinical trial material at the time of administration to subjects to account for any changes after storage for product used in studies.
- API solubility in DMSO and rationale for its use in the drug product.
- Data verifying that DMSO is incorporated into the [redacted] (b) (4) and a discussion about the potential for changes in physico-chemical properties with different amounts of DMSO [redacted] (b) (4)
- Safety assessment for the proposed upper limit for DMSO content.

GSK acknowledged FDA's request and committed to providing [redacted] (b) (4) XRD data, other relevant physico-chemical characterization information, and complete details on DMSO content in clinical trial material in the NDA.

Question 8: As discussed with the Agency at the EOP1/Pre-Phase 3 meeting, GSK has included [redacted] (b) (4) in the stability program. GSK has assessed the data and propose not to include [redacted] (b) (4) at release or on stability for commercial product. [redacted] (b) (4) will continue to be monitored as an in-process control during the [redacted] (b) (4). Does the Agency agree with this proposal?

***FDA Response to Question 8*:** **No, it is premature at this time to** [redacted] (b) (4) **at drug product batch release. If you propose the** [redacted] (b) (4) **at drug product batch release in the initial NDA submission, provide sufficient scientific justification in the NDA, including data to demonstrate process understanding. The adequacy of this approach will be determined during the NDA review.**

Discussion: GSK acknowledged receipt of FDA's response. No further discussion occurred during the teleconference.

Question 9: In consideration of the cGMP manufacturing of the product, the [redacted] (b) (4) of Trametinib Tablets, and [redacted] (b) (4) results observed on stability, does the Agency agree with the proposal [redacted] (b) (4) in the commercial specification for Trametinib Tablets?

***FDA Response to Question 9*:** **See the response to Question 4.**

Discussion: GSK acknowledged receipt of FDA's response. No further discussion occurred during the teleconference.

Question 10: Does the Agency agree that the primary NDA stability package for Trametinib Tablets described in the briefing document will support filing of the NDA?

***FDA Response to Question 10*:** **Yes, your proposal to include 12 months of stability data from 3 primary batches of each strength and packaging configuration at the time of NDA submission is acceptable. If the stability data from three production batches are not available at the time of NDA submission, provide a post approval stability commitment as per ICHQ1A(R2). A filing decision will be made at the time of NDA receipt.**

Discussion: GSK acknowledged receipt of FDA's response. No further discussion occurred during the teleconference.

Question 11: Does the Agency agree that commercial doses of 1 mg and (b) (4)

***FDA Response to Question 11*:** **A 0.5 mg trametinib tablet may be used to achieve a 1 mg (b) (4) provided that there are sufficient clinical and pharmacokinetic data in your NDA to evaluate the proportionality of the dose response over the 0.5 mg to 2.0 mg range and (b) (4) are bioequivalent to a single dose of equivalent strength. Your NDA should include all relevant bioavailability/bioequivalence information, in addition to data demonstrating comparative dissolution performance. We note that you have requested another Type B meeting with the Agency (letter date of 31 January 2012) to discuss the adequacy of your clinical package to support an NDA filing. You may also consider raising your question of dosing strategy at that meeting, if granted, to identify any other Agency concerns.**

Discussion: GSK acknowledged receipt of FDA's response. GSK referred to slides 13–15 in Section 6.0 to facilitate the discussion. FDA's meeting participants indicated that (b) (4) is not strictly a CMC issue, but requires input from the other members of the review team, specifically, the clinical and clinical pharmacology teams. FDA recommended that GSK raise the issue of dosing strategy during the April, 2012 meeting scheduled with the Division.

2.3. ADDITIONAL FDA COMMENTS:

- Include Heavy Metals as one of the quality attributes of drug substance.
- Provide justification for the acceptance criteria of DMSO in drug substance.
- Since the proposed commercial manufacturing process (b) (4)

Discussion: GSK acknowledged receipt of FDA's response. No further discussion occurred during the teleconference.

2.4. MANUFACTURING FACILITIES:

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Discussion: GSK acknowledged receipt of FDA's response. No further discussion occurred during the teleconference.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no specific issues requiring further discussion at this time.

4.0 ACTION ITEMS

There are no specific due dates or time lines for submission of information or other action items. General agreements and commitments are included in the Discussion section (2.0) above.

5.0 CONCURRENCE:

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Senior Regulatory Health Project Manager for Product Quality
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

{See appended electronic signature page}

Richard T Lostritto, Ph.D.
Director
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

6.0 ATTACHMENTS AND HANDOUTS

The attached slides were submitted by GSK to facilitate the discussion during the meeting. These slides are referred to in the Discussion Section (2.0) above.

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

/s/

JEWELL D MARTIN
03/02/2012
on behalf of Scott Goldie

RICHARD T LOSTRITTO
03/02/2012

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

GlaxoSmithKline LLC
Attention: Kathleen Church, Assistant Director
CMC Regulatory Affairs
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Dear Ms. Church:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GSK2118436 (BRAF Inhibitor).

We also refer to the teleconference between representatives of your firm and the FDA on Tuesday, January 31, 2012. The purpose of the meeting was to discuss your pre NDA Chemistry, Manufacturing and Controls (CMC) package.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any *significant* differences in understanding regarding the meeting outcomes.

If you have any questions, call Jewell Martin at (301) 796-2072.

Sincerely,

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Senior Regulatory Health Project Manager for Product Quality
Office of New Drug Quality Assessment
Office of Pharmaceutical Science
Center for Drug Evaluation and Research
Food and Drug Administration

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	pre-NDA CMC Guidance
Meeting Date and Time:	Tuesday, January 31, 2012, 1100 ET
Meeting Location:	Teleconference
Application Number:	IND 105032
Product Name:	GSK2118436 (BRAF Inhibitor)
Indication:	Treatment of patients with BRAF V600E mutation positive advanced or metastatic melanoma
Sponsor/Applicant Name:	GlaxoSmithKline, LLC
Meeting Chair:	Sarah Pope Miksinski, Ph.D.
Meeting Recorder:	Scott N. Goldie, Ph.D.

FDA ATTENDEES

Tapash Ghosh, Ph.D.	Biopharmaceutics Reviewer
Scott N. Goldie, Ph.D.	Senior Regulatory Health Project Manager for Product Quality
Sue Ching Lin, M.S, R.Ph.	Product Quality Reviewer
Sarah Pope Miksinski, Ph.D.	Branch Chief
Liang Zhou, Ph.D.	CMC Team Leader

SPONSOR ATTENDEES

Giselle Limentani, PhD,	Director, Product Development
Girish Pande, PhD,	Manager, Product Development
Kevin Lan, PhD,	Senior Scientific Investigator, Product Development
Lara Knowles,	Investigator, Product Development
Leon Zhou, PhD,	Senior Scientific Investigator, Synthetic Chemistry
Steve Goodman, PhD,	Senior Scientific Investigator, Synthetic Chemistry
James Wertman,	Investigator, Synthetic Chemistry
Kendal Pitt, PhD,	Director, Global Manufacturing and Supply
Kathleen Church,	Assoc. Director, CMC Regulatory Affairs
Jim Zisek	Director, CMC Regulatory Affairs
Dr. Rachel Forcino	Investigator, Product Development

1.0 BACKGROUND

The purpose of this Chemistry, Manufacturing and Controls (CMC) briefing package is to provide information for the CMC pre-NDA meeting for Dabrafenib (GSK2118436) Capsules (IND 105,032). Reference is made to the CMC pre-NDA meeting request submitted on November 17, 2011 (Serial No. 0226, Sequence No. 0227). GlaxoSmithKline is studying GSK2118436 for the treatment of patients with V600 mutation positive unresectable or metastatic melanoma. The purpose of this Type B Chemistry, Manufacturing and Controls Guidance pre NDA meeting is to discuss with the Agency the proposed starting materials and stability information package supporting the planned NDA.
Meeting Chronology: Meeting requested 17 November 2010 (Meeting 032726 SD-233); Meeting granted 04 January 2012; Briefing package submitted 22 December 2011 (SD-143); Preliminary responses sent 30 January 2012; Teleconference held as scheduled on 31 January 2012.

2.0 DISCUSSION

2.1. Drug Substance Questions:

Question 1: The drug substance synthesis was developed using Quality by Design concepts. The control strategy, which will be provided in detail in the NDA, is based on controlling the variables that impact drug substance CQAs, which will be justified by extensive process knowledge.

Question 1a: GSK proposes to include proven acceptable ranges (PAR) for critical process parameters (CPP) and other relevant process parameters for completeness in the registered process description in m3.2.S.2.2 of the NDA. Information and data to justify these designations will be provided in m3.2.S.2.6. Future changes to PARs for CPPs will be filed in conformance with post-approval regulations and guidance. Future changes to the values of other relevant process parameters are considered minor change and will be filed via the Annual Report. Does the Agency agree with this approach?

FDA Response to Question 1a: Your approach to drug substance process development is reasonable. Use ICHQ8, Q9 and Q10 principles to describe the process understanding in Section 3.2.S.2.6. Include detailed regulatory process description in Section 3.2.S.2.2 providing operating ranges for all process variables including non-critical process parameters. Please note that the reporting mechanism for future changes of process variables will be determined at the time NDA review.

Discussion: GSK acknowledged receipt of FDA's response. No further discussion occurred during the teleconference.

b. GSK proposes (b) (4)

***FDA Response to Question 1b*:** It is acceptable (b) (4) will be determined during NDA review.

Discussion: GSK acknowledged receipt of FDA's response. No further discussion occurred during the teleconference.

Question 2: All genotoxic impurities related to the manufacturing process for dabrafenib mesylate are well purged to a level below TTC from the process and are extremely low risk.

Question 2a: (b) (4)

***FDA Response to Question 2a*:** Your approach is reasonable based on the information you have included in the briefing package. However, the final determination will be made at the time of NDA review based on the data submitted.

Discussion: GSK acknowledged receipt of FDA's response. No further discussion occurred during the teleconference.

Question 2b: (b) (4)

***FDA Response to Question 2b*:** Same as 2a

Discussion: GSK acknowledged receipt of FDA's response. No further discussion occurred during the teleconference.

Question 2c: (b) (4)

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***FDA Response to Question 2c*:** Same as 2a

Discussion: GSK acknowledged receipt of FDA's response. No further discussion occurred during the teleconference.

Question 2d: (b) (4)

***FDA Response to Question 2d*:** Same as 2a

Discussion: GSK acknowledged receipt of FDA's response. No further discussion occurred during the teleconference.

Question 2e: (b) (4)

***FDA Response to Question 2e*:** Same as 2a

Discussion: GSK acknowledged receipt of FDA's response. No further discussion occurred during the teleconference.

Question 3: Based on an understanding of the synthesis, and in consideration of regulatory guidance, the proposed specification tests and specification limits provide appropriate control of the quality of dabrafenib mesylate. Does the Agency agree with the proposed specification tests and limits?

FDA Response to Question 3: Provide scientific justification for the proposed acceptance criterion of [redacted] (b) (4) in the NDA. The adequacy of the justification will be a review issue.

Your proposals to [redacted] (b) (4) will be evaluated during NDA review based on the data and justification submitted.

Discussion: GSK acknowledged receipt of FDA's response. No further discussion occurred during the teleconference.

Question 4: [redacted] (b) (4)

FDA Response to Question 4: No, the Agency does not agree with the proposed testing intervals (Table 27 on page 67) for [redacted] (b) (4) and does not conform with ICH Q1A. The testing interval should be the same as that for the primary batches (i.e., every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf life).

Discussion: GSK acknowledged receipt of FDA's response. No further discussion occurred during the teleconference.

2.2. Drug Product Questions:

Question 5: Based on an understanding of the manufacturing of Dabrafenib Capsules, and in consideration of regulatory guidance, the proposed specification tests and specification limits provide appropriate control of the quality of Dabrafenib Capsules. Does the Agency agree with the proposed specification tests and limits, in particular our proposal to tighten the dissolution specification?

FDA Response to Question 5: No, we do not agree with the proposed drug product specification. It is not acceptable to [redacted] (b) (4) The description test should include the appearance of the capsule content. It is recommended that testing for [redacted] (b) (4). See the FDA Response to Question 6 for the acceptance criteria for dissolution.

Discussion: GSK acknowledged receipt of FDA's response. FDA stated that it is premature at this time [redacted] (b) (4) FDA stated that GSK could propose [redacted] (b) (4) in the initial NDA submission by providing sufficient scientific justification, including data to demonstrate sufficient process understanding. Additionally, FDA recommended that description testing include evaluation of appearance of [redacted] (b) (4) in addition to the appearance of capsules. FDA expressed concerns [redacted] (b) (4) It is ultimately a review issue for the NDA, based on data provided in the NDA submission. FDA also confirmed that the biopharmaceutics (dissolution) data will be reviewed to check batch to batch uniformity at release and to pick up any signal for any kind of changes [redacted] (b) (4) GSK committed to provide additional data in the NDA to support their proposal.

Question 6: A discriminating dissolution method has been developed. Does the Agency agree that the proposed dissolution method is appropriate for release of commercial product and stability testing?

FDA Response to Question 6: Your approach is reasonable. However, final decision on the acceptance of dissolution procedure and acceptance criteria is a review issue during NDA review. Submit full detail of the statistical procedures used in the development of the dissolution method (e.g., multivariate confidence region procedure, fractional factorial DOE to evaluate the robustness etc.). Also, provide raw dissolution data that were used to justify your proposed dissolution acceptance criteria.

Discussion: GSK acknowledged receipt of FDA's response. GSK asked for FDA's comments on GSK's proposal for [redacted] (b) (4) dissolution acceptance criteria. FDA indicated that [redacted] (b) (4) dissolution acceptance criteria is viewed as [redacted] (b) (4) control of drug product and is not a filing issue.

Question 7: Primary stability batches have been manufactured at production scale at the GSK facility [redacted] (b) (4) according to the commercial process and using the same manufacturing equipment intended for commercial manufacturing. Twelve months of stability data on these batches will be presented in the NDA. Does the Agency agree that the data are sufficient to support filing of the NDA?

FDA Response to Question 7: Yes, your proposal to include 12 months of stability data from 3 primary batches of each strength and packaging configuration at the time of NDA submission is acceptable. A determination of fileability will be made at the time of NDA submission.

Discussion: GSK acknowledged receipt of FDA's response. No further discussion occurred regarding this question during the teleconference.

Question 8: (b) (4) [redacted]). **Does the Agency agree with the proposal?**

FDA Response to Question 8: No, we do not agree with the proposed testing intervals and alternate packaging configuration. Stability studies need to be performed for each strength in each proposed packaging configuration and the frequency of testing at the long term storage condition should be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf life.

Discussion: GSK acknowledged receipt of FDA's response. No further discussion occurred during the teleconference.

2.3. Manufacturing Facilities

To facilitate our inspectional process, the Office of Manufacturing and Product Quality in CDER's Office of Compliance requests that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Discussion: GSK acknowledged receipt of FDA's response. No further discussion occurred during the teleconference.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no outstanding issues that require further discussion at the conclusion of the teleconference.

4.0 ACTION ITEMS

There are no other action items other than those recorded in the Discussion section (2.0) above.

5.0 CONCURRENCE:

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Senior Regulatory Health Project Manager for Product Quality
Office of New Drug Quality Assessment
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

{See appended electronic signature page}

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6.0 ATTACHMENTS AND HANDOUTS

There were no attachments, handouts or slides distributed for the teleconference.

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

/s/

SCOTT N GOLDIE
02/27/2012

SARAH P MIKSINSKI
02/27/2012

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End of Phase 1, Pre-Phase 3
Meeting Date and Time:	February 24, 2011
Meeting Location:	White Oak, Bldg. #22, Conf. Room 2201
Application Number:	INDs 102175 & 105032
Product Name:	GSK1120212 (MEK 1/2 Inhibitor) and GSK2118436 (BRAF Inhibitor)
Indication:	**Patients with BRAF V600E/K(b) (4) mutation positive advanced or metastatic melanoma**
Sponsor/Applicant Name:	GlaxoSmithKline
Meeting Request Date:	December 14, 2010
Meeting BGP date:	January 27, 2011
Meeting Chair:	V. Ellen Maher, M.D.
Meeting Recorder:	Kim J. Robertson

FDA ATTENDEES

Robert Justice, M.D., M.S., Director DDOP
Amna Ibrahim, M.D., Deputy Division Director, Medical Officer Team Leader
Anthony Murgo, M.D., M.S., FACP, Associate Director OODP IO, Acting Deputy Director DDOP
V. Ellen Maher, M.D., Clinical Team Leader
Geoffrey Kim, M.D., Medical Officer
Shenghui Tang, Ph.D, Team Leader, DB 5
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Rafael Amado, M.D., Clinical Development
Vicki Goodman, M.D., Clinical Development
Jeff Legos, Ph.D., Clinical Development
Michele Casey, Ph.D., Biostatics
Agnes Westelinck, Pharm D., Regulatory Affairs
Ellen Cutler, Regulatory Affairs
Eric Richards, MS, MPH, Regulatory Affairs

1.0 BACKGROUND

Preclinical and preliminary clinical evidence support the development of the combination of B-RAF and MEK inhibitors in B-RAF V600 E/K mutation associated advanced or metastatic melanoma. GSK2118436 is an orally available kinase inhibitor of B-RAF while GSK1120212 is an orally available kinase inhibitor of MEK1/MEK2. Currently, the sponsor is planning on conducting two separate phase III trials comparing each drug against chemotherapy in metastatic melanoma. GSK2118436 will be compared against DTIC in untreated, BRAF V600E mutation positive metastatic melanoma while GSK1120212 will be compared against DTIC or Taxol in previously treated BRAF V600E/K mutation positive advanced or metastatic melanoma. Currently, there is a phase I/II study assessing the combination of GSK2118436 and GSK1120212 in solid tumors. To date, 37 patients with BRAF mutation positive solid tumors have been enrolled. 13 partial responses were reported in 16 evaluable patients. Enrollment in an expansion cohort of BRAF mutant positive metastatic melanoma is ongoing. Preliminary reports of safety in the combination study reveal no major events, most notably there have been no reports of the development of secondary malignancies such as the squamous cell carcinomas of the skin that have been reported in the clinical experience of BRAF inhibitors. The sponsor suggests that the addition of a MEK inhibitor to a BRAF may potentially suppress the development of such malignancies, but this still remains a major safety concern, as does the decreased left ventricular ejection fraction seen in the MEK inhibitors.

In a Type-A Revised Clinical Development Plan Meeting held October 7, 2010 regarding the development of GSK2118436 in BRAF mutation positive melanoma; the FDA recommended a 3 arm randomized study of GSK1120212 vs. GSK2118436 vs. the combination. At this time, the FDA stated it would consider approval of both agents in combination if the combination arm is markedly superior. The sponsor has subsequently designed a three-arm, double-blind, randomized Phase III study (MEK115306) comparing the combination of GSK2118436 and GSK112012 to single agent GSK2118436 + placebo and single agent GSK1120212 + placebo in subjects with BRAF mutation positive metastatic melanoma. This trial intends to support the proposed indication of: GSK2118436 capsules and GSK112012 tablets used in combination are indicated for the treatment of patients with B-RAF V600 mutation positive advanced or metastatic melanoma.

2.0 DISCUSSION

MEK-B-RAF COMBINATION

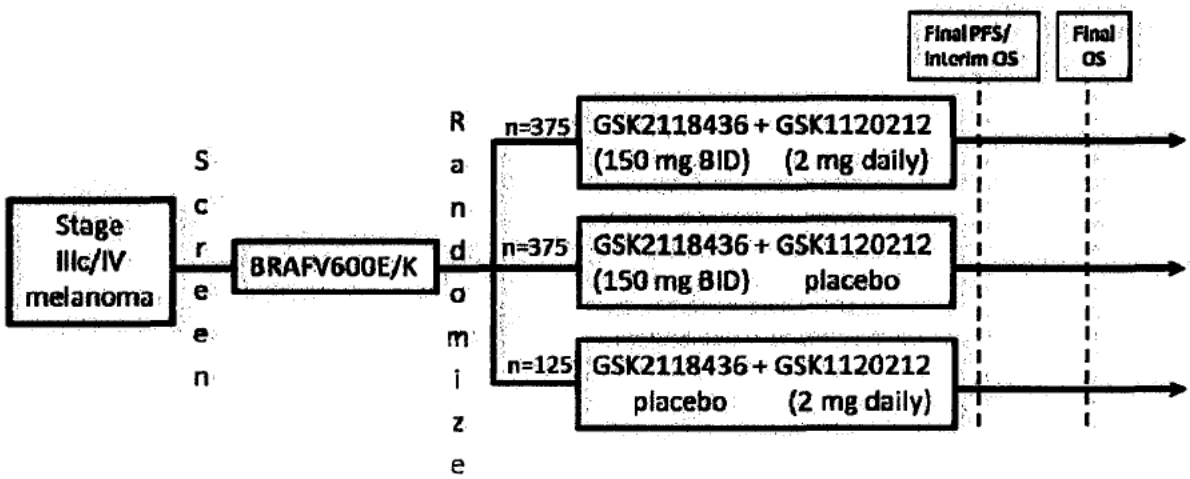
Questions and company positions

Company Position:

GSK is proposing a 3-arm study utilizing GSK1120212 and GSK2118436 in combination, as suggested by the FDA on 10OCT10. A Concept Protocol for this proposed study is included in Attachment 2. The MEK115306 study design is shown below [Figure 1]. This phase III, double-

blinded study will randomize subjects in a 3:3:1 fashion and will compare the combination of the B-RAF inhibitor GSK2118436 and the MEK inhibitor GSK1120212 to each single agent combined with placebo in subjects with advanced or metastatic B-RAF V600E/K mutation-positive melanoma. Approximately 875 subjects will be randomized - 375 subjects will randomize to the combination arm and to the GSK2118436 arm and 125 subjects will randomize to the GSK1120212 arm. See section 1.4 of the concept protocol (attachment b) for details.

Figure 1 Study Scheme for MEK115306



The goal of the MEK115306 study is to demonstrate that the combination of the B-RAF inhibitor, GSK2118436 and the MEK inhibitor, GSK1120212, is superior to treatment with either agent alone in B-RAF mutant melanoma subjects. To that end, the combination will be compared to each mono-therapy treatment. To ensure that the effect is properly evaluated, both PFS and OS will be analyzed. PFS will be based on investigator assessments. The trial will be randomized, and double blinded to minimize investigator bias. The comparison between the combination and B-RAFi mono-therapy will be powered for both PFS and OS (co-primary endpoints), whereas the comparison between the combination and MEKi mono-therapy is powered only for PFS (secondary endpoint; see Section 2 of the concept protocol (attachment b) for statistical details, and questions 2 and 3 below for rationale regarding endpoints).

The three-arm study design with a 3:3:1 randomization (combination arm: GSK2118436: GSK1120212, respectively) will evaluate the contribution of combination against each investigational agent. The PFS endpoint will be utilized to demonstrate the relative contribution of GSK1120212 and to demonstrate that the benefit observed with the combination is not due solely to the contribution from GSK1120212.

To address the contribution of the B-RAF inhibitor, the study will use GSK2118436 as a comparator. A B-RAF inhibitor that has completed enrolment of a pivotal Phase III study, PLX4032, was not chosen for several reasons. Using PLX4032 as a comparator would not address the contribution of GSK2118436 to the effect of the combination. Also, PLX4032 is not currently approved in any country and might not be in 3Q2011, when GSK anticipate that the MEK115306 study will begin. Even if PLX4032 is approved by that time, the availability of this

agent is unknown. Lastly, GSK2118436 demonstrated a robust response rate with an acceptable safety profile in a first-in-human study and, like GSK1120212, is currently in Phase II and III mono-therapy studies in subjects with B-RAF mutant melanoma. Thus, GSK believe that this study design is the most feasible and expeditious approach to evaluating MEK+B-RAF inhibitor combination therapy.

QUESTION 1

Does the Agency agree with the three-arm study design comparing the combination against each investigational agent?
FDA Preliminary Response (February 17, 2011):

Our understanding is that your primary analysis will compare:

1. ***GSK2118436 (BRAFi) + GSK1120212 (MEKi) vs. GSK2118436 (BRAFi) to isolate the effect of GSK1120212 (MEKi).***

We also understand that a secondary analysis will compare:

2. ***GSK2118436 (BRAFi) + GSK1120212 (MEKi) vs. GSK1120212 (MEKi) to isolate the effect of GSK 2118436 (BRAFi).***

This design appears acceptable; however, you must demonstrate the BRAF Inhibitor has high single agent activity in other studies. We recommend that you carefully review the wording of your design submission and that you submit the protocol for Special Protocol Assessment prior to study initiation.

Additional Question for FDA (February 21, 2011):

Does FDA agree that the phase II study BRF113370 should be sufficient to demonstrate "high single agent activity" if the response rate is high (e.g. > 50% RR) and durable?
Company Position
FDA made the following preliminary comments: "*This design appears acceptable; however, you must demonstrate the BRAF Inhibitor has high single agent activity in other studies*". GSK is currently running BRF113370: a Phase II, single-arm, open-label study to assess the efficacy, safety, and tolerability of GSK2118436 administered twice daily as a single agent in subjects with BRAF mutant metastatic melanoma. This study utilizes the same dose of GSK2118436 as proposed for the phase III combination study. GSK believes that study BRF113370 will provide significance evidence of the high clinical activity of GSK2118436 (BRAFi) should the phase II study demonstrate a high response rate (e.g. > 50% RR). A final study report for BRF113370 will be available well before completion of the proposed phase III combination study.
Please Note: GSK is also running a Phase III study with GSK2118436 (BRAFi): BRF113683, a two-arm, open-label, randomised study comparing dacarbazine (DTIC) to the single agent GSK2118436 in subjects with previously untreated B-RAF V600E mutation positive metastatic melanoma. BRF113683 will provide evidence of clinical benefit via PFS for GSK2118346 (BRAFi) monotherapy. A final study report for

BRF113370 will be available well before completion of the proposed phase III combination study.

Additional information with regard to Question 1

GSK intends to submit the protocol for Special Protocol Assessment prior to study initiation.

To clarify, there seems to be a typo in the FDA preliminary comments above:

Our intent is that the primary analysis will compare:

1. **GSK2118436 (BRAFi) + GSK1120212 (MEKi) vs. GSK2118436 (BRAFi) to isolate the effect of GSK1120212 (MEKi).**

We also understand that a secondary analysis will compare:

2. **GSK2118436 (BRAFi) + GSK1120212 (MEKi) vs. GSK1120212 (MEKi) to isolate the effect of GSK2118436 (BRAFi)**

FDA Response (February 24, 2011):

GSK went over their drug development plan and the timelines for their various studies. The Agency asks that GSK submits this information to their new IND. The Agency stated that their Phase 2 study should show a response rate of at least 50%, but that the evaluation of this study and the required response rate will ultimately be a review issue.

Company Position:

The benefit of the combination compared to GSK2118436 mono-therapy will be evaluated through the co-primary endpoints of PFS and OS. For evaluating the effect of treatment regimens in metastatic melanoma, OS is the traditional gold standard for efficacy. OS is considered the most reliable cancer endpoint and usually the preferred endpoint as there is no bias in endpoint measurement. However, the OS endpoint has the disadvantage of potentially being influenced by subsequent treatment. In the past, concerns of such confounding treatments in metastatic melanoma were minimal as no treatments have demonstrated significant improvement in survival. However, new experimental treatments (e.g., anti-CTLA4 agents, PI3K inhibitors, and anti-angiogenics) that will be available to patients after progression on MEK115306 study could potentially influence the OS endpoint. Indeed, some of these agents could be approved before or during the conduct of this trial.

To minimize the risk of a confounded OS endpoint, PFS will be evaluated as a co-primary endpoint. It is noteworthy that PFS, which is based directly on tumour growth, can be assessed before the final OS endpoint. The magnitude of effect for PFS using a given sample size is anticipated to be larger than for OS. In the MEK115306 study, the combination is anticipated to cause a 57% increase in PFS (median of 11 months versus 7 months on GSK2118436 mono-therapy) and a 38% increase in OS (median of 16.5 months versus 12 months on GSK2118436). To achieve 90% power for the OS comparison, a total of 750 subjects will be enrolled in two arms to observe the required 429 survival events. An overall Type I error rate (one-sided) will be set to 2.5%, and a hierarchical testing procedure will be used for the co-primary endpoints to protect the overall error rate, with PFS required to show statistical superiority prior to OS being

tested. The sample size calculations and timing of the final PFS/interim OS analyses will be based on survival events. (See Section 2.2 of the MEK115306 concept protocol (Attachment b) for details on sample size assumptions.)
PFS and OS each provide a different-but-important perspective on the value of experimental treatments. GSK believe it is appropriate to have both PFS and OS as co-primary endpoints, to use a hierarchical testing procedure to maintain the overall Type I error rate, and that the study is adequately powered for the co-primary endpoints.

QUESTION 2

Does the Agency agree with the co-primary endpoints of PFS/OS comparing the combination arm to the GSK2118436 single agent arm?

FDA Preliminary Response (February 17, 2011):

No. OS should be the sole primary endpoint. The magnitude of this effect must be clinically robust in order to support the approval of the combination of the two drugs.
Please note that this trial will not support the approval of a single drug for this indication.

GSK Response (February 21, 2011):

GSK agrees to OS as the sole primary endpoint. PFS will be included as a secondary endpoint. GSK intends to submit the protocol for Special Protocol Assessment prior to study initiation

FDA Response (February 24, 2011): No further discussions were necessary.

Company Position:

As described in Question 2, the primary objective/endpoint will be the comparison of PFS/OS between the combination and GSK2218436. In order to demonstrate that the benefit observed with the combination is not due solely to GSK1120212, a key secondary objective/endpoint will be the comparison of PFS between the combination and GSK1120212. The study will be powered for this key secondary endpoint; however adjustments to alpha will not be made as all secondary endpoints/analyses will be considered supportive. Because evaluation of PFS requires fewer events than OS, the GSK1120212 mono-therapy arm can enroll fewer patients.
The study is powered to detect a 57.1% improvement in PFS of the combination over GSK1120212 mono-therapy (hazard ratio 0.636; median PFS of 11 and 7 months in the combination and GSK1120212 mono-therapy arms, respectively). Given a 3:1 randomization (375:125 subjects) for the combination and GSK1120212 mono-therapy arms, it is anticipated that approximately 255 PFS events across two arms will provide 91% power with a one-sided alpha of 0.025 at the time of the final PFS analysis.
GSK believe that a PFS benefit (Δ) of 4 months, as hypothesized in the proposed protocol, is an appropriate measurement to demonstrate that the benefit observed with the combination is not due solely to GSK1120212. In addition, it is very possible that patients in the GSK1120212

monotherapy arm will subsequently receive an approved B-RAF inhibitor outside of the study upon progression, thus confounding an Overall Survival endpoint. Due to these reasons, GSK believe that the comparison of the Combination arm to the GSK1120212 monotherapy arm via a PFS secondary endpoint is an appropriate and efficient way of adequately demonstrating the relative contribution of GSK1120212.

QUESTION 3

Does the Agency agree with the secondary endpoint of PFS comparing the combination arm to the GSK1120212 mono-therapy arm to demonstrate the contribution of GSK1120212?

FDA Preliminary Response (February 17, 2011):

Please see the response to question 1 in regards to isolating the effect of the individual drug.

PFS can be used to demonstrate the contribution of GSK2118436 (BRAFi); however in order to support registration of the proposed indication, the combination arm should demonstrate an improvement in OS when compared to single agent GSK2218436 (BRAFi). Please note that an improvement in PFS of the combination compared to MEK Inhibitor will provide supportive data for the combination but will not result in approval of the drug as a single agent.

GSK Response (February 21, 2011):

GSK acknowledges FDA's comment.

FDA Response (February 24, 2011): No further discussions were required.

Company Position:

An interim analysis will provide an opportunity to terminate the study early only if there is strong evidence of superiority or futility of overall survival of the combination over single agent GSK2118436. An independent data monitoring committee (IDMC) will convene to review the prospectively planned interim efficacy analysis at the time the study is fully enrolled and approximately 70% or 300 survival events have occurred.
Although statistical stopping guidelines are pre-specified for the OS comparison, a number of factors, including clinically relevant benefit, the PFS benefit, and the potential for subsequent therapies to confound OS, must be considered thoroughly as part of the decision to modify or terminate the study for futility. Therefore a recommendation to modify or terminate the study will not be based solely on statistical grounds.
For the purposes of evaluating whether to stop the **trial due to 'Dramatic Benefit', a Lan and DeMets version of the O'Brien-Fleming alpha** spending function [Lan, 1983] will be utilized.
For purposes of evaluating whether to stop the trial **due to 'Futility' a Rho beta spending function** will be utilized with rho=3 [Kim 1987].

The nominal significance levels corresponding to the error spending functions as well as the planned stopping boundaries and decision rules are as follows:

- 70% of expected events (α=0.007):
  - Stop for efficacy if one-sided p-value <0.0074 (HR<0.7538)
  - Stop for futility if one-sided p-value>0.1772 (HR>0.8982)
- 100% of expected events (α=0.025):
  - Claim success if one-sided p-value<0.0238 (HR<0.8252)

Hazard ratios are presented above to enable the reader to understand what the boundary crossing would mean in terms of efficacy and futility. The final boundaries will be in the form of an adjusted p-value, which will be compared to the stratified log-rank p-value calculated on the stratified log-rank test statistic.
As it is possible that the amount of information (i.e. fraction of expected events) available at the scheduled interim analysis may differ from what has been planned, the nominal significance values at the interim and final analyses will be adjusted accordingly to preserve an overall 2.5% one-sided significance level.

QUESTION 4

Does the agency agree with the proposed interim analysis and planned alpha and beta spending at the interim analysis?

FDA Preliminary Response (February 17, 2011):

Please see response to Question 2.

You will need to revise your statistical analysis plan based on the sole primary endpoint of OS.

GSK Response (February 21, 2011):

OS will be the sole primary endpoint. GSK still intends to conduct an interim analysis on survival events only, when 70% of events survival events have occurred. Details regarding this interim analysis will be provided in the upcoming SPA.

FDA Response (February 24, 2011):

The timing of the interim analysis on OS is acceptable. Further comments depend upon your upcoming SPA. Please submit a detailed Statistical Analysis Plan (SAP) with the SPA.

The benefit of the combination compared to GSK2118436 mono-therapy will be evaluated through the co-primary endpoints of PFS and OS. The comparison of the combination to GSK1120212 mono-therapy will be powered for PFS as a secondary endpoint.

A blinded independent central review is useful in minimizing bias when investigators are not blinded to study treatment. However this study is a double-blind study which will utilize GSK2118436-placebo and GSK1120212-placebo thereby minimizing bias on the part of the investigator. GSK plans to collect and store scans for all subjects in the event that questions arise necessitating a review.

QUESTION 5

Does the Agency agree with the proposal to use investigator assessments of response and progression without an independent central review?

FDA Preliminary Response (February 17, 2011):

If OS is the only primary endpoint, then no independent review committee is required.

GSK Response (February 21, 2011):
GSK agrees

FDA Response (February 24, 2011): No further discussions were required.

Company Position:

GSK projects the application for registration of the combination of GSK2118436 and GSK1120212 would occur in 4Q2013. The submission will contain safety data from the Phase I-II (BRF113220) and Phase III (MEK115306) combination studies. Both studies evaluate only B-RAF mutation-positive melanoma subjects. The BRF113220 study will evaluate approximately 75 subjects for safety at the Phase III combination dose (150 mg BID GSK2118436 + 2 mg once daily GSK1120212) and approximately 75 subjects at a lower combination dose (150 mg BID GSK2118436 + 1 mg once daily GSK1120212). MEK115306 study described herein will evaluate 375 patients that have not received prior anti-cancer therapy in the metastatic setting. Thus, safety data will be available for approximately 450 subjects at the Phase III dose and approximately 75 subjects at a reduced dose. In addition to the safety database for the combination, it is anticipated that mono-therapy safety data will be available as follows: for GSK2118436 - at least 300 B-RAF mutation-positive melanoma subjects and 640 cancer subjects and for GSK1120212 - at least 330B-RAF mutation-positive melanoma subjects and at least 800 cancer subjects.
GSK believe that sufficient safety data for the combination of GSK2118436 and GSK1120212 will exist at the time of registration.

QUESTION 6

Does the Agency agree the combination of GSK2118436 and GSK1120212 will have an adequate safety database at the time of the marketing authorization?

FDA Preliminary Response (February 17, 2011):

Probably, but this will be a review issue.

GSK Response (February 21, 2011):
GSK acknowledges FDA's comment.

FDA Response (February 24, 2011): No further discussions were required.

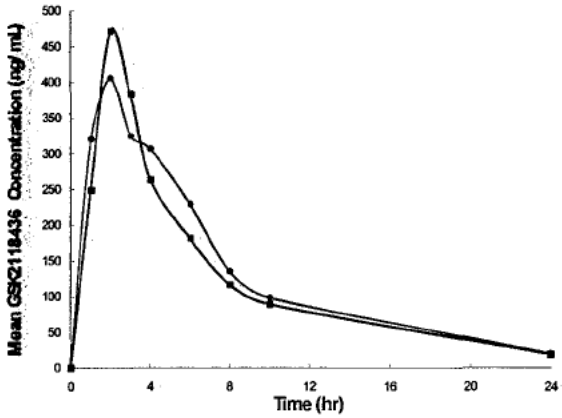
Company position:

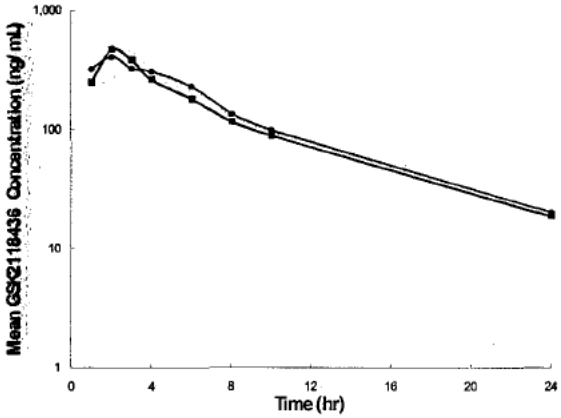
Results from the *in vitro* metabolism and inhibition studies as well as preliminary DDI data are summarized below. Pharmacokinetic data on the combination were obtained in Study BRF113220; Part A evaluated the effect of repeat dose GSK1120212 on the single dose pharmacokinetics of GSK2118436 and in Part B, the repeat dose pharmacokinetics of GSK1120212 and GSK2118436 administered in combination were characterized and compared to historical controls. For Part B, PK data are available in different cohorts in 21 subjects either on Day 15 or Day 21. Additional PK samples will be available in at least 34 subjects with data at the recommended dose (150 mg BID GSK2118436 and 2 mg QD GSK1120212) in approximately 15 subjects. Detailed PK results in Study BRF113220 are provided separately (Attachment 3).

Effect of GSK1120212 on GSK2118436:

In vitro studies demonstrated that the oxidative metabolism of GSK2118436 is primarily mediated by CYP2C8, CYP3A4 and, to a lesser extent, CYP2C9. GSK1120212 was found to be an *in vitro* inhibitor of CYP2C8 (IC50 of 0.34 μM) at concentrations 8.5-fold greater than the mean steady-state Cmax of 23 ng/mL (0.04 μM) observed at the proposed dose of 2 mg daily. Based on free concentration (Fbound=97.4%), the risk of DDI is considered minimal (>50-fold margin). In Study BRF113220 Part A (data available in 7 out of 8 subjects), GSK2118436 exposure, measured as Cmax and AUC(0-inf) following a 75 mg-single-dose, were similar when administered alone (Day 1, reference) and with 2 mg QD GSK1120212 (Day 15, test), with geometric least-squares mean ratio (90%CI) of 0.97 (0.73, 1.29) and 0.95 (0.82, 1.10), respectively (Figure 2 and Table 1). The 90% CIs were contained within the 80-125% acceptance range for AUC. For Cmax, the LS mean ratio was close to 1 although the 90%CI were outside the boundaries, due to the small number of subjects and larger variability observed for Cmax compared to AUC. These results suggest that GSK1120212 has no clinically meaningful effect on the pharmacokinetics of single dose GSK2118436.

Figure 2. Mean Linear (left) and Log-linear (right) GSK2118436 Concentration-Time Profiles of 75 mg Single Dose of GSK2118436 Administered Alone (circles; Day 1) and in Combination with 2 mg QD of GSK1120212 (squares; Day 15)





In Study Part B, the repeat dose PK of GSK2118436 was characterized when dosed in combination with GSK1120212. The mean (CV%) AUC(0-τ) of GSK2118436 in subjects receiving 150 mg BID in combination with 1 mg (n=5), 1.5 mg (n=3) and 2 mg (n=1) QD of GSK1120212 was 3773 ng*hr/mL (44%) on Day 15. Results from the first time in human study (BRF112680, n=7), were generally consistent with mean (CV%) AUC(0-τ) on Day 15 of 3021 ng*hr/mL (47%).

Table 1. Summary of Plasma GSK2118436 PK Parameters Alone and in Combination with GSK1120212 in Study BRF112680

	GSK2118436 (Part A) Single-Dose (n=7)			GSK2118436 (Part B) Repeat-Dose	BRF112680 Repeat-Dose
GSK2118436 PK parameter	**GSK2118436 Alone**	**GSK2118436 + GSK1120212**	**Combination: Alone Ratio**	**GSK2118436 + GSK1120212 (N = 8)**	**GSK2118436 Alone (N = 7)**
AUC(0-∞) or (0- τ) (ng·hr/mL)	3170 (22)	3029 (26)	0.95 (0.82, 1.10)	3773 (44)	3021 (47)
Cmax (ng/mL)	537 (37)	523 (37)	0.97 (0.73, 1.29)	969 (62)	971 (73)

Mean (CV%) for AUC and Cmax and GLS mean ratio (90% CI) for treatment comparison
Part A: single-dose GSK2118436 75mg and single-dose GSK2118436 75mg + repeat-dose GSK1120212 2mg QD
Part B: repeat-dose GSK2118436 150mg BID + repeat-dose GSK1120212 1, 1.5 or 2mg QD

These results suggest that repeat-dose GSK1120212 had no clinically meaningful effect on the pharmacokinetics GSK2118436 following single- or repeat-dose administration.

Effect of GSK2118436 on GSK1120212:
Based on *in vitro* studies, the metabolism of GSK1120212 is predominantly mediated by non-cytochrome P450 processes and potentially by CYP3A4. The contribution of the CYP3A4 pathway to the elimination of GSK1120212 in humans is presently unknown. GSK2118436 produced dose dependent increases in CYP2B6 and CYP3A4 mRNA levels up to 32 times the control levels in human hepatocytes, suggesting that it may be an inducer of these enzymes. The effect of repeat dose GSK2118436 on the pharmacokinetics of single-dose midazolam, a CYP3A4 probe substrate, was evaluated in Study BRF112680 (n=12). Administration of repeat dose of GSK2118436 (150 mg BID for 15 days) resulted in decreases in single dose midazolam Cmax and AUC with LSmean ratio (90% CI) of 0.39 (0.24, 0.63) and 0.26 (0.21, 0.32), respectively, confirming that GSK2118436 is a CYP3A4 inducer in vivo.
In Study BRF113220 (Part B), repeat dose GSK1120212 PK following administration of 1, 1.5, and 2 mg QD were characterized when dosed in combination with 75 and 150 mg BID of GSK2118436. The mean (CV%) AUC(0-τ) of GSK1120212 (dose normalized for 2 mg) when dosed in combination with GSK2118436 150 mg BID was 286 ng*hr/mL (19%) (n=8) on Day 15 (Table 2). Comparison to historical PK data from Study MEK111054, in which the mean (CV%) AUC0-τ on Day 15 was 360 ng*hr/mL (31%), suggests that CYP induction by GSK2118436 does not have a clinically significant effect on GSK1120212 plasma exposure. Exposure data obtained on Day 21 were generally greater than on Day 15 and support these results (Attachment 3).

Table 2. Summary of Plasma GSK1120212 PK Parameters When dosed in Combination with GSK2118436 in Study BRF112680

	GSK1120212 (Part B) Repeat-Dose	**MEK111054 Repeat-Dose**
GSK1120212 PK parameter	**GSK1120212 + GSK2118436 (N = 8)**	**GSK1120212 Alone (N = 14)**
AUC (0- τ) (ng·hr/mL)	286 (19)	360 (31)
Cmax (ng/mL)	16.3 (29)	23.3 (25)

Mean (CV%) for AUC and Cmax
Part B: repeat-dose GSK1120212 1, 1.5 or 2 mg QD + repeat-dose GSK2118436 150mg BID; GSK1120212 PK parameters were dose normalized to 2 mg.

These results have shown no clinically meaningful effect of GSK2118436 on the pharmacokinetics of GSK1120212 following repeat-dose administration.
Therefore, preliminary pharmacokinetic results from Study BRF113220 have shown no clinically meaningful drug-drug interactions between GSK2118436 and GSK1120212, when combined. Study BRF113220 is ongoing and PK data will be available in additional subjects at the target dose of 150 mg BID GSK2118436 and 2 mg QD GSK1120212.
Study MEK115306
GSK will collect sparse PK samples in the proposed Phase III study MEK115306, a three-arm, double-blinded, randomized study comparing GSK2118436 and GSK1120212 in combination to

each agent dosed as monotherapy with placebo. One blood sample from each visit will be collected for population PK analysis on Weeks 4, 8, 16, and 24 from subjects receiving GSK2118436 and GSK1120212 in combination or alone. These data will provide additional information to support DDI results in Study BRF113220 in context with clinical response.

QUESTION 7

Preliminary pharmacokinetic data from the Phase I/II combination study of GSK2118436 and GSK1120212 (Study BRF113220) showed no clinically meaningful drug-drug interaction (DDI) between GSK2118436 and GSK1120212. In addition, GSK plans to conduct sparse pharmacokinetic (PK) sampling in the proposed Phase III study (Study MEK115306) to further characterize the pharmacokinetics of GSK2118436 and GSK1120212 when dosed in combination and compare to monotherapy. GSK considers that the PK data from Studies BRF113220 and MEK115306 will provide the data required to evaluate any clinically significant DDI between GSK1120212 and GSK2118436 in the advanced cancer patient population, and that a separate DDI study is not required. Does the Agency agree?
FDA Preliminary Response (February 21, 2011):

The proposal appears reasonable. However, a final decision regarding whether a separate DDI study is required will be an NDA review issue.

GSK Response (February 21, 2011):
GSK acknowledges FDA's comment.

FDA Response (February 24, 2011): No further discussions were required.

Company Position:

The phase III, double-blinded MEK115306 study will compare the combination of the B-RAF inhibitor GSK2118436 and the MEK inhibitor GSK1120212 to each single agent combined with placebo in subjects with advanced or metastatic B-RAF V600E/K mutation-positive melanoma. The comparison between the combination and GSK2118436 mono-therapy will be powered for both PFS and OS (co-primary endpoints), whereas the comparison between the combination and GSk1120212 mono-therapy is powered only for PFS (secondary endpoint; see Section 2 of the concept protocol (Attachment 2)) for statistical details, and questions 2 and 3 below for rationale regarding endpoints).

This Phase III MEK115306 study is supported by an open-label, dose-escalation, phase I/II study to investigate the safety, pharmacokinetics, pharmacodynamics and clinical activity of the B-RAF Inhibitor GSK2118436 in combination with the MEK inhibitor GSK1120212 in subjects with B-RAF mutant metastatic melanoma (BRF113220).

GSK believes the data from these two studies will support registration of GSK2118436 capsules and GSK1120212 tablets in combination for the following indication:

GSK2118436 capsules and GSK1120212 tablets in combination is indicated for the treatment of patients with B-RAF mutation positive advanced or metastatic melanoma.

QUESTION 8

Does the Agency agree with the overall registration plan to support the marketing authorisation application of GSK2118436 capsules and GSK1120212 tablets used in combination in patients with B-RAF mutation positive advanced or metastatic melanoma?

FDA Preliminary Response (February 17, 2011:

Please see the response to Question 2.
Please note that for a single randomized trial to support an NDA, the trial should be well designed, well conducted, internally consistent and provide statistically persuasive and clinically meaningful efficacy findings so that a second trial would be ethically or practically impossible to perform.

GSK Response (February 21, 2011):
GSK acknowledges FDA's comment.

FDA Response (February 24, 2011): No further discussions were required.

ADDITIONAL COMMENTS (February 17, 2011)

- **Please submit a new IND for this combination study.**

GSK Response (February 21), 2011:

GSK will submit a new IND for this combination study. GSK will work with Kim Robertson, Regulatory Project Manager, to ensure that all components of the IND are agreed upon. GSK will clarify the following with Ms. Robertson:

- **The ongoing Phase I/II study of the combination, Study BRF113220, should be moved from the GSK1128432 IND (IND 105032) to the new IND**
- **Only the Phase III protocol (i.e. MEK115306) and related documents that involve the co-administration of the two agents (e.g. nonclinical study reports) will be submitted to the new IND. Most documents in the new IND may be cross-referenced to the two existing INDs.**
- **There will be a waiver of the 30-day review period for this IND**
- **The new IND will be filed to the attention of Dr. Justice**

FDA Response (February 24, 2011): The Agency finds GSK's proposal for the components of the new IND acceptable.

- **There is insufficient objective response data and safety data to have confidence in the combination arm dose of GSK1120212. On page 4, Table 1, there were 37 patients enrolled but your response data is based on 16 patients. The available objective response data suggested that the 3rd dose level, GSK2118436 150 mg bid +**

GSK1120212 1.5 mg QD appeared to have a better response rate than your proposed dose of 2 mg of GSK1120212. There is no categorization of toxicity based on dose level. Although you indicated that a recurrent grade 2 neutrophilic panniculitis was DLT, you did not indicate the dose level and whether it was DLT for the grade 4 toxicity of a sepsis-like syndrome with fever and hypotension.

GSK Response (February 21, 2011):

Updated safety and efficacy data from the ongoing Phase II (BRF113220) will be provided to the Agency in the upcoming SPA.
One DLT, a recurrent grade 2 neutrophilic panniculitis was observed at 2 mg QD GSK1120212 and 150 mg BID of GSK2118436. The only grade 4 adverse event of "sepsis-like syndrome with fever and hypotension" was observed at 2 mg GSK1120212 and 150 mg BID of GSK2118436 (The event is now revised to grade 3 hypotension). This event was not considered DLT as it occurred after the protocol defined time for assessing DLT.

FDA Response (February 24, 2011): GSK should submit detailed information with their SPA. Please also provide a detailed development plan.

- **From your meeting package, it is not clear whether simultaneous administration of the drugs is ideal or whether prior administration of one of the drugs followed by the other gives better results in the in vitro models.**

GSK Response (February 21, 2011):

GSK has only conducted in vitro studies with simultaneous administration of both GSK2118436 and GSK1120212 versus the two single agents and the combination demonstrated activity that is synergistic or better than either agent alone. Preclinical in vivo efficacy studies in a BRAF V600E mutant melanoma xenograft model in mice showed the simultaneous administration of both compounds or the alternating administration of the compounds was significantly better than either agent alone.
GSK will provide final nonclinical study reports or synopses for those not-yet-completed reports, in the IND submission.

FDA Response (February 24, 2011): No further discussions were required.

- **You plan to collect tumor measurements at weeks 8, 16 and 24 and then every 12 weeks. However, you have assumed that the median time to progression will increase from 28 to 44 weeks in your primary analysis. We are concerned that this change in the timing of the assessments will minimize the time to progression in the control arm while maximizing the time to progression in the combination arm. We recommend that you use the same frequency of assessment throughout the study.**

GSK Response (February 21, 2011):

GSK accepts this comment. GSK will plan to collect tumor measurements at 8 week intervals for 56 weeks and then every 12 weeks thereafter.

FDA Response (February 24, 2011): No further discussions were required.

- **A marked treatment effect in either the GSK2118436 or GSK1120212 single agent arm may make it difficult to demonstrate the superiority of the combination.**

GSK Response (February 21, 2011):
GSK acknowledges FDA's comment.

FDA Response (February 24, 2011): No further discussions were required.

- **Will there be stratification of BRAF V600E and V600K patients?**

GSK Response (February 21, 2011):
GSK does not intend to stratify by BRAF mutational subtype status. The expected number of subjects with BRAF V600K mutations will be less than 10% of the total sample population, and is not expected to be a substantive predictive factor in outcome. GSK will remove the following as a secondary objective/endpoint: "compare PFS and overall RR in the subgroups of subjects with BRAF V600E and V600K mutation-positive melanoma"

FDA Response (February 24, 2011): No further discussions were required.

- **On page 6 of the clinical study proposal, you calculated the response rate in V600E melanoma as 72% in 36 patients and in V600K melanoma as 44% in 9 patients. You calculated the rate of squamous cell carcinoma as 10% in 151 patients. This is not how you reported the response rate and squamous cell carcinoma on pages 6 and 7 for PLX4032.**

GSK Response (February 21, 2011):

GSK will clarify this wording in the upcoming SPA submission.

FDA Response (February 24, 2011): No further discussions were required.

- **On page 9 of the clinical study proposal, 1.3.3 Summary, "Data generated in cell line, mouse xenograft, and rat safety models with BRAF/MEK inhibitor combinations suggest enhanced effects on efficacy, and less potential for proliferative lesions/secondary malignancies as compared to BRAF inhibitor treatment alone" is an interesting statement relative to the safety of your BRAF inhibitor. Please share the data generated in cell line, mouse xenograft, and rat**

safety models, pertaining to the potential for proliferative lesions/secondary malignancies.

GSK Response (February 21, 2011):

GSK will provide final nonclinical study reports or synopses for those not-yet-completed reports, in the new IND submission.

FDA Response (February 24, 2011): No further discussions were required.

- **On pages 26-27 of the clinical study proposal, Appendix 1, add oral and neck exams to Physical examination. Also, for your final clinical protocol, we recommend a comprehensive dermatological evaluation prior to initiation of therapy with removal of any possible pre-cancerous or non-melanoma cancerous lesions. This dermatologic evaluation should be serially repeated at pre-specified timepoints to evaluate the development the development of secondary cutaneous malignancies.**

GSK Response (February 21, 2011):

GSK acknowledges the above comment. GSK will incorporate oral and neck exams to physical examination and re-evaluate the types of dermatological assessments incorporated into the MEK115306 study protocol.

FDA Response (February 24, 2011): No further discussions were required.

- **Validation of a companion diagnostic is a requirement, and the expectation is that a PMA submission for the test will be submitted (preferably at the same time) and supported by the data used to obtain the therapeutic approval.**

GSK Response (February 21, 2011):

GSK acknowledges this requirement. GSK is working with bioMerieux (bMx) to develop an investigational use only (IUO) assay based on the Response Genetics (RGI) BRAF LDT, currently in use in our ongoing clinical trials for melanoma. It is anticipated that the IUO will be ready and an IDE will be submitted at around the time the Phase III combination study will be initiated. To this end, we propose to continue screening patients with the RGI LDT, until approval of the bMx IDE has been granted, after which time patients will be screened using the bMx IUO for study eligibility. GSK, RGI and bMx are in communication with CDRH/OIVD for the development of the BRAF mutation assay and will continue to seek their guidance.

FDA Response (February 24, 2011): No further discussions were required.

Minutes Preparer:

{See appended electronic signature page}

Kim J. Robertson
Regulatory Health Project Manager

Meeting Chair:

{See appended electronic signature page}

V. Ellen Maher, M.D.
Clinical Team Leader

Meeting Adjourned:
11:40 AM

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

/s/

KIM J ROBERTSON
03/03/2011
24February11 Sponsor Meeting Minutes MEK and BRAF INDs 102175 & 105032; GSK

VIRGINIA E MAHER
03/08/2011

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102175

MEETING MINUTES

GlaxoSmithKline LLC
Attention: Dorothea Roberts, Assistant Director
Global Pre-Approval, CMC Regulatory Affairs
PO Box 13398, Bldg 5.5425
5 Moore Drive
Research Triangle Park, NC 27709

Dear Ms. Roberts:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GSK1120212 MEK1/2 Inhibitor.

We also refer to the teleconference between representatives of your firm and the FDA on Tuesday, November 09, 2010. The purpose of the meeting was to discuss the chemistry, manufacturing, and controls for GSK1120212.

A copy of the official minutes of the teleconference is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Scott N. Goldie, PhD
Sr. Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End-of-Phase 1/Pre-Phase 3 Chemistry, Manufacturing and Controls (CMC)
Meeting Date and Time:	Tuesday, November 09, 2010, 1400 – 1500 ET
Meeting Location:	Teleconference
Application Number:	IND 102175
Product Name:	GSK1120212 MEK1/2 Inhibitor
Indication:	Treatment of Subjects with Solid Tumors or Lymphoma
Sponsor/Applicant Name:	GlaxoSmithKline LLC (GSK)
Meeting Chair:	Sarah Pope Miksinski, Ph.D.
Meeting Recorder:	Scott N. Goldie, Ph.D.

FDA ATTENDEES

John Z. Duan, Ph.D.	Biopharmaceutics Reviewer, ONDQA
Scott N. Goldie, Ph.D.	Senior Regulatory Health Manager for Quality, ONDQA
Sarah Pope Miksinski, Ph.D.	Chief, Branch II, ONDQA
Anne Marie Russell, Ph.D.	Quality Reviewer, Branch II, ONDQA
Haripada Sarker, Ph.D.	CMC Lead, Branch II, ONDQA

SPONSOR ATTENDEES

Choon Oh, Ph.D.	Director, Product Development
Francisco Henriquez	Team Leader, Product Development
Lihong Wang	Lead Analyst, Product Development
Richard Ward, Ph.D.	Manager, Synthetic Chemistry
Jeff Brum, Ph.D.	Manager, Physical Properties
Richard Smith, Ph.D.	Director, Analytical Sciences
Kevin Miller	Director, Global Pre-Approval CMC Regulatory Affairs
Dorothea Roberts	Assistant Director, Global Pre-Approval CMC Regulatory Affairs

1.0 BACKGROUND

GSK1120212, a potent and selective inhibitor of MEK1 and MEK2 activation and kinase activity, is under development for the treatment of patients with BRAF V600E/K/ [redacted] (b) (4) metastatic melanoma. A Type B End-of-Phase 1/Pre-Phase 3 Chemistry, Manufacturing and Controls (CMC) meeting was requested by GSK on August 19, 2010, and granted on September 08, 2010. The meeting package to support the discussion was submitted on October 1, 2010. FDA sent responses to the questions in the meeting briefing package on November 5, 2010. In response, GSK requested that the format of the meeting be modified to a teleconference and the agenda be focused to specific description topics, recorded in Section 2.0. The teleconference, to discuss the acceptability of the proposed CMC development plan to support the Phase 3 clinical studies, and ultimately the filing of the NDA, occurred on November 9, 2010. The minutes of that teleconference are recorded below.

2.0 DISCUSSION

2.1. DRUG SUBSTANCE QUESTIONS

Question 1: **GlaxoSmithKline propose to use the following materials as the registered starting materials for the manufacture of GSK1120212B. Does the Agency support our proposal?**

[redacted] (b) (4)

FDA Response to Question 1: For [redacted] (b) (4), the Agency does not agree with your proposal to designate the material as a starting material because the submitted information did not establish that future changes in the proposed starting material are unlikely to affect the quality of the drug substance. We recommend that you propose starting materials used earlier in the synthesis of the drug substance. The Agency does agree that [redacted] (b) (4) may be designated a starting material. The overall acceptability of any proposed starting materials will be assessed during the NDA review.

The designation of starting materials may be addressed in a Pre-NDA meeting when further information is available from your Phase 3 studies and your commercial process is finalized. Include the following information for each proposed starting material:

- Complete impurity profile and description of the impurity source (e.g. process impurity, degradant, etc.).
- In-house acceptance criteria, supplier information and Vendors' Certificates of Analysis.
- Brief description of the synthetic strategies and methods used for the manufacture of each proposed starting material.

- Detailed discussion regarding any impurities found in the proposed starting material, which may be carried forward into the drug substance.
- Description of the proposed controls and analytical methods that are suitable to quantitate the appropriate impurities. Validated analytical methods such as HPLC to assess the chemical and chiral purity of the proposed starting materials.
- Data from purging studies performed using potential impurities in the proposed starting materials to demonstrate the ability of the manufacturing process to remove and control the impurities to the desired levels in the drug substance.
- Change control strategies for any potential revisions to the manufacture of proposed starting materials, including the mechanism for vendor reporting of any manufacturing changes made for any proposed starting material.
- Supportive literature data, if available
- Description of the analytical methodology used for the drug substance that is capable of resolving and quantifying impurities carried over from the proposed starting materials as well as any process impurities that may result from the synthesis of the drug substance from the proposed starting materials.
- Data confirming the stability of the proposed starting materials.
- Reference standards for each proposed starting material and appropriate impurities, with appropriate impurity and characterization data.

Discussion: GSK acknowledged receipt of the responses from FDA. GSK acknowledged FDA's assessment that [redacted] (b) (4) may be a possible starting material, but due to the lack of data regarding [redacted] (b) (4) in the briefing package, the acceptability of it as a starting material could not be established at the meeting. GSK committed to provide additional data and revisit this discussion topic during their preNDA meeting.

Question 2: **Does the Agency agree that the testing proposed will suitably control the quality of the starting materials and support an appropriate control strategy for the NDA?**

FDA Response to Question 2: See response to Question 1.

Discussion: GSK acknowledged receipt of the FDA response. No further discussion occurred during the teleconference.

Question 3: **Based on the design intent of the drug product, GSK proposes** [redacted] (b) (4) **for control of particle size distribution of GSK1120212B for the NDA. Does the Agency agree with this proposal?**

FDA Response to Question 3: No particle size distribution data were provided in your meeting package, and insufficient information has been provided to justify this specification. It is unclear why you propose to limit the control of particle size to (b) (4) [redacted] Given the early stages of your understanding of the particle size distribution, which can affect bioavailability, content uniformity and dissolution behavior of your drug substance and drug product, a more complete characterization and control of your particle size distribution is advised at this point in your drug development. Revise your drug substance specifications to include a standard two-sided, three-point specification for the particle size distribution.

Discussion: GSK acknowledged receipt of the FDA response. No further discussion occurred during the teleconference.

Question 4: **Does the Agency agree with the proposed approach to control of (b) (4) [redacted] and setting of specification for DMSO solvate content in GSK1120212B?**

FDA Response to Question 4: Your approach to monitor the (b) (4) [redacted] of your drug substance using X-Ray Powder Diffraction (XRPD) method is reasonable (b) (4) [redacted] although the (b) (4) limit of detection may not provide sufficient control for the drug product (bioavailability, dissolution, etc) as development progresses.

The specification for DMSO solvate content (b) (4) [redacted] in your drug substance is acceptable from a quality standpoint as it meets the ICH Q3C limits for a Class 3 solvent. However, it may be a review issue for the pharmacology/toxicology discipline and should be addressed in your Pre-NDA meeting.

Discussion: GSK acknowledged receipt of the FDA response. No further discussion occurred during the teleconference.

Question 5: **Does the Agency agree that the tests proposed are suitable to control the quality of GSK1120212B drug substance and support an appropriate control strategy for the NDA?**

FDA Response to Question 5: The proposed Phase 3 specification for the drug substance in Table 14 is acceptable for control of the quality of Phase 3 clinical materials. See response to Question 4. For an NDA, the appropriate control strategy will be a review issue.

Discussion: GSK acknowledged receipt of the FDA response. No further discussion occurred during the teleconference.

Question 6: **GlaxoSmithKline propose the stability protocol as described in the briefing package for long term, accelerated, and stress testing of GSK1120212B drug substance. Does the Agency agree that this proposal is sufficient to support the Phase 3 clinical trials and the NDA?**

FDA Response to Question 6: No stability data for the drug substance were provided in the meeting package. While the stability proposal is acceptable for Phase 3 clinical trials, there is insufficient information provided to determine if the proposal is sufficient to support an NDA.

In your stability program, include a test and acceptance criterion for DMSO content in the drug substance stability specifications.

In your submission, you did not clearly specify how the three batches of drug substance manufactured at GSK, Jurong will differ from your commercial drug substance. Therefore, we cannot confirm acceptability of their use to generate primary NDA stability data.

Discussion: GSK acknowledged receipt of FDA's response and committed to provide further information, including a request for written responses to specific questions in their in the form of a submission to the IND in the 1Q 2011. FDA committed to review and respond to the questions in written form as time and reviewer resources allowed. Meeting participants acknowledged that this review would not occur under a PDUFA review clock.

GSK clarified that DMSO content is included in their drug substance stability program.

FDA emphasized that the batches of drug substance used to generate primary NDA stability data should be manufactured using the intended commercial process.

2.2. DRUG PRODUCT QUESTIONS

Question 1: **Does the Agency agree with the proposed approach to assess the impact of changes between Phase 3 and commercial for the product and manufacturing process?**

FDA Response to Question 1: There was insufficient information provided on the manufacturing process changes [redacted] (b) (4) intended for the 2 mg tablet (b) (4) [redacted] (b) (4) to assess the viability of your approach to show equivalence of the intended commercial tablets to the Phase 3 tablets by means of release testing and comparative dissolution. Note that demonstrating comparability in a low dose tablet with a [redacted] (b) (4) [redacted] may not be possible. See also our response to Question 2 below regarding the quality tests for your drug products.

Discussion: GSK acknowledged receipt of FDA's response and committed to provide further information, including a request for written responses to specific questions in their in the form of a submission to the IND in the 1Q 2011. FDA committed to review and respond to the questions in written form as time and reviewer resources allowed. Meeting participants acknowledged that this review would not occur under a PDUFA review clock.

Question 2: **Does the Agency agree that the tests proposed are suitable to control the quality of GSK1120212B Tablets and support an appropriate control strategy for the NDA?**

FDA Response to Question 2: Your approach is reasonable. However, add controls for (b) (4) and DMSO content to the drug product release and stability specifications. This is especially important as the drug substance (b) (4)

See also the response for question 3 for comments regarding the dissolution specifications.

Discussion: GSK acknowledged receipt of FDA's response and stated that (b) (4) DMSO content would be monitored (b) (4) For (b) (4) GSK proposed that it would be monitored (b) (4) FDA clarified that controls for (b) (4) DMSO content should include a test and numerical acceptance criteria for each of these quality attributes in release and stability specifications. GSK said that they would take this advice under consideration.

FDA asked for confirmation that this NDA would or would not be a QbD containing application. GSK stated that while it was unlikely that they would file the design space, QbD components and control strategy have been in place during development and in general they have followed a QbD approach.

Question 3: **Based on the drug product design intent, GlaxoSmithKline proposes a dissolution test procedure and preliminary specification (b) (4) . Does the Agency agree that the proposed method and specification are suitable for controlling the quality of GSK1120212B Tablets?**

FDA Response to Question 3: There seems to be inconsistent dissolution behavior between the data presented in Figure 12 (Table 29) and Figure 8 (or Figure 14). While the means of dissolution in (b) (4) are about (b) (4) respectively, in Figure 12 (page 56), the means in Figure 8 are more than (b) (4) respectively, especially considering that Figure 8 included data from the stability batches.

The proposed dissolution acceptance criterion of [redacted] (b) (4) is not adequate. From the variability plot in Fig 8, the lowest individual value of dissolution at [redacted] (b) (4) is more than [redacted] (b) (4)

According to these observations, we recommend the following:

1. Please explain the inconsistency observed in the submitted data.
2. If Figure 14 reflects the true behavior, consider optimizing the dissolution conditions.

Discussion: GSK acknowledged FDA's response and discussed the inconsistencies noted by FDA with respect to the dissolution method development and data presented in the briefing package. GSK will investigate these inconsistencies and discuss them at a future preNDA meeting. FDA committed to provide future feedback as part of the preNDA meeting preparation and discussion.

Question 4: **GlaxoSmithKline propose the stability protocol as described in the briefing package for long term, accelerated, and stress testing of GSK1120212B Tablets. Does the Agency agree that this proposal is sufficient to support the Phase 3 clinical trials and the NDA?**

FDA Response to Question 4: No stability data for the drug product were provided in the meeting package. While the stability proposal is acceptable for Phase 3 clinical trials, there is insufficient information provided to determine if the proposal is sufficient to support an NDA.

As advised in response to Question 2 (DP), add DMSO content to the stability specifications to monitor the content of unsolvated (parent) drug substance.

In your submission, you did not clearly specify how the three batches of drug product manufactured at GSK, Parma, Italy will differ from your commercial drug substance. Therefore, we cannot confirm acceptability of their use to generate primary NDA stability data.

Discussion: GSK acknowledged receipt of FDA's response and committed to provide further information, including a request for written responses to specific questions in their in the form of a submission to the IND in the 1Q 2011. FDA committed to review and respond to the questions in written form as time and reviewer resources allowed. Meeting participants acknowledged that this review would not occur under a PDUFA review clock.

GSK stated that they would add DMSO content to their stability program for the drug product and would consider establishing a numeric acceptance criteria. FDA advised GSK to include test and numeric acceptance criteria to control the DMSO content on stability.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

GSK confirmed that their intent to submit the NDA with all aspects of a Quality by Design containing application, save for a design space. FDA acknowledged GSK's intent for their records.

4.0 ACTION ITEMS

There are no other action items other than those included in the discussion section for each question included in section 2.0 (above).

5.0 CONCURRENCE

{See appended electronic signature page}

Scott N. Goldie, Ph.D.
Senior Regulatory Health Project Manager for Quality
Office of New Drug Quality Assessment
Office of Pharmaceutical Science
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Sarah Pope Miksinski, Ph.D.
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6.0 ATTACHMENTS AND HANDOUTS

There are no attachments or handouts for the meeting minutes.

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

/s/

SCOTT N GOLDIE
11/23/2010

SARAH P MIKSINSKI
11/29/2010

MEETING MINUTES

DATE: July 30, 2010 **TIME:** 10:00AM **LOCATION:** Room 1421

IND/NDA: IND: 102175 **Meeting Request Submission Date:** May 12, 2010
FDA Response Date: June 2, 2010
Briefing Document Submission Date: July 1, 2010

DRUG: GSK1120212 MEK1/2 Inhibitor

SPONSOR/APPLICANT: GlaxoSmithKline

TYPE of MEETING: Type B, EOP1/2, Pre Phase 3

Proposed Indication: Treatment of patients with BRAF V600E (b)(4)/K mutation positive advanced or metastatic melanoma.

FDA PARTICIPANTS:

Robert L. Justice, M.D., Acting Div. Director
Anthony Murgo, M.D., Associate Director
Virginia Maher, M.D., Clinical Team Leader *(Meeting Chair)*
Nancy Scher, M.D., Clinical Reviewer
Robeena Aziz, Ph.D., Pharmacology/Toxicology Reviewer
Leigh Verbois, Ph.D., Pharmacology/Toxicology Team Leader
Qi Liu, Ph.D., Clinical Pharmacology Team Leader
Pengfei Song, Ph.D., Clinical Pharmacology Reviewer
Shenghui Tang, Ph.D., Statistical Team Leader
Lijun Zhang, Ph.D., Statistical Reviewer
CDRH (waiting conf. from Donna Roscoe)
Kim Robertson, Consumer Safety Officer *(Minutes Recorder/Facilitator)*

GSK PARTICIPANTS:

Peter Lebowitz, M.D., Ph.D.., Clinical Development
Ngocdiep Lee, M.D., Ph.D.., Clinical Development
Kiran Patel, M.D.., Clinical Development
Doug DeMarini, Ph.D., Clinical Development
Michele Casey, Ph.D., Biostatistics
Ohad Amit, Ph.D., Biostatistics

Daniel Ouellet, Ph.D., Clinical Pharmacology
Kevin French, Ph.D., Non clinical Safety Assessment
Ann-Marie Martin, Ph.D., Oncology Biomarkers
Agnes Westelinck, PharmD., Regulatory Affairs
Eric Richards, MS, MPH, Regulatory Affairs

BACKGROUND:

GSK submitted a randomized, open-label, Phase 3 study comparing GSK 1120212 to dacarbazine or paclitaxel in patients that have received up to one prior therapy and have B-RAF V600E (b)(4)/K mutation positive advanced or metastatic melanoma. A 2:1 randomization scheme (GSK1120212:chemotherapy) will be utilized. Patients will be randomized to receive either GSK 1120212: 2 mg once daily, or one of the following two chemotherapies (chosen at the discretion of the investigator): DTIC 1000mg/m^2 once every 3 weeks or Paclitaxel 175mg/m^2. Both groups will continue, until disease progression, or premature withdrawal. The primary objective for this study is to establish the superiority of GSK1120212 over chemotherapy with respect to both progression-free and overall survival for patients with advanced/metastatic BRAF V600E/K/D mutation-positive melanoma. The secondary objectives for this study are to further characterize the efficacy, safety, and tolerability of GSK1120212 administered as a single agent for advanced or metastatic melanoma.

Clinical Draft Responses
IND 102,175
Internal: July 28, 2010

Clinical / Statistical Question 1

Question 2.1.1

Does the Agency agree with the inclusion of only B-RAF mutation positive melanoma subjects in the proposed Phase III MEK 114267 study?

FDA Response: Preliminary results in MEK111054 (at doses ≥ 2mg) show 8/20 responders (40%). Two subjects have had a CR. For subjects with B-RAF WT tumors, there were 2/22 responses (9%) with 3 subjects who were response-unknown. We recommend that you collect more data before concluding a lack of efficacy for B-RAF non-mutated tumors. However, it is your decision whether to include mutation positive subjects only in the proposed phase 3 trial, assuming adequate and timely co-development of an appropriate assay.

Discussion Point: No discussion necessary.

Clinical / Statistical Question 2

Question 2.1.2 Does the Agency agree with the Phase III MEK 114267 study population?

FDA Response: This is acceptable. Whether labeling will include both treatment-naïve patients and those who have received 1 prior cytotoxic regimen is a review issue.

Discussion Point: No discussion necessary.

Clinical / Statistical Question 3

Question 2.1.3 Does the Agency agree with allowing the investigator to choose a comparator of either dacarbazine or paclitaxel for subjects who are randomized to the control arm of the Phase III MEK 114267 study?

FDA Response: The proposed control arm is satisfactory, choice by investigator of either dacarbazine or paclitaxel.

Discussion Point: No discussion necessary.

Clinical / Statistical Question 4

Question 2.1.4 Does the agency agree with the dose rationale for the recommended Phase III dose of 2 mg QD?

FDA Response: The dose rationale for 2 mg daily dose of GSK1120212 appears acceptable.

Discussion Point: No discussion necessary.

Clinical / Statistical Question 5

Question 2.1.5 Does the agency agree with the co-primary endpoints of overall survival (OS) and PFS tested in a hierarchical fashion to maintain the overall Type I error rate for the Phase III MEK114267 study?

a. Given the possibility of changing treatment modalities that may affect the study's endpoints, does the agency agree that a stand-alone statistically-significant and clinically-meaningful benefit in PFS would be considered for an approval?

FDA Response: The relationship between progression free survival and clinical benefit has not been established in melanoma. We recommend that you evaluate OS as your sole primary endpoint.

Discussion Point: The Agency continues to recommend that OS be the sole primary endpoint. It is GSK's decision whether to use PFS as a primary endpoint and to cross patients over at progression. GSK may submit the protocol for comment. It is unlikely that an SPA agreement can be reached, unless the primary endpoint is OS.

Certainly, if GSK intends to conduct a study using PFS as the primary endpoint, the Agency will be willing to discuss the results including the magnitude of the difference between arms and the clinical relevance of this difference.

The Agency recommends that if GSK chooses to use PFS as the primary endpoint, that all scans be centrally and independently reviewed. The Agency is interested in a prospective examination of GSK's auditing procedure within this study.

Clinical / Statistical Question 6

Question 2.1.6 Does the agency agree that the Phase III MEK114267 study is adequately powered for PFS and OS?

FDA Response: The study is adequately powered for OS at the final analysis.

Discussion Point: No discussion necessary.

Clinical / Statistical Question 7

Question 2.1.7 Does the agency agree with the proposed interim analysis and planned alpha spending at the interim for the Phase III MEK114267 study?

FDA Response: No. Please see our response to 2.1.5.

Discussion Point: The Agency recommends using an O'Brien-Fleming spending function for the OS interim analysis.

Clinical / Statistical Question 8

Question 2.1.8 In determination of disease progression, does the agency agree with the proposal of investigator assessment as primary with blinded independent central review of a subgroup of subjects to audit the results in the local evaluation of the Phase III MEK114267 study?

FDA Response: See response to Question 2.1.5.

Although there has been discussion regarding the auditing approach, there has been no experience regarding this. We recommend that in this study you attempt to validate the approach by comparing blinded central review of all scans to your proposed audit approach.

Discussion Point: No discussion necessary.

Clinical / Statistical Question 9

Question 2.1.9 Does the agency agree with the proposed plan to address the B-RAF inhibitor-failure population in a label for B-RAF V600e/k/d mutation positive metastatic melanoma?

a. Given the high unmet need, which a B-RAF inhibitor-failure population would represent, does the agency agree with the proposed plan concerning the potential for accelerated approval in the B-RAF inhibitor - failure population?

FDA Response: There is an unmet medical need at the present time, but this would be reassessed at the time of action. It is premature to discuss the possibility of accelerated approval for this patient population.

Please note that it is unclear whether progression on a single B-RAF inhibitor will lead to resistance to other B-RAF inhibitors. Please state whether activity has been seen with GSK11202120 at the 2 mg level or whether a higher dose level has been tested in patients who have progressed on a B-RAF inhibitor.

Discussion Point: No discussion necessary.

Clinical / Statistical Question 10

Question 2.1.10 Does the agency agree with the proposed cardiac monitoring guidelines for the Phase III MEK114267 study?

FDA Response: The plan appears satisfactory.

Discussion Point: No discussion necessary.

Clinical / Statistical Question 11

Question 2.1.11 Does the agency agree that the Phase III pivotal study, supported by data from the Phase II study (MEK113583) in subjects who have received prior therapy, could support an indication similar to the following: "for the treatment of advanced or metastatic melanoma subjects with B-RAF V600E/K (b)(4) mutations"?

FDA Response: Possibly. The companion diagnostic used to select the population must be appropriately co-developed and approved by the time of drug approval.

Discussion Point: No discussion necessary.

Clinical Pharmacology

Clinical Pharmacology Question 1

Question 2.2.1 Does the Agency agree that the proposed clinical pharmacology study plan and associated timings is adequate to support a future NDA?

FDA response: No. Please also address the following issues:

a. **Determine the bioavailability (absolute or relative) of GSK1120212 in humans.**

Discussion Point: A micro-tracer study may be acceptable. The Agency asked that GSK submit their protocol for comments. GSK agreed.

b. **We recommend that you collect sparse PK samples from all patients that are treated with GSK1120212 in your Phase 3 trial to explore exposure-response relationships for efficacy and safety.**

Discussion Point: GSK agrees.

Clinical Pharmacology Question 2

Question 2.2.2 Does the Agency agree with the plan to initiate a prospective QTc study in cancer subjects for GSK1120212 based on ICH E14 principles to be initiated late in Phase III development with results available after submission of a future NDA?

FDA response: In general the design and timing of you proposed prospective QTc study is acceptable. Please submit your protocol for QT-IRT review before the initiation of the study.

In addition, you should continue to collect routine ECGs at steady state post-dose in the on-going clinical studies. For the registration submission, we recommend that you perform central tendency analysis and categorical analysis, in addition to the PK/PD analysis. Regarding your PK/PD analysis, please include the model predictions (together with the 90% confidence interval) at the steady state mean maximum concentration of GSK1120212.

Discussion Point: No discussion necessary.

Drug and Device Co-development

Question 2.3.1 Does the agency agree that the appropriate steps are being taken to co-develop a diagnostic device with GSK1120212?

FDA Response: CDRH discussion with GSK for pre-IDE I100245 on diagnostic device co-development for GSK2118436 is generally applicable for GSK1120212.

Key issues from previous discussion include implementation of measures to minimize patient prescreening by local labs before study entry and development of a sample banking protocol for both screen negative and screen positive samples. CDRH recommends using the final version of the device to accrue to the Phase III trial as early as possible. Please refer to pre-IDE I100245 comments for additional concerns including issues for analytical validation. CDRH has also indicated that there are scenarios in which a PMA supplement may not be appropriate (e.g. if there are different intended patient populations). GSK is advised to follow-up with CDRH.

Discussion Point: No discussion necessary.

Nonclinical PK and Toxicology

Nonclinical PK and Toxicology Question 1

Question 2.4.1 Does the Agency agree that, other than the planned studies described below, no additional toxicology studies would be required to support the proposed indication through to submission?

FDA Response: Yes; the non-clinical studies proposed in the current submission would appear to be sufficient to support the NDA submission. However, the submission of 3-month repeat dose toxicology studies is required prior to beginning Phase 3 clinical trials (please refer to ICH S9). Please confirm that completed studies have been submitted to the Agency at this time.

Discussion Point: No discussion necessary.

Pediatric Plans

Pediatric Plans Question 1

Question 2.5.1 Does the Agency agree that the proposed indication qualifies for a waiver of the Pediatric Rule for all applicable age groups (birth through 18 years)?

FDA Response: The request for a pediatric waiver should be made at the time of NDA filing.

Discussion Point: No discussion necessary.

GSK's July 19, 2010 Addendum Questions:

Does the FDA believe that the advice given to GSK concerning GSK2118436 has relevance for GSK1120212?

a) If so, does the agency agree with Progression Free Survival as a stand-alone primary endpoint for the proposed Phase III study?

FDA Response: No. Please see our response to Question 2.1.5.

Discussion Point: No discussion necessary.

b) Does the Agency agree with allowing patients on the comparator arm to crossover to GSK1120212 once they have progressed?

FDA Response: This will be your decision.

Discussion Point: No discussion necessary.

ADDITIONAL MEETING COMMENTS:

GSK intends to use a similar approach to assay development as that discussed under IND 105032. CDRH recommends that the Phase 3 study be conducted with the to be marketed assay.

Meeting Adjourned:
10:50AM

Meeting Chair:
V. Ellen Maher, M.D.

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/s/

VIRGINIA E MAHER
09/29/2010

Reference ID: 2842380
