

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202806Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 202806

SUPPL #

HFD # 107

Trade Name TAFINLAR

Generic Name dabrafenib

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

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
05/22/2013

PATRICIA KEEGAN
05/23/2013

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

NDA/BLA#: 202806 Supplement Number: _____ NDA Supplement Type (e.g. SE5): _____

Division Name: DOP2/OHOP PDUFA Goal Date: _____ Stamp Date: 7/30/2012
01/30/2013

Proprietary Name: Rafinlar

Established/Generic Name: dabrafenib

Dosage Form: capsules, 50 mg and 75 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

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 ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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.

Action 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	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

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
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	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?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

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 QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

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 ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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 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 †
				Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum					
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
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?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

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
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	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?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

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

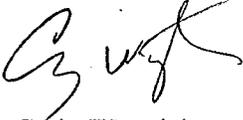
(Revised: 6/2008)

CONFIDENTIAL

m1.3.3 Debarment Certification

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 202806 Original NDA for dabrafenib for the treatment of patients with BRAF V600 mutation positive metastatic melanoma).



Craig Wozniak

May 2012

Head, Americas Clinical Operations

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 202806 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Tafinlar Established/Proper Name: dabrafenib Dosage Form: Capsule		Applicant: GlaxoSmithKline, LLC Agent for Applicant (if applicable): Not Applicable
RPM: Norma Griffin		Division: Division of Oncology Products 2 (DOP2)
<p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(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.)</p>		<p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>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.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>May 30, 2013</u> 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> 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., new listed drug, patent certification revised).

<p>❖ 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 _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics³</p> <p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): Type 1</p> <p><input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart I Subpart H <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Communication Plan <input type="checkbox"/> Submitted in response to a Pediatric Written Request <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required</p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action 	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> • Press Office notified of action (by OEP) 	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> • Indicate what types (if any) of information dissemination are anticipated 	<p><input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other OHOP ASCO Burst</p>

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	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>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.</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(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.)</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10-year limitation expires:
<p>❖ Patent Information (NDAs only)</p>	
<ul style="list-style-type: none"> 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. <i>Initial information verified. New information received on 5.1.2013 – trade name on the forms is ‘RAFINLAR’ and should be ‘TAFINLAR’. Corrected patent forms received on 5.9.2013.</i> 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> 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) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [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). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [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). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

(Summary Reviews)).

- [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?

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 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.

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist⁴

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

7/30/2012

- Example of class labeling, if applicable

N/A

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

<p>❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)</p> <p>Please note: This is attached with the PI.</p>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	5/29/2013
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	7/30/2012
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	N/A
<p>❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</p>	
<ul style="list-style-type: none"> • Most-recent draft labeling 	3/27/2013
<p>❖ Proprietary Name</p> <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • <i>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.</i> 	2/12/2013 (conditionally accepted letter) 2/12/2013 (review) 10/27/2012 (proprietary name request unacceptable letter) 10/26/2012 (review)
<p>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</p>	<input checked="" type="checkbox"/> RPM 5/9/2013 <input checked="" type="checkbox"/> DMEPA 4/23/2013 (final); 12/7/2012 (initial) <input checked="" type="checkbox"/> DMPP/PLT; 4/19/2013 <input type="checkbox"/> ODPD (DDMAC) 4/29/2013 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews 4/22/2013 (Maternal Health)
Administrative / Regulatory Documents	
<p>❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</p> <p>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</p> <p>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</p>	5/9/2013 (RPM Labeling Review) 10/2/2012 (RPM Filing Review) <input checked="" type="checkbox"/> Not a (b)(2) <input checked="" type="checkbox"/> Not a (b)(2)
<p>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</p>	<input checked="" type="checkbox"/> Included 5/23/2013
<p>❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</p>	
<ul style="list-style-type: none"> • Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Not an AP action

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

<p>Pediatrics (<i>approvals only</i>)</p> <ul style="list-style-type: none"> Date reviewed by PeRC <u>N/A</u> If PeRC review not necessary, explain: <u>Orphan Drug status – does not trigger PREA.</u> Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<p><input checked="" type="checkbox"/> Included <i>Orphan Drug status – does not trigger PREA.</i></p>
<p>❖ 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 (<i>include certification</i>)</p>	<p><input checked="" type="checkbox"/> Verified, statement is acceptable</p>
<p>❖ Outgoing communications (<i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i>)</p>	<p>5/29/2013 Labeling – 8th Round 5/28/2013 (evening) Labeling – 7th Round 5/28/2013 Labeling – 6th Round 5/24/2013 Labeling – 5th Round 5/23/2013 Labeling – 4th Round 5/22/2013 Labeling – 3rd Round 5/10/2013 Labeling – 2nd Round 5/8/2013 Request for New (corrected Patent Forms) 4/26/2013 Revised DRAFT Clinical PMRs 4/18/2013 Clinical IR 4/12/2013 Labeling (Proposed edits) 4/12/2013 Clinical IR 4/9/2013 Compliance Letter (blending uniformity) 4/4/2013 Clinical IR 4/3/2013 ClinPharm IR 4/2/2013 STATS IR 4/1/2013 CMC IR 3/29/2013 ClinPharm IR 3/27/2013 STATS IR 3/22/2013 ClinPharm (proposed PMR language) 3/20/2013 Labeling (DMEPA Container comments) 3/19/2013 Clinical IR 3/17/2013 STAT IR 3/14/2013 STATS IR (amended) 3/14/2013 STATS IR 3/8/2013 STS IR 3/6/2013 Labeling IR (nonREMSMG) 3/5/2013 STATS IR 3/5/2013 Clinical IR 2/1/2013 ClinPharm IR 1/29/2013 CMC IR 1/11/2013 CMC IR 1/2/2013 Clinical IR 12/27/2012 Clinical IR 12/21/2012 CMC IR 12/13/2012 ClinPharm IR (pharmacometrics) 12/5/2012 ClinPharm IR 12/3/2012 Method Validation Materials 10/31/2012 STATS IR 10/12/2012 Filing/74d Def. Letter</p>

	<p>9/20/2012 Clinical IR 9/17/2012 Labeling (SPL) IR 9/17/2012 CDRH & BIMO IR 9/14/2012 OSI IR 9/10/2012 STAT IR 9/6/2012 Clinical IR 9/6/2012 ClinPharm IR 9/4/2012 Labeling IR 8/15/2012 Ack Letter 8/14/2012 STATS IR 8/13/2012 STATS IR 7/20/2012 Presub Ack Letter 7/2/2012 STATS IR</p>
<p>❖ Internal memoranda, telecons, etc.4</p>	<p>5/31/2013 Memo to File – STATs Meetings 5/3/2013 Team Mtg 7 Final Issues (uploaded in DARRTS 5/8/2013) 4/2/2013 WrapUp Mtg Summary (uploaded in DARRTS 4/17/2013) 3/6/2013 Team Mtg 6 Summary (uploaded in DARRTS 4/17/2013) 1/30/2013 Labeling Mtg 4 (uploaded in DARRTS 4/17/2013) 1/29/2013 Labeling Mtg 3 (uploaded in DARRTS 4/17/2013) 1/25/2013 Labeling Mtg 2 (uploaded in DARRTS 4/17/2013) 1/22/2013 Labeling Mtg 1 (uploaded in DARRTS 4/17/2013) 1/9/2013 Team Mtg 5 Cancelled (uploaded in DARRTS 4/17/2013) 1/4/2013 Mid-Cycle Mtg Summary (uploaded in DARRTS 4/17/2013) 12/18/2012 Team Mtg 4 Summary (uploaded in DARRTS 4/17/2013) 11/15/2012 Team Mtg 3 Summary (uploaded in DARRTS 4/17/2013) 10/16/2012 Team Mtg 2 Summary (uploaded in DARRTS 4/17/2013) 9/18/2012 Team Mtg 1 Summary (uploaded in DARRTS 4/17/2013) 8/31/2012 Filing Mtg Summary (uploaded in DARRTS 4/17/2013) 8/15/2012 Planning Mtg Summary (uploaded in DARRTS 4/17/2013)</p>
<p>❖ Minutes of Meetings</p>	
<ul style="list-style-type: none"> Regulatory Briefing (<i>indicate date of mtg</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg May 9, 2012

<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> No mtg 2/24/2011 (EOP1/2 / PP3 w/ IND 102175) 7/6/2010 (EOP1 / PP3)
<ul style="list-style-type: none"> Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>) 	1/31/2012 (preNDA CMC Guidance)
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date(s) of Meeting(s) 	
<ul style="list-style-type: none"> 48-hour alert or minutes, if available (<i>do not include transcript</i>) 	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5/28/2013
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5/28/2013 (addendum) 5/20/2013
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5/16/2013
PMR/PMC Development Templates (<i>indicate total number</i>) – Total # PMR/PMCs = 11	<input type="checkbox"/> None 5/24/2013 (Clinical) 4/15/2013 (ClinPharm)
Clinical Information⁶	
❖ Clinical Reviews	
<ul style="list-style-type: none"> Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	5/15/2013 (final)
<ul style="list-style-type: none"> Clinical review(s) (<i>indicate date for each review</i>) 	5/15/2013 (final) 9/27/2012 (filing)
<ul style="list-style-type: none"> Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	5/15/2013 Clinical Review [See page 21 of 5/15/2013 Clinical Review (final)]
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not applicable
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input type="checkbox"/> None 4/29/2013
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input type="checkbox"/> None requested 3/20/2013 Clinical Inspection Russia (VAI) 2/8/2013 (OSI Summary Inspection) 1/22/2013 Clinical Investigator Program – US - NAI

⁶ Filing reviews should be filed with the discipline reviews.

	1/22/2013 Clinical Investigator Program – France - NAI
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None Concurred 4/10/2013 ¹
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None Concurred 4/10/2013 ¹
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None 4/10/2013 ¹ All combined 9/4/2012 (filing)
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None Concurred 4/4/2013 ²
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None Concurred 4/4/2013 ²
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None 4/4/2013 ² All combined 10/2/2012 (filing)
❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input type="checkbox"/> None 4/25/2013
• Supervisory Review(s) (indicate date for each review)	<input type="checkbox"/> None 4/17/2013
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None 4/11/2013 8/31/2012 (filing)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None requested

Product Quality <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
<ul style="list-style-type: none"> • ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i> 	<input type="checkbox"/> None 5/28/2013
<ul style="list-style-type: none"> • Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i> 	<input type="checkbox"/> None Concurred 4/10/2013 (for drug substance and drug product – included with Reviewer’s) 2/8/2013 (biopharmaceutics – included with Reviewer’s)
<ul style="list-style-type: none"> • Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i> 	<input type="checkbox"/> None 5/2/2013 Memos to File for drug substance and drug product – memo also refers to Facilities inspection) 4/10/2013 (drug substance) 4/10/2013 (drug product) 2/8/2013 (biopharmaceutics) 8/31/2012 (ONDQA CMC filing) 8/31/2012 (biopharmaceutics-filing)
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed 2/13/2013
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	4/10/2013 (drug product review) – see page 83 of 94 of the review.
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(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 sites⁷)</i>	Date completed: 5/21/2013 <input checked="" type="checkbox"/> Acceptable – April 30, 2013 <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

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.

❖ NDAs: Methods Validation (*check box only, do not include documents*)

- Completed
- Requested
- Not yet requested
- Not needed (per review)



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 12:42 PM
To: 'Eric Richards'; Ellen Cutler
Cc: Hughes, Monica L; Libeg, Meredith
Subject: NDA 202806 - FDA Request for TCON to finalize Labels

Importance: High

Attachments: TAFINLAR FDA 5.28.2013 Edits to GSK CLEAN.doc; TAFINLAR FDA 5.28.2013 Edits to GSK Tracked Changes.pdf
Ellen,

Please see the attached FDA proposed labeling for NDA 202806 - 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
US dial-in number

(b) (4)

Thanks,

Eric Richards
Global Regulatory Affairs
Internal phone: 8-202-6842
External: 610-917-6842
Mobile: [REDACTED] ^{(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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NORMA S GRIFFIN
05/30/2013

From: Griffin, Norma
Sent: Friday, May 24, 2013 4:34 PM
To: 'ellen.s.cutler@gsk.com'
Cc: 'eric.2.richards@gsk.com'; Libeg, Meredith; Hughes, Monica L
Subject: NDA 202806 TAFINLAR (dabrafenib) - FDA Proposed Edits 5.23.2013

Importance: High

Attachments: TAFINLAR dabrafenib FDA 5.24.2013 Edits to GSK Agreed During TCON.pdf; TAFINLAR dabrafenib FDA 5.24.2013 Edits to GSK Agreed During TCON CLEAN.doc

Good Afternoon Ellen,

Please see the attached proposed labeling edits (5.24.2013) for NDA 202806 as agreed to in our TCON held this afternoon. I have included both a CLEAN WORD (as much as could be finalized) document and a Tracked Changes PDF document. There are still a few items that need to be addressed.



TAFINLAR
brafenib FDA 5.24.2



TAFINLAR
brafenib FDA 5.24.2

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
05/30/2013



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

Memorandum

Date: May 22, 2013
From: Norma Griffin, Regulatory Health Project Manager DOP2/OHOP
Subject: NDA 202806: Financial Disclosure

Financial disclosure information submitted under this NDA was reviewed in the clinical review prepared by Dr. Marc Theoret. Please refer to page 21 of the May 15, 2013, clinical review.

From: Griffin, Norma
Sent: Thursday, May 23, 2013 1:38 PM
To: 'ellen.s.cutler@gsk.com'
Cc: 'eric.2.richards@gsk.com'; Libeg, Meredith; Hughes, Monica L
Subject: RE: NDA 202806 TAFINLAR (dabrafenib) - FDA Proposed Edits 5.23.2013

Importance: High

Attachments: FDA 5.23.2013 MedGuide Edits to GSK Tracked Changes.pdf; FDA 5.23.2013 MedGuide Edits to GSK CLEAN.doc

Good Afternoon Ellen,

Please see the attached proposed labeling edits (5.23.2013-MedGuide) for NDA 202806. 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.



FDA 5.23.2013
MedGuide Edits t...



FDA 5.23.2013
MedGuide Edits t...

As I had indicated to you yesterday, this version is the one that you received yesterday with the addition of edits from our Patient Labeling reviewer for the Medication Guide. This version also includes the deletion (b) (4) from section 17, and the deletion (b) (4) from Table 2 in section 6.1.

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

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
05/23/2013

From: Griffin, Norma
Sent: Tuesday, May 28, 2013 7:21 PM
To: 'Ellen Cutler'
Cc: Eric Richards; Hughes, Monica L
Subject: NDA 202806 TAFINLAR (dabrafenib) - Final Agreed Labeling

Importance: High

Attachments: TAFINLAR FDA 5 28 2013 Edits to GSK Tracked Changes During TCON FINAL.doc;
TAFINLAR FDA 5 28 2013 Edits to GSK Tracked Changes During TCON FINAL.pdf
Good Evening Ellen,

Attached is the final labeling for NDA 202806 TAFINLAR (dabrafenib) 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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/s/

NORMA S GRIFFIN
05/30/2013

From: Griffin, Norma
Sent: Wednesday, May 22, 2013 9:18 AM
To: 'ellen.s.cutler@gsk.com'
Cc: 'eric.2.richards@gsk.com'; Libeg, Meredith; Hughes, Monica L
Subject: NDA 202806 TAFINLAR (dabrafenib) - 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 Tracked Changes.pdf

Good Morning Ellen,

Please see the attached proposed labeling edits (5.22.2013) for NDA 202806. 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 Tra...

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
05/22/2013

From: Griffin, Norma
Sent: Friday, May 10, 2013 5:24 PM
To: 'ellen.s.cutler@gsk.com'
Cc: 'eric.2.richards@gsk.com'; Libeg, Meredith; Hughes, Monica L
Subject: NDA 202806 TAFINLAR (dabrafenib) - FDA Proposed Edits 5.10.2013

Importance: High

Attachments: FDA Proposed Edits 5.10.2013 to GSK 4.23.2013 Response CLEAN.doc;
FDA Proposed Edits 5.10.2013 to GSK 4.23.2013 Response Trkd Chngs.pdf

Good Afternoon Ellen,

Please see the attached proposed labeling edits (5.10.2013) for NDA 202806. I have included both a CLEAN WORD document and a Tracked Changes PDF document. In addition, this round of edits includes edits from Patient Labeling jfor the proposed MedGuide. 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 Edits
5.10.2013 t...



FDA Proposed Edits
5.10.2013 t...

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

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.

From: Griffin, Norma
Sent: Wednesday, May 08, 2013 1:52 PM
To: 'Ellen Cutler'
Subject: NDA 202806 GSK - Trade Name on new Patent Forms (Sequence 0060)

Importance: High
Good Afternoon Ellen,

For your Sequence 0060 submission (new Patent information), the Trade name listed on the Forms 3542a was [REDACTED] (b) (4)
Please resubmit with the correct name 'TAFINLAR'.

Thanks and kindly respond to confirm receipt of this email.

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

**Team Meeting #7 – Final Issues - Summary
May 3, 2013**

NDA: 202806

Product: Tafinlar (dabrafenib)
Submission Date: July 29, 2012
Received Date: July 30, 2012
Sponsor: GlaxoSmithKline (GSK), LLC
Action Goal Date: **Thursday, May 30, 2013.**

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation

Meeting Participants

Patricia Keegan, M.D., Director DOP2
Monica Hughes, CPMS
Norma Griffin., Regulatory Health Project Manager
Meredith Libeg, Regulatory Health Project Manager
Suzanne Demko, Clinical TL and CDTL
Marc Theoret, M.D., Clinical Reviewer
Vivian Yuan, Statistics
Hong Zhao, Ph.D, Clinical Pharmacology (TL)
Jian Wang, Clinical Pharmacology Reviewer
Whitney Helms, Nonclinical (TL)
Alex Putman, Nonclinical Reviewer
Mahesh Ramanadham, OC (Facilities)
Sue Kang, OSE, Safety RPM
James Schlick, OSE Proprietary Name Reviewer
Melissa Tassinari, Maternal Health (for Tammie Brent Howard)
Latonia Ford, Patient Labeling
Amarilys Vega, DRISK
Donna Roscoe, CDRH Consultant

Discussion Items

1. Action Goal Date (10-month review): Standard 10-month review with the PDUFA

Action Goal Date of Thursday, May 30, 2013.

- Final EES (facilities inspection associated with (b) (4) issue) was receive and acceptable.

2. Outstanding Issues:
 - a. Need Clinical Review

- b.** Clinical to review GSK response to Clinical PMR templates – will update/modify and finalize to upload into DARRTS.
- c.** Information for DRAFT Press Release
 - i. Will provide sections from CDTL Summary next week.
- d.** Burst – DRAFT is with Division Director for review before going to OHOP.
- e.** Agreement on Proposed Labeling
 - i. Clinical – GSK is pushing back on brain mets.
 - ii. RPM to add in OPDP’s labeling comments.
 - iii. Schedule one final meeting for Tuesday, 5.7.2013 to address GSK response of 4.23.2013. Will include Patient Labeling edits (MedGuide), comments and edits from Maternal Health (section 5 and 8), ClinPharm (section 7 and 12), CMC (section 11), Nonclinical (sections with maternal health), and Clinical.
- f.** DRAFT Approval Letter – with CPMS (Monica Hughes) before going to the TEAM.
 - i. Clinical PMRs to be finalized in the letter – PMR/PMC set number is assigned (2044)
 - ii. Labeling to be finalized in the letter
- g.** Action Package – with CPMS as of 5.2.2013

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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: April 26, 2013
From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 202806; GlaxoSmithKline, LLC
Proposed Clinical PMRs – Revised DRAFT

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

Dear Ms. Cutler:

Please see FDA's post-marketing requirement proposal for the Tafinlar (dabrafenib) NDA application 202806. This language has been revised based on our teleconference held on April 19, 2013 and your email response for PMR #3 provided on April 24, 2013. Please submit your response and provide timelines to our proposal by Tuesday, April 30, 2013.

Post Marketing Requirements (PMRs) Under 505(o)

CLINICAL

1. Submit the final analyses of safety from all ongoing randomized controlled clinical trial(s) using the hydroxypropyl methylcellulose formulation of dabrafenib as monotherapy to identify and characterize unexpected serious risks from longer duration of exposure.

Milestones

Final Analysis Plan Submission:

Trial Completion (last patient enrolled last assessment):

Final Report Submission:

2. 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 new primary malignancies, including cutaneous squamous cell carcinoma, in all ongoing and subsequently initiated randomized controlled clinical trials through 2020 that use dabrafenib alone or in combination. In addition to a cumulative listing of all cases, include the following summary analyses as well as any additional informative analyses of new primary malignancies in each report:
 - Incidence rates, overall and stratified by tumor type, for each arm of the trial(s)
 - Timing of onset in regard to exposure to dabrafenib (i.e., timing from first and last dose)

- Prognostic features relevant to each tumor type (e.g., clinicopathological features, including pertinent molecular characteristics, as well as disease staging information)
- Treatment(s) administered by tumor type
- Outcome

Milestones

Final Analysis Plan Submission:

Interim Report Submission:

Final Report Submission:

3. Submit integrated safety analyses of cardiac valvular abnormalities based on centralized, blinded, independent review assessment of all echocardiograms from an adequate number of randomized controlled clinical trials that use dabrafenib as monotherapy or in combination to inform the label regarding incidence rate and natural history of the safety signal.

Submit the first interim report within six months of the date of FDA-approval of NDA 202806 and every two years thereafter until FDA determines that the final report submission fulfills this postmarketing requirement.

Milestones

Final Analysis Plan Submission:

Trial Completion (last patient enrolled last assessment):

Interim Report Submission:

[To GSK: Propose milestone dates for the estimated number of interim report submissions]

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
04/26/2013



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

Memorandum

Date: April 18, 2013
From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 202806; GlaxoSmithKline, LLC
Clinical Comments and Information Request

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

Dear Ms. Cutler:

Please refer to your New Drug Application (NDA) NDA 202806 for product “(dabrafenib)” received on July 31, 2012.

Our Clinical Reviewer has the following comments and information request and requests a response by close of business Friday, April 19, 2013, **or sooner if possible**.

1. According to the most recent follow-up IND Safety Report submitted for patient BRF113220/2858 (patient who developed a pancreatic adenocarcinoma second primary malignancy), the patient was going to undergo a biopsy of the pancreatic adenocarcinoma for the purposes of RAS testing. Please provide the results of RAS testing for this patient, if performed.
2. In follow-up to Item # 4 of your March 11, 2013, response to our March 6, 2013, Information Request, please provide the results of the RAS testing for the squamous cell carcinoma of the head neck tumor (Patient BRF113220/2183).

In addition, please provide the timing (Study Day) of the onset of the new primary malignancy in relation to the first dose of dabrafenib and the last dose of dabrafenib for the following patients:

Study/ Pt ID/ Age/Gender	Second Malignancy
BRF114144/ 101113/ 50/F	Myelodysplastic syndrome
BRF113252/ IT78/ 72/M	Gastric adenocarcinoma
BRF113252/ US5/ 64/F	Invasive ductal carcinoma of the breast
BRF113220/ 951/ 48/M	Renal cell carcinoma
BRF113220/ 2183/ 62/M	Squamous cell carcinoma of the head and neck
BRF113220/ 2442/ 55/F	Glioblastoma
BRF113220/ 2858/ 62/M	Pancreatic adenocarcinoma
BRF113220/ 2918 BRF113252/ AUS66 57/M	Recurrent metastatic colon adenocarcinoma

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
04/18/2013



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

Memorandum

Date: April 12, 2013
From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 202806; GlaxoSmithKline, LLC
Proposed PMRs

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

Dear Ms. Cutler:

Please see FDA's post-marketing requirement proposal for the Tafinlar (dabrafenib) NDA application 202806. Please submit your response and provide timelines to our proposal by Tuesday, April 16, 2013.

Post Marketing Requirements (PMRs) Under 505(o)

CLINICAL

- Submit safety analyses from additional randomized controlled clinical trial(s) of adequate size to allow for the identification and characterization of adverse reactions that occur at 1% or greater incidence rate associated with longer duration exposure.
- Submit safety analyses annually, and for one year after the last patient has completed clinical trial treatment, of new primary malignancies-from all ongoing and subsequently initiated randomized controlled clinical trials using dabrafenib alone or in combination.
- Submit an integrated safety analysis of cardiac valvular abnormalities based on centralized, blinded, independent review assessment of all echocardiograms from an adequate number of randomized controlled clinical trials using dabrafenib to inform the label regarding incidence rate and natural history of this safety signal.

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
04/12/2013

From: Griffin, Norma
Sent: Friday, April 12, 2013 5:02 PM
To: 'ellen.s.cutler@gsk.com'
Cc: 'Amita.M.Chaudhari@gsk.com'; 'eric.2.richards@gsk.com'
Subject: FW: NDA 202806 GSK - FDA Proposed Labeling

Importance: High

Attachments: FDA Proposed Edits as of 4.12.2013 CLEAN.doc; FDA Proposed Edits as of 4.12.2013 Tracked Changes.pdf
Sorry All, my subject line was incorrectly included from my email this morning.

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: Friday, April 12, 2013 4:58 PM
To: 'ellen.s.cutler@gsk.com'
Cc: 'Amita.M.Chaudhari@gsk.com'; 'eric.2.richards@gsk.com'
Subject: RE: NDA 202806 GSK - FDA Memorandum - Proposed Clinical PMRs
Importance: High

Good Afternoon Ellen,

Please see the attached proposed labeling edits for NDA 202806. I have included both a CLEAN WORD document and a Tracked Changes PDF document. In addition, your recently proposed MedGuide is attached to the PI, however, we have not completed our edits for the MED GUIDE yet. There are only a few edits from DMEPA at the section of "How Should I Take Tafinlar". Patient Labeling still needs to review the Med Guide and provide comments.

We ask that you provide a response by Friday, April 19, 2013.

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*

65 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page



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. Ellen Cutler
Senior Director, Regulatory Affairs, Oncology
1250 South Collegeville Road
Collegeville, PA, 19426

Dear Ms. Cutler:

We have completed our review of response to question #2 the Information Request sent on January 11, 2013.

Your evaluation to demonstrate uniformity (b) (4) is limited (b) (4)

The absence of this data does not equate to a lack of variability within each location, but limits the ability to conclude uniformity.

(b) (4)

The acceptance criteria presented in your response will not demonstrate adequacy of mix 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 of mix testing to conform to Current Good Manufacturing Practices.

Please reply to this letter by email by April 19, 2013. 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 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 Goen
Branch Chief (Acting)
New Drug Manufacturing Assessment Branch
Division of Good Manufacturing Practice Assessment
CDER / OC / OMPQ



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 202806; GlaxoSmithKline, LLC
Specific Dates for Proposed PMR

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

Dear Ellen/Amita:

We refer to your New Drug Application (NDA) NDA 202806 for product “(dabrafenib)” received on July 31, 2012.

I also refer to the following proposed PMR language:

PMR - QT/QTc interval prolongation Trial:

Complete a clinical trial evaluating the potential for dabrafenib to prolong the QT/QTc interval in accordance with the principles of the FDA Guidance for Industry entitled “E14 Clinical Evaluation of QT/QTc Interval Prolongation”. Submit the final report that includes central tendency, categorical and concentration-QT analyses, along with a thorough review of cardiac safety data.

<i>Final protocol Submission:</i>	<i>Submitted</i>
<i>Study/Trial Completion:</i>	<i>1Q 2014</i>
<i>Final Report Submission:</i>	<i>4Q 2015</i>

PMR - Hepatic Impairment Pharmacokinetic Trial:

Complete a clinical pharmacokinetic trial to determine the appropriate dabrafenib dose in patients with moderate to severe 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”.

<i>Final protocol Submission:</i>	<i>Submitted</i>
<i>Study/Trial Completion:</i>	<i>3Q 2014</i>
<i>Final Report Submission:</i>	<i>2Q 2015</i>

PMR - Renal Impairment Pharmacokinetic Trial

Complete a clinical pharmacokinetic trial to determine the appropriate dabrafenib dose in patients with severe renal impairment in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling”.

<i>Final protocol Submission:</i>	<i>Submitted</i>
<i>Study/Trial Completion:</i>	<i>3Q 2014</i>
<i>Final Report Submission:</i>	<i>2Q 2015</i>

PMR - Drug Drug Interaction Trial

Conduct a drug interaction trial to evaluate the effect of rifampin (a strong CYP3A4 and CYP2C8 inducer) on the repeat dose pharmacokinetics of dabrafenib in accordance with the FDA Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations”. The results of this clinical trial should allow for a determination on how to dose dabrafenib with regard to concomitant strong CYP3A4 and CYP2C8 inducers.

<i>Final protocol Submission:</i>	<i>2Q 2013</i>
<i>Study/Trial Completion:</i>	<i>4Q 2014</i>
<i>Final Report Submission:</i>	<i>2Q 2015</i>

For the dates listed above in **RED** that only list the quarter, please indicate the specific milestone (month) date for these and provide your response by April 4, 2013 in order to incorporate the timelines into our clinical pharmacology review. If the specific dates (**month**) were already submitted to the NDA, please indicate the submission date and serial/sequence number.

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

Wrap-Up Meeting Summary
April 2, 2013

NDA: 202806

Product: Tafinlar (dabrafenib)
Submission Date: July 29, 2012
Received Date: July 30, 2012
Sponsor: GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation

Participants:

Patricia Keegan, M.D., Director, DOP2
Joseph Gootenberg, M.D., Deputy Director, DOP2
Karen Jones, CPMS, DOP2
Monica Hughes, CPMS, DOP2
Norma Griffin, Regulatory Health Project Manager
Marc Theoret, Clinical Reviewer, DOP2
Kun He, Statistics (TL)
Weishi (Vivian) Yuan, Statistics
Hong Zhao, Clinical Pharmacology (TL)
Rosane Charlab Orbach, Genomics (TL)
Christian Grimstein, Genomics Reviewer
Whitney Helms, Nonclinical (TL)
Alexander Putman, Nonclinical Reviewer
Nallaperumal Chidambaram, Acting Branch Chief, ONDQA
Liang Zhou, ONDQA
Amit Mitra, Product Quality Reviewer, ONDQA
Gaetan Ladouceur, Product Quality Reviewer, ONDQA
Mahesh Ramanadham, OC (Facilities)
Sue Kang, OSE, Safety RPM
James Schlick, DMEPA
Todd Bridges, DMEPA
Donna Roscoe, CDRH Consultant
Katherine Coyle, DPVII
Peter Waldron, DPVII
Amarylis Vega, DRISK
Vicki Moyer, Maternal Health
Adel Abou-Ali, OSE, DEPII
Latonia Ford, Patient Labeling

Discussion Points

Important Goal Dates

Primary Review Due	April 4, 2013
Secondary Review Due	April 11, 2013
CDTL Review Due	April 18, 2013
Division Director Review Due	May 9, 2013
Send proposed labeling/PMR/PMC/REMS to applicant	April 11, 2013

PDUFA Goal Date **May 30, 2013**

Discipline Specific Reviews of Application

- a. Clinical: Presented summary of review. Will have possibly 2 Clinical PMRs. Need to finish review to incorporate into the labeling. Need information from STATS (to be provided by Friday, April 5, 2013). Scheduled to have review complete by April 15, 2013. DRAFT review to be provided to DRISK.

Clinical Protocol/Site inspection: Clinical Inspection Summary completed and uploaded into DARRTS as of 2.8.2013
- b. Statistics: In response to recent IR, Sponsor has come back with new algorithm. STATS will rerun the efficacy analysis. STATS will provide information to Clinical, and CDRH. Scheduled to have review done between 4.6-4.9.2013
- c. Clinical Pharmacology: Review is currently under review by DD and will be ready to upload to DARRTS by 4.4.2013. All the milestone timelines for PMR/PMC have been confirmed by the sponsor. Sponsor to confirm PMR/PMC dates (specific date vs. 'specified quarter'). PMR/PMC language to be sent to RPM for inclusion in the DRAFT letter.
- d. Genomics: No PMR/PMCs – review to be included with ClinPharm.
- e. CMC: IR Comments to be sent to Sponsor regarding Heavy Metals testing (request to remove the footnote regarding Heavy Metals testing in the specifications).
- f. CMC (Microbiology): Review in DARRTS 2.13.2013
- g. CMC (facilities): [REDACTED] ^{(b) (4)} issue. FDA to state to Sponsor that they do not agree with the Sponsor [REDACTED] ^{(b) (4)}. This issue is also associated with the trametinib NDA. FDA to contact sponsor by end of week.
- h. Biopharmaceutics: Review in DARRTS 2.8.2013
- i. Nonclinical: Review is currently in secondary review. Review should have final signature by 4.11.2013.

j. CDRH: Waiting on data from Clinical.

Pending Consults

- a. DMEPA – Proprietary Name (TAFINLAR) is acceptable – Proprietary Name Request Conditionally Acceptable letter issued on 2.12.2013. No additional final letter is needed.
- b. DSI Inspection – Clinical Inspection Summary in DARRTS on 2.8.2013
 - VAI-Foreign Inspection - Russia – in DARRTS on 3.20.2013
 - SM Inspection (NAI) – Collegeville, PA – in DARRTS on 1.22.2013
 - CI Foreign (NAI) – France – in DARRTS on 1.22.2013
- c. Maternal Health – review will be signed on or before 4.18.2013.
- d. DRISK – review is ready but need final Clinical labeling comments.

Labeling Discussion

FDA proposed edits due to Sponsor by Thursday, 4.11.2013. All labeling revisions complete by Wednesday, April 10, 2013. Clinical to work on completing labeling revisions by next week.

- Requested non-REMS MedGuide which was received 3.14.2013.
- Container Labeling comments sent to the Sponsor on 3.20.2013 with response from Sponsor on 3.27.2013.

Discuss Postmarketing Commitments

There will be 6 Clin/Pharm PMRs, 1 Clin/Pharm PMC, and possibly 2 Clinical PMRs. RPM to contact Sponsor to request that they provide specific dates in their proposed language – not listing as a ‘specified quarter’.

Discuss Postmarketing Safety Surveillance Plan: This will be routine safety surveillance.

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.

Discussion of sign-off procedure and schedule

Final primary and secondary reviews need to be completed (by April 11, 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 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

From: Martin, Jewell
To: ["Kathleen Church"](#)
Cc: [Griffin, Norma](#)
Subject: NDA 202806 Information Request
Date: Monday, April 01, 2013 12:47:00 PM

Hello Kathleen,

Please provide the following information by COB April 2, 2013:

We do not agree with your proposal (b) (4)
(Footnote 2. in
Specification for Dabrafenib Mesylate, Micronized (b) (4)
(b) (4)
) . Remove Footnote 2 in section
S.4.1 and provide a revised specification Table of dabrafenib mesylate.

In addition to formally submitting this information. Please provide me with a courtesy copy via email.

Best,

Jewell

Jewell D. Martin, MA, MBA, PMP
Product Quality Regulatory Project Manager
Office of New Drug Quality Assessment
Food and Drug Administration
White Oak Building 21, Rm 2625
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002
(301) 796-2072
jewell.martin@fda.hhs.gov

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/s/

JEWELL D MARTIN
04/02/2013

From: Griffin, Norma
Sent: Friday, March 29, 2013 2:23 PM
To: Amita.M.Chaudhari@gsk.com; ellen.s.cutler@gsk.com
Cc: eric.2.richards@gsk.com
Subject: NDA 202806 GSK - ClinPharm IR 3.29.2013 - Update on Drug-Drug Interaction Trial BRF113771

Importance: High

Amita/Ellen:

Could you please provide an update regarding the Drug-Drug Interaction Trial BRF113771?

"A Four-Part, Open-Label Study to Evaluate the Effects of Repeat Dose GSK2118436 on the Single Dose Pharmacokinetics of Warfarin, the Effects of Repeat Dose Oral Ketoconazole and Oral Gemfibrozil on the Repeat Dose Pharmacokinetics of GSK2118436, and the Repeat Dose Pharmacokinetics of GSK2118436 in Subjects with BRAF Mutant Solid Tumors "

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

Reference ID: 3305644

file:///N:/...29.2013 Update on Drug-Drug Interaction Study/ClinPharm IR 3.29.2013 - Update on Drug-Drug Interaction Trial BRF113771.htm[5/8/2013 2:34:06 PM]

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/s/

NORMA S GRIFFIN

05/08/2013

This memo (IR) was sent on 3.29.2013 but 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: 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 22, 2013
From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 202806; GlaxoSmithKline, LLC
Proposed PMC Language

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

Dear Ms Cutler:

We refer to your New Drug Application (NDA) NDA 202806 for product “(dabrafenib)” received on July 31, 2012.

Clinical Pharmacology proposed the following **Post Marketing Commitments (PMC) for “dabrafenib”**:

Conduct a clinical trial to evaluate if proton pump inhibitors, H₂ antagonists, and antacids alter the bioavailability of dabrafenib. You may study the worst case scenario first, and then determine if further studies of other drugs are necessary. The study results should allow for a determination on how to dose dabrafenib with regard to these gastric pH elevating agents.

Please provide the milestone timelines for this trial by March 29, 2013 in order to incorporate the timelines into our clinical pharmacology review.

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
03/22/2013



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 202806; GlaxoSmithKline, LLC
Tafinlar Container Labeling – Comments and Proposed Edits

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

Dear Ms. Cutler:

Please refer to your New Drug Application (NDA) NDA 202806 for product “Tafinlar (dabrafenib)” received on July 31, 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**.

1. Relocate “120 Capsules” further to the bottom of the principal display panel and unbold the statement. Additionally, relocate the product strength to just under “(dabrafenib) Capsules”. 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. Relocate “Rx only” statement further to the bottom of the principal display panel and unbold.
3. Capitalize the letter ‘d’ in the established name that is immediately below the proprietary name on the principal display panel.
4. Choose a color (b) (4) to express the strength on the 50 mg label (b) (4)
[REDACTED]
When selecting a new color to express the 50 mg strength, ensure that the color is not a color used on the 75 mg label.
5. Include a space between “50” and “mg” on the principal display panel so that the strength presentation is easier to read. Do the same for the 75 mg label.

6. Ensure the established name is at least $\frac{1}{2}$ 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).

In addition, please advise on when you will submit the container labeling bearing the new proprietary name ‘Tafinlar’.

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
03/20/2013



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

Memorandum

Date: March 19, 2013
From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 202806; GlaxoSmithKline, LLC
Clinical Comments and Information Request

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

Dear Ms. Cutler:

Please refer to your New Drug Application (NDA) NDA 202806 for product “(dabrafenib)” received on July 31, 2012.

Our Clinical Reviewer has the following comments and information request and requests a response by close of business Wednesday, March 20, 2012, **or sooner if possible**.

1. Please provide further clarification of your March 11, 2013, response to FDA request #1. Specifically, it is not clear whether listings where the derived variable “SDCPRSCD” is coded to 91 (disease progression) represents information that was missing and subsequently imputed or information that was derived from a raw variable or variables recorded in a different eCRF. According to the annotated case report form for the “GSK2118436 Discontinuation” form, the SDRSCD raw variable that came directly from the eCRF included a date entry selection for disease progression (SDRSCD=91) which could have been selected directly by Investigators, in addition to the data entry selections for AE (SDRSCD=1), investigator discretion (SDRSCD=7), and subject decision (SDRSCD=8).
 - a. Why was information concerning discontinuation due to disease progression excluded from the SDRSCD raw variable in the listings in the RIPDISC.xpt dataset since, according to the “GSK2118436 Discontinuation” eCRF, investigators could have directly selected disease progression as the reason for early discontinuation?
 - b. If not SDRSCD, what raw variable recorded the investigator’s selection of “disease progression” as the reason discontinuation of GSK2118436.

- c. If the data for patients who discontinued GSK2118436 based on disease progression (SDCPRSCD = 91) was imputed or derived, please detail the method used to determine that the 115 patients discontinued due to disease progression.

Please state whether the method for coding patients as discontinuing GSK1120212 due to disease progression (SDCPRSCD variable code = 91) was the same in the datasets submitted for Trial MEK114267 (NDA 204114) as that used in the datasets submitted for Trial BRF113683.

2. According to the most recent follow-up IND Safety Report submitted for patient BRF113220/2442, the patient who developed a glioblastoma second malignancy while participating in Trial BRF113220, additional molecular testing was to be performed (studies for EGFR, PTEN, MGMT, and 1P19Q deletion). Please submit the results of this testing.

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
03/19/2013



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 14, 2013
From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDAs 202806; GlaxoSmithKline, LLC
Amended IR and SAS Codes

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

Dear Ms. Cutler:

Please refer to your New Drug Applications (NDA) 202806 for “dabrafenib” received on July 30, 2012.

In response to your ‘Response algorithms’ email of 2:35 pm 3/13/2013, our Statistical Reviewer has provided the following SAS codes for NDA 202806 so that you can complete the information request of 3.13.2013 outlined below:

“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 15, 2013.”

In addition, please provide PFS analysis results in following Table 1 and Table 2.

Table 1. PFS Analysis Per Independent Radiologist Assessment

	Dabrafenib n= 187	DTIC n=63
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

	Dabrafenib n= 187	DTIC n=63
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]		

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

03/14/2013

Amended from previous memorandum for additional information request with Tables 1 and 2



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

Memorandum

Date: March 14, 2013
From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDAs 202806; GlaxoSmithKline, LLC
SAS Codes

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

Dear Ms. Cutler:

Please refer to your New Drug Applications (NDA) 202806 for “dabrafenib” received on July 30, 2012.

In response to your ‘Response algorithms’ email of 2:35 pm 3/13/2013, our Statistical Reviewer has provided the following SAS codes for NDA 202806 so that you can complete the information request of 3.13.2013 outlined below:

“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 15, 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
03/14/2013



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

**Team Meeting #6 Summary
March 6, 2013**

NDA: 202806

Product: Tafinlar (dabrafenib)
Submission Date: July 29, 2012
Received Date: July 30, 2012
Sponsor: GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation

Meeting Participant:

Patricia Keegan, M.D., Director DOP2
Norma Griffin., Regulatory Health Project Manager
Suzanne Demko, Clinical TL and VDTL
Marc Theoret, M.D., Clinical Reviewer
Weishi (Vivian) Yuan, Statistics
Hong Zhao, Ph.D, Clinical Pharmacology (TL)
Jian Wang., Clinical Pharmacology
Justin Earp, Pharmacometrics Reviewer
Christian Grimstein, Genomics Reviewer
Whitney Helms, Nonclinical (TL)
Alexander Putman, Nonclinical Reviewer
Amit Mitra, Product Quality Reviewer
Gaetan Ladouceur, Product Quality Reviewer
Jean Mulinde, OSI Reviewer
Sue Kang, OSE, Safety RPM
James Schlick, OSE Proprietary Name Reviewer
Donna Roscoe, CDRH Consultant
Amarilys Vega, DRISK
Katherine Coyle, OSE
Tammie Brent-Howard, Maternal Health

Discussion Items

1. Action Goal Date (10-month review): Standard 10-month review with the PDUFA **Action Goal Date of Thursday, May 30, 2013.**
2. Discuss by Primary Discipline:
 - a. Clinical: Difficulties with efficacy analyses (PFS analyses). More IRs to be sent to the Sponsor. J.Mulinde just sent the IRC Charters for dabrafenib to Clinical – will check to see if they were formally submitted to the NDA. Due to
Need to request non-REMS Medication Guide.
Valvular abnormalities – may be a potential PMR.
 - i. Clinical Protocol/Site inspection: Clinical Inspection Summary completed and uploaded into DARRTS as of 2.8.2013.
 - b. Statistics: Discussion regarding data for PFS and difference in Hazard Ratio.
 - c. Clinical Pharmacology: Final review in progress and finalizing PMR/PMC template. Noted that GSK will submit three drug-drug interaction studies at the end of the month.
 - d. Genomics: Review is on-going.
 - e. CMC: Drug Substance – need final with API assessment. Drug Product – working with Office of Compliance on (b)(4) issue. Also working with Pharm/Tox which has confirmed the levels. More data is need but it is thought that this will not hold up an action. Currently following up with CMC Facilities.
 - f. Biopharmaceutics: Review is on-going and currently no issues.
 - g. Nonclinical: Review is on-going and currently no issues.
 - h. CDRH: Explanation of bridging study data. Wants to know from Clinical what the data support to ‘approve’ – V600E (b)(4)? Per Clinical, the data does not support (b)(4) CDRH data is dependent on STATS PFS data.
 - i. Regulatory
 - i. On 1.30.2013, the CDTL (with Director agreement) decided that the timing of this application would not be accelerated as was initially planned and would instead be the Standard 10-month review with the PDUFA **Action Goal Date of Thursday, May 30, 2013.**
 - ii. DMEPA found Proprietary Name “TAFINLAR’ acceptable. Proprietary Name Request Conditionally Acceptable’ letter issued on 2.12.2013.
 - iii. All day working STATS meeting scheduled with GSK for Friday, March 8, 2013 (for both NDAs 202806 and 204114). This meeting is to go over the whole process of how the derived data were derived from raw data. STATS goal for the meeting is to get a final version of the SAS program and therefore they plan to run through ~2000 lines of SAS program.

- iv. Tentative TCON scheduled with GSK, bioMerieux, and CDRH for both NDAs 202806 and 204114 and companion diagnostic to discuss CDRH's multiple information requests. TCON is scheduled for Wednesday, March 13, 2013.
- v. Reviews completed and uploaded in DARRTS: Biopharmaceutics (2.8.2013); Quality Micro (2.13.2013)

3. Upcoming Meetings:

- Wrap- Up Meeting: Tuesday, April 2, 2013.
- Labeling Meetings were held January 22- February 5, 2013. Still need one more labeling meeting to finalize Clinical portions.

4. Milestone Dates:

Milestone	6-month review	8½-month review (targeted completion April 15, 2012)	10-month Review	Comments
Application Received	July 30, 2012			
Acknowledgment Letter				Issued 8/15/2012
Filing Action Letter	Due September 28, 2012 (Friday)			GSK submitted Withdrawal of Request for Priority Review – therefore this application ‘filed’ as of 9/28/2012
Deficiencies Identified Letter (74 Day Letter)	October 12, 2012 (Friday)			Issued October 15, 2012
Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner’s Target date)	January 2, 2013 (Wednesday)	February 25, 2013 (Monday)	Thursday, April 11, 2013	
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	January 9, 2013 (Wednesday)	March 4, 2013 (Monday)	Thursday, April 18, 2013	
Review Target Due Dates:				
<i>Primary Review Due</i>	1/2/2013	2/18/2013	April 4, 2013 April 11, 2013 April 18, 2013 May 9, 2013 May 30, 2013	Thursday
<i>Secondary Review Due</i>	1/4/2013	2/25/2013		
<i>CDTL Review Due</i>	1/9/2013	3/4/2013		
<i>Division Director Review</i>	1/18/2013	3/25/2013		
<i>Due</i>	1/30/ 2013	4/15/2013		

Milestone	6-month review	8½-month review (targeted completion April 15, 2012)	10-month Review	Comments
<i>Office Director Review Due/Sign-Off</i>				
Compile and circulate Action Letter and Action Package	1/9/2013 (Wednesday)	3/4/2013 (Monday)	April 18, 2013 (Thursday)	
FINAL Action Letter Due	1/30/2013 (Wednesday)	4/15/2013 (Monday)	May 30, 2013 (Thursday)	

5. ODAC Needed/Not Needed: Not needed - this drug/biologic is not the first in its class

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

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

Dear Ms. Cutler:

Please refer to your New Drug Application (NDA) NDA 202806 for product “(dabrafenib)” received on July 31, 2012.

The Review Team has the following comments and request.

Because of the serious risk of developing secondary malignancies that are associated with this drug Tafinlar (dabrafenib), which could affect the patients decision to use the product, or to continue to use the product, FDA is requesting that GSK provide as part of their required labeling for this drug Tafinlar (dabrafenib), a draft non-REMS patient medication guide by Thursday, March 14, 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
03/06/2013



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

Memorandum

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

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

Dear Ms. Cutler/Mr. Richards:

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

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

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

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

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/s/

NORMA S GRIFFIN
03/05/2013



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; GlaxoSmithKline, LLC
Clinical Comments and Information Request

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

Dear Ms. Cutler:

Please refer to your New Drug Application (NDA) NDA 202806 for product “(dabrafenib)” received on July 31, 2012.

Our Clinical Reviewer has the following comments and information request and requests a response by Friday, March 8, 2012, **or sooner if possible**.

1. No subjects listed in the IPDISC.xpt (Trial BRF113683; September 21, 2012 submission of the dataset) were coded (i.e., SDRSCD = 91) as having discontinued the investigational product based on the investigator selection of “[91] Disease progression (including death due to disease progression)” on the “BRF113683_SV3 : GSK2118436 DISCONTINUATION (GSK2118436 DISCON)” eCRF.

Please clarify how line listings with no value for variable “SDRSCD” were determined to be discontinuations due to disease progression (variable “SDENRSCD” = 91 in the analysis dataset IPDISC.xpt) rather than missing data.

2. Please confirm that none of the 110 adverse event listings in the Adverse event of special interest category “Cutaneous Squamous Cell Carcinoma (including keratoacanthoma)” (AESSCCD=60) contained in the 120-Day Safety Update AE.xpt dataset were non-cutaneous squamous cell carcinomas. In addition, provide a tabular listing of all cutaneous squamous cell carcinomas (cuSCC) in the integrated safety database which includes the following information:

- tumor location
- tumor thickness and/or depth
- tumor diameter
- high-risk histological features such as degree of differentiation, perineural invasion, or vascular involvement
- staging evaluation
- treatment(s) administered for the cutaneous squamous cell carcinoma

3. Please clarify the reason(s) that following cuSCCs AESIs were ongoing at the time of the ISS 120-Day safety update:

USUBJID	AEPT
BRF112680.0002106	Keratoacanthoma
BRF113683.D007260	Keratoacanthoma
BRF113683.0001534	Squamous cell carcinoma
BRF113683.0001513	Keratoacanthoma
BRF113683.0003083	Keratoacanthoma
BRF113683.D012383	Keratoacanthoma
BRF113683.D012383	Keratoacanthoma
BRF113683.D012383	Keratoacanthoma
BRF113929.0000861	Squamous cell carcinoma

4. Please send an up-to-date tabular listing of all second primary malignancies (excluding cuSCC/keratoacanthoma and basal cell carcinoma), reported in the development program for dabrafenib as monotherapy (b) (4). For each case of second primary malignancy, include the following information in the listing:

- Protocol that the patient was enrolled on
- Indication for treatment on-study (i.e., primary malignancy)
- Pertinent past medical history including prior anti-cancer treatment history
- Staging work-up performed for the second primary malignancy
- Stage (based on the relevant conventional staging system)
- Other pertinent clinical and/or pathological prognostic factors specific to the second primary malignancy
- Treatment(s) administered for the second primary malignancy
- Outcome
- Results from all molecular analyses that have been performed on the second primary malignancy
- List of any molecular analyses that are planned but have not yet been performed

5. Please clarify the following potential discrepancy in the 120-Day safety update:

In the 120-Day Safety Update, the narrative provided for patient BRF11383.0000600, a patient with infiltrating ductal adenocarcinoma of the left breast based on a biopsy performed on Study Day 350, stated that on re-review of past scans, the mass was visible on 23-Jun-2011, 42 days since the first dose of GSK2118436 (first dose of GSK2118436 was 13-May-2011). This narrative does not include a description of a scan performed prior to initiation of dabrafenib that demonstrated the left breast mass. However, the summary of the case provided in Section 4.4.5.4 of the 120-Day Safety Update (page 37) states that, upon review of prior imaging, the left breast mass was determined to be present prior to initiating therapy with dabrafenib.

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 & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 202806

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

GlaxoSmithKline, LLC
1250 South Collegeville Road
Collegeville, PA 19426

ATTENTION: Ellen Cutler
Senior Director, Regulatory Affairs

Dear Ms. Cutler:

Please refer to your New Drug Application (NDA) submitted July 29, 2012, received July 30, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Dabrafenib Capsules, 50 mg and 75 mg.

We also refer to your November 27, 2012, correspondence, received November 27, 2012, requesting review of your proposed proprietary name, Tafinlar. We have completed our review of the proposed proprietary name, Tafinlar and have concluded that it is acceptable.

The proposed proprietary name, Tafinlar, 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 November 27, 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
02/12/2013



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

Memorandum

Date: February 1, 2013
From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 202806; GlaxoSmithKline, LLC
Clinical Pharmacology Comments

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

Dear Ms Cutler:

Please refer to your New Drug Application (NDA) NDA 202806 for product “(dabrafenib)” received on July 31, 2012.

Our Clinical Pharmacology Reviewer has the following comments and request for information. Please provide your response to me via email by Wednesday, February 6, 2013, or sooner if possible, and follow that with a formal submission to the NDA.

Clinical Pharmacology Comments:

Your proposed labeling states that “Dabrafenib mesylate is a white to slightly colored solid. It is very slightly soluble at pH 1 and practically insoluble above pH 4 in aqueous media.” Please provide a plan to evaluate the potential effect of concomitant pH elevating agents on the dabrafenib pharmacokinetics or provide any available data to justify such a study is unnecessary.

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
02/01/2013

**Labeling Meeting #4 Summary
January 30, 2013**

NDA: 202806

Product: Tafinlar (dabrafenib)

Submission Date: July 29, 2012

Received Date: July 30, 2012

Sponsor: GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation

Meeting Participant:

Patricia Keegan, M.D., Director DOP2

Suzanne Demko, Clinical TL and CDTL, DOP2

Marc Theoret, Clinical Reviewer, DOP2

Norma Griffin., Regulatory Health Project Manager

Hong Zhao, Clinical Pharmacology (TL)

Justin Earp, Clinical Pharmacology

James Schlick, OSE Proprietary Name Reviewer

Rosane Charlab-Orbach, Genomics Reviewer

Amarilys Vega, DRISK

Latonia Ford, Patient Labeling

Donna Roscoe, CDRH

1. **Labeling Sections Reviewed:** Sections to be reviewed: Highlights, Indications and Usage, and Patient Counseling
2. Actual sections reviewed included Patient Counseling.
3. Refer to DMEPA's review – regarding the capsule and accidental exposure, inquire with ClinPharm and CMC.
4. Request a Non-REMS MedGuide.
5. Sections still to be reviewed: Warnings and Precautions (2.2), Section 5, Section 6, and Section 14.
6. **Next Meeting (#5):** Schedule to be determined with Clinical.

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/s/

NORMA S GRIFFIN
04/17/2013

**Labeling Meeting #3 Summary
January 29, 2013**

NDA: 202806

Product: Tafinlar (dabrafenib)

Submission Date: July 29, 2012

Received Date: July 30, 2012

Sponsor: GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation

Meeting Participant:

Patricia Keegan, M.D., Director DOP2

Suzanne Demko, Clinical TL and CDTL, DOP2

Marc Theoret, Clinical Reviewer, DOP2

Norma Griffin., Regulatory Health Project Manager

Hong Zhao, Clinical Pharmacology (TL)

Justin Earp, Clinical Pharmacology

James Schlick, OSE Proprietary Name Reviewer

Rosane Charlab-Orbach, Genomics Reviewer

Amarilys Vega, DRISK

Latonia Ford, Patient Labeling

Donna Roscoe, CDRH

- 1. Labeling Sections Reviewed:** Sections to be reviewed: Dosage and Administration, Drug Interactions, Use in Specific Populations, Overdosage, Contraindications, and Clinical Pharmacology
- 2.** Actual sections reviewed included Dosage and Administration (2.2), Drug Interactions (7), Use in Specific Populations (8.7 Hepatic Impairment and 8.8 Renal Impairment), Clinical Pharmacology (12.3 Pharmacokinetics), Table 4 (line 567), and DMEPA's review for Dosage and Administration (2.1), and Line 734-736, and container comments.
- 3.** Section 4 not covered as there are no Contraindications.
- 4. Next Meeting (#4):** Scheduled for January 30, 2013, to review Highlights, Indications and Usage, and Patient Counseling.

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/s/

NORMA S GRIFFIN
04/17/2013



NDA 202806

INFORMATION REQUEST

GlaxoSmithKline, LLC
Ellen Cutler
Senior Director, Regulatory Affairs, Oncology
1250 South Collegeville Road
Collegeville, PA, 19426

Dear Ms. Cutler:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dabrafenib Capsules, 50 mg and 75mg.

We also refer to your July 30, 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 February 4, 2013, in order to continue our evaluation of your NDA.

Drug Substance

The following comments refer to your January 11, 2013 submission.

- Clarify what is the trigger mechanism [REDACTED] (b) (4)
- The [REDACTED] (b) (4) process [REDACTED] (b) (4) has been demonstrated only at the lab scale. Either provide data to support inclusion [REDACTED] (b) (4) at commercial scale (e.g. demonstration of the [REDACTED] (b) (4) process [REDACTED] (b) (4) at pilot plant scale) or remove it from section 2.2
- To facilitate our evaluation of the manufacturing process and control strategy of drug substance synthesis, provide the following information. You can either include a manufacturing batch record and/or provide a detailed manufacturing process description in S 2.2. The Agency's expectation is that the potential impact of changes to process parameters, including those with low criticality, be assessed under the firm's quality system at the time of the change. As appropriate, changes with a potential to adversely affect product quality should be notified to the Agency in accordance with 21 CFR 314.70. Information is sought for the following:
 - Time [REDACTED] (b) (4) and in-process controls for each applicable stages in the dabrafenib mesylate manufacturing process.
 - Ranges for all CPPs described in the dabrafenib mesylate manufacturing process.

- Set points (target values) or appropriate ranges for the *open-ended* non-critical process parameters listed in the dabrafenib mesylate manufacturing process.

Microbiology

- (b) (4)
you should add microbial limits testing to the post-approval stability protocol. Microbial limits testing should be performed at the initial time point on at least one batch per year. You should provide validated test methods and acceptance criteria for total aerobic microbial counts, total yeast and mold counts and the absence of specified organisms as appropriate. Microbial limits tests in accordance with USP Chapters <61> and <62> and acceptance criteria in agreement with USP Chapter <1111> would be acceptable. Please provide summaries of the method validation/verification studies performed with the drug product for each proposed test method.

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
01/29/2013

**Labeling Meeting #2 Summary
January 25, 2013**

NDA: 202806

Product: Tafinlar (dabrafenib)

Submission Date: July 29, 2012

Received Date: July 30, 2012

Sponsor: GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation

Meeting Participant:

Patricia Keegan, M.D., Director DOP2

Marc Theoret, Clinical Reviewer, DOP2

Norma Griffin., Regulatory Health Project Manager

Whitney Helms, Nonclinical (TL)

Alexander Putman, Nonclinical Reviewer

Gaetan Ladouceur, CMC Reviewer

Akm Khairuzzaman, Biopharmaceutics Reviewer

Rosane Charlab-Orbach, Genomics Reviewer

Tammie Brent-Howard, Maternal Health

Melissa Tassinari, Maternal Health

James Schlick, OSE Proprietary Name Reviewer

Latonia Ford, Patient Labeling

Carole Broadnax, OPDP

Katherine Coyle, OSE

- 1. Labeling Sections Reviewed:** Sections to be reviewed: Dosage Forms and Strengths, Description, How Supplied/Storage and Handling, Nonclinical Sections, Nonclinical Toxicology, Clinical Studies.
- 2.** Actual sections reviewed included Dosage Forms and Strengths, Description, How Supplied/Storage and Handling, Nonclinical Sections, Nonclinical Toxicology.
- 3.** DMEPA provided their DRAFT Review with comments for PI and Container (see attached). Will go over again at next meeting.
- 4. Next Meeting (#3):** Scheduled for January 29, 2013. Dosage and Administration, Drug Interactions, Use in Specific Population Overdosage, Contraindications, and Clinical Pharmacology.

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/s/

NORMA S GRIFFIN
04/17/2013



NDA 202806

**METHODS VALIDATION
MATERIALS RECEIVED**

GlaxoSmithKline LLC
Attention: Ellen S. Cutler, Senior Director, Regulatory Affairs
1250 South Collegeville Road, PA 19426
FAX: (610) 917-5772

Dear Ellen S. Cutler:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for (b) (4) (dabrafenib) capsules, 50 mg and 75 mg and to our December 3, 2012, letter requesting sample materials for methods validation testing.

We acknowledge receipt on January 24, 2013, 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, 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
01/24/2013

**Labeling Meeting #1 Summary
January 22, 2013**

NDA: 202806

Product: Tafinlar (dabrafenib)

Submission Date: July 29, 2012

Received Date: July 30, 2012

Sponsor: GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation

Meeting Participant:

Patricia Keegan, M.D., Director DOP2

Norma Griffin., Regulatory Health Project Manager

Marc Theoret, M.D., Clinical Reviewer

Weishi (Vivian) Yuan, Statistics

Whitney Helms, Nonclinical (TL)

Rosane Charlab-Orbach, Genomics (TL)

Tammie Brent-Howard, Maternal Health

Melissa Tassinari, Maternal Health

James Schlick, OSE Proprietary Name Reviewer

Amarilys Vega, DRISK

Katherine Coyle, OSE

1. **Labeling Sections Reviewed:** Indications and Usage and Adverse Reactions. Per Clinical, will pick up Warnings and Precautions at later meeting.
2. Reviewed input in Table from SEALD.
3. Will compare what is the same and the difference between this label and the Zelboraf label.
4. **Next Meeting (#2):** Scheduled for January 25, 2013. Sections to be reviewed: Dosage Forms and Strengths, Description, How Supplied/Storage and Handling, Nonclinical Sections, Nonclinical Toxicology, Clinical Studies.

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/s/

NORMA S GRIFFIN
04/17/2013



NDA 202806

INFORMATION REQUEST

GlaxoSmithKline, LLC
Ellen Cutler
Senior Director, Regulatory Affairs, Oncology
1250 South Collegeville Road
Collegeville, PA, 19426

Dear Ms. Cutler:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dabrafenib Capsules, 50 mg and 75mg.

We also refer to your July 30, 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 January 24, 2013, in order to continue our evaluation of your NDA.

Drug Product

- Discuss if lot-to-lot variability in excipient properties (e.g. bulk density, particle size, surface area) would have an impact on drug product quality. If there is an adverse impact, include appropriate mitigations steps in your control strategy.
- The Agency notes that your submission proposes weight variation as an in-process control to demonstrate adequacy of mix for commercial batches of Dabrafenib. Please provide a summary of how your firm intends to demonstrate adequacy of mix (b) (4) for all commercial batches of Dabrafenib manufactured (b) (4). Your current plan does not appear to be in accordance with 21 CFR §211.110.
- Provide further clarification for the ranges proposed to be used (b) (4) in a specific encapsulator for a specific batch and their impact (b) (4).
- The Agency notes that you have indicated in section P.3.3 that regulatory action for post approval changes to non-critical process parameters (NCP) would be taken in conformance with regulations and guidance for minor changes. We would like to remind you that, if a change to an NCP 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 21 CFR §314.70 (b) or (c).

- Clarify [REDACTED] ^{(b) (4)} during release and on stability, and provide supporting data to justify your assertion.
- Provide 21CFR citation for individual composition of the container/closure system to assure safety upon food contact. Clarify whether the USP<671> for the bottles was conducted after removal of the inner seal of the closure. If not, conduct and report the results of USP<671> after removal of the inner seal for the bottles. For guidance, see section “G” of the “Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics”.
- Provide the EIC calculation in support of the claim of categorical exclusion from environmental assessment.

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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NALLAPERUM CHIDAMBARAM
01/11/2013

**Team Meeting #5 Summary
January 9, 2013**

NDA: 202806

Product: **Tafinlar** (dabrafenib)
Submission Date: July 29, 2012
Received Date: July 30, 2012
Sponsor: GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation

Note: This Team meeting was cancelled due to the mid-cycle meeting being held in the same month (January 4, 2013).

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/s/

NORMA S GRIFFIN
04/17/2013

Mid-Cycle Meeting Summary
January 4, 2013

NDA: 202806

Product: (b) (4) (dabrafenib)
Submission Date: July 29, 2012
Received Date: July 30, 2012
Sponsor: GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation

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, DOP2
Marc Theoret, Clinical Reviewer, DOP2
Kun He, Statistics (TL)
Weishi (Vivian) Yuan, Statistics
Hong Zhao, Clinical Pharmacology (TL)
Jian Wang, Clinical Pharmacology
Rosane Charlab Orbach, Genomics (TL)
Christian Grimstein, Genomics Reviewer
Stacy Shord, Genomics
Justin Earp, Pharmacometrics Reviewer
Whitney Helms, Nonclinical (TL)
Nallaperumal Chidambaram, Acting Branch Chief, ONDQA
Debasis Ghosh, ONDQA
Amit Mitra, Product Quality Reviewer, ONDQA
Akm Khairuzzaman, Biopharmaceutics Reviewer
Mahesh Ramanadham, OC (Facilities)
Derek Smith, OC (Facilities)
Sue Kang, OSE, Safety RPM
James Schlick, DMEPA
Donna Roscoe, CDRH Consultant
Jade Chen, Biometrics Reviewer (for trametinib)
Katherine Coyle, DPVII
Peter Waldron, DPVII
Amarylis Vega, DRISK
Tammie Brent-Howard, Maternal Health

Discussion Items

Slides were presented by (in order).

- RPM Regulatory
- Clinical and Statistical, Efficacy & Safety
- Clinical Pharmacology
- CMC and Biopharmaceutics
- Non-Clinical
- CDRH

Benefit-Risk Overview (summarized from Clinical)

- Median OS ~9 months in metastatic melanoma
- OS improved with Zelboraf (BRAf V600E) and Yervoy
- Efficacy of dabrafenib is **improved PFS (BRAfV600E)**, anti-tumor activity (large ORR) is supportive
- Primary safety risks (under evaluation) include second primary malignancies, serious non-infectious febrile events, renal failure, uveitis
- Product labeling should be adequate for risk management

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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: January 2, 2013
From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 202806; GlaxoSmithKline, LLC
Clinical Comments and Information Request

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

Dear Ms. Cutler:

Please refer to your New Drug Application (NDA) NDA 202806 for product “(dabrafenib)” received on July 31, 2012.

Our Clinical Reviewer has the following comments and information request and requests a response by Wednesday, January 16, 2012 **or sooner if possible**.

1. An audit of a sample of the data contained in the RDEATH.xpt and RAE.xpt datasets for trial BRF113683, both submitted to NDA 202806 on September 21, 2012, identified discrepancies between values for variables listed in the datasets and the corresponding values reported in the case report forms (CRF). In both instances, the dataset variable contained a value which was subsequently corrected in the CRFs after data queries. Please identify the reason for the following discrepancies:
 - a. RDEATH.xpt dataset, the primary cause of death for Patient BRF113683.0007350 is listed as “disease under study” in the dataset based on a value of “1” for the variable “DTHCSCD.” However, the submitted “End of Study” CRF (page 895 of 4933) for this patient reported the primary cause of death as “Other, specify: SAE unrelated to study medication.” On review of the audit trail for this record (CRF pages 4929 – 4931), the user (Yuliya Havaleshko) initially recorded the primary cause of death as disease under study in an entry dated July 7, 2011 (consistent with the value recorded for the variable DTHCSCD in the RDEATH.xpt dataset) but subsequently corrected the primary cause of death to “Other, specify: SAE unrelated to study medication” in response to a data query opened on April 10, 2012.

- b. RAE.xpt dataset, the serious adverse event of “worsening diabetes” line listing for Patient BRF113683.0004660 reports that this SAE did not recur after the investigational product was restarted based on a value of “N” listed for the variable “SAEIP.” However, the “Serious Adverse Events” CRF that was submitted for this patient reported that the event “worsening diabetes” did recur after rechallenge with the investigational product (Item #12, Page 485 of 2010). On review of the Audit trail of the Serious Adverse Events CRFs (pages 1898-1901), the user (Lukasz Lebkowski) initially recorded the answer to Item #12 (*i.e., If investigational product(s) were stopped temporarily, did the reported event(s) recur after investigational products were restarted?*) as "No" on September 14, 2011 (consistent with the value recorded for the variable “SAEIP” in the RAE.xpt dataset) but corrected the response to Item #12 on October 26, 2011, to “Yes” following a data query on September 22, 2011.

Although review of the cases described in each of the above examples was able to determine the source of the discrepancies, these discrepancies raise concerns about the quality of the datasets as a whole, as well as the validity of analyses based on these datasets, since the above examples appear to contain data which were recorded prior to queries in regard to inconsistencies in the initial captured data.

Please submit the results of an audit of the datasets submitted to support safety and efficacy of dabrafenib to identify the extent that these datasets contain data entries which precede the entry of corrected data by investigators. The method used for this audit should be included in this report.

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
01/02/2013



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

Memorandum

Date: December 27, 2012
From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 202806; GlaxoSmithKline, LLC
Clinical Comments and Information Request

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

Dear Ms. Cutler:

Please refer to your New Drug Application (NDA) NDA 202806 for product “(dabrafenib)” received on July 31, 2012.

Our Clinical Reviewer has the following comments and information request and requests a response by Thursday, January 10, 2012 **or sooner if possible**.

1. Clarify which variable(s) in the analysis datasets for trial BRF113683 identifies the as treated (i.e., safety population). Based on the define file provided, the variable intended to identify the safety population would appear to be “ATRTGRP.” However, across multiple analysis datasets (e.g., “Demography”, “Population”, “LAB” the “ATRTGRP” variable identifies 188 patients in the GSK2118436 treatment-group and 62 patients in the DTIC-treatment group. These numbers are inconsistent with the number of subjects reported for the safety population (GSK2118436, n=187; DTIC, n=59) in the BRF113683 clinical study report.

If “ATRTGRP” is indeed the identifier for the safety population of BRF113683, please resubmit all affected datasets with the corrected values for this variable. In addition, any analyses of safety which are impacted by this potential error should be resubmitted.

2. There are more than 578 subjects (i.e., the integrated safety population) included in the ISS dataset “AE.xpt” as it contains 6,349 rows for 609 unique USUBJID. The variable “PNSAFE” in the “POP.xpt” dataset failed to identify which of the 609 subjects are included in the ISS safety population because the PNSAFE variable flags all 637 patients included in the POP.xpt, which is inclusive of the 609 subjects in the ISS AE.xpt dataset, as being part of the ISS safety population.

- a. Submit revised ISS datasets to include an ISS safety population flag which identifies only the 578 patients who were used to perform the ISS (submit for all safety datasets including AE.xpt, CRDSCN.xpt, DEATH.xpt, EGANAL.xpt, ECG.xpt, Lab.xpt, and VSANAL.XPT).
 - b. Confirm that the “ATTYPER” variable is the treatment-emergent flag used to identify all adverse events within the ISS AE.xpt dataset which meet the criteria as specified in the applicable protocols for collection and reporting of adverse events (e.g., within 28 days of last dose of investigational product for trial BRF113683).
3. For the raw dataset REXPOSUR.xpt for trial BRF113683, the investigational product start dates of dosing (“EXSTDT”) and end dates (“EXENDT”) of dosing for each visit appears to be missing (with the exception of the start date recorded at the time of PKs). For example in the REXPOSUR.xpt, there is missing information for both the “EXSTDT” and the “EXENDT” variables within the line listings for USUBJID = BRF113.683.0000050 (SUBJID = 50) for line listings where “Visit” = ‘Week 1, Week 3, Week 6, Week 9, Week 12, Week 15, Week 18, Week 21, Week 24, Week 27, Week 30, Week 33, or Week 36’. However, line listings for the same subject where “Visit” = ‘Exposure Log’ contains dates for both the “EXSTDT” and the “EXENDT” variables.

Based on the definitions of the “EXSTDT” and “EXENDT” variables provided in the define file for the raw datasets, it is not clear when Investigator’s would record the start dates and the end dates for GSK2118436 on the “BRF113683_SV3 : GSK2118436 EXPOSURE (GSK2118436 EXP) - Repeating Form” which is located on page 225 of the blank CRF.

- a. Provide a detailed description for the procedures followed to derive (or capture) the data for start date of dosing, “EXSTDT”, and the end date for dosing, “EXENDT”, that is provided in the line listings of the REXPOSUR.xpt dataset where “VISIT” = ‘Exposure Log’.
- b. Similarly, provide a detailed description for the procedures followed to derive (or capture) the data for start date of dosing, “EXSTDT”, and the end date for dosing, “EXENDT”, that is provided in the line listings of the REXPOSUR.xpt dataset where “VISIT” = ‘Crossover Exposure Log’.
- c. Provide a tabular listing of all CRFs that were to be completed by Investigators, at each Visit type, in the randomized phase of the trial as well as in the cross-over portion of the trial. In addition, if a study procedures manual (SPM) was submitted to NDA 202806, please identify its location within the NDA. If an SPM is available but has not been submitted, please submit this to the NDA.

4. Provide the submission date and serial number of the final BRF113683 reporting and analysis plan in IND 105032.

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
12/27/2012



NDA 202806

INFORMATION REQUEST

GlaxoSmithKline, LLC
Ellen Cutler
Senior Director, Regulatory Affairs, Oncology
1250 South Collegeville Road
Collegeville, PA, 19426

Dear Ms. Cutler:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dabrafenib Capsules, 50 mg and 75mg.

We also refer to your July 30, 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 **January 11, 2013**, in order to continue our evaluation of your NDA.

Drug Substance

1. The description of the drug substance manufacturing process as presented in Section S.2.2 does not adequately describe the manufacturing process of dabrafenib mesylate. The use of terms such as “not greater than (NGT)” or “not less than (NLT)” are vague and do not specify the operating range that is normally used during routine manufacturing. In order to allow us to evaluate your control strategy for drug substance synthesis, provide a complete description for the drug substance manufacturing process, including normal operating ranges (NOR) or scientifically justified ranges for process variables including process parameters, reagents, reaction and process temperatures, solvent volumes for reaction, etc.. 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 if the (b) (4) processes (b) (4) in Section S.2.2 have been demonstrated. If yes, revise the (b) (4) process description (b) (4) to include normal operating ranges (NOR) for all process variables. Otherwise, remove (b) (4) processes from section S.2.2.

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/

SUE CHING LIN

12/21/2012

On behalf of Dr. Nallaperumal Chidambaram, Acting Branch Chief

Team Meeting #4 Summary
December 18, 2012

NDA: 202806

Product: **Tafinlar** (dabrafenib)

Submission Date: July 29, 2012

Received Date: July 30, 2012

Sponsor: GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation

Meeting Participants:

Norma Griffin., Regulatory Health Project Manager

Suzanne Demko, Clinical TL and VDTL

Marc Theoret, M.D., Clinical Reviewer

Kun He, Ph.D., Statistics (TL)

Weishi (Vivian) Yuan, Statistics

Hong Zhao, Ph.D, Clinical Pharmacology (TL)

Jian Wang., Clinical Pharmacology

Justin Earp, Pharmacometrics Reviewer

Rosane Charlab-Orbach, Acting Genomics TL

Whitney Helms, Nonclinical (TL)

Alexander Putman, Nonclinical Reviewer

Nallaperumal Chidambaram, Acting Branch Chief

Gaetan Ladouceur, Product Quality Reviewer

Jewell Martin, Product (ONDQA RPM)

Debasis Ghosh, QbD Liason

Akm Khairuzzaman, Biopharmaceutics Reviewer

Mahesh Ramanadham, OC (Facilities)

Jean Mulinde, OSI Reviewer

Donna Roscoe, CDRH Consultant

James Schlick, OSE Proprietary Name Reviewer

Jeff Summers, Deputy Director for Safety, DOP2

Amarilys Vega, DRISK

Katherine Coyle, OSE

Tammie Brent-Howard, Maternal Health

Discussion Items

1. Review the timing of this application and the Division's **Action Goal Date of April 15th, 2013**. Given the on-going problems that exist regarding the STATS data, discussed (by discipline) any issues that exist that would affect meeting the Division's goal Action Date of April 15th, 2013.
2. Discuss by Primary Discipline:
 - a. Clinical: Needs information regarding cross-over and start date of exposure. Requesting one-week turn around to receive this information.
 - i. Clinical Protocol/Site inspection (per Jean Mulinde):
 - Inspections in France (Grob) - Nov 9 - Dec 1, 2012 completed - NAI
 - Inspection in Russia (Demidov) - Nov 30 - Dec 15, 2012 – Complete but there were 483 issues. This should probably not impact action.
 - GSK Sponsor inspection – completed - NAI
 - b. Statistics: Working on meeting the February deadlines. Plan to provide Clinical data 2 weeks prior.
 - c. Clinical Pharmacology: Have agreement on proposed PMR language and timelines. Templates have been completed and can be uploaded into DARRTS.
 - d. Genomics: No issues to report.
 - e. CMC: IR to go out regarding drug substance stability (moisture content) and requesting response by January 4, 2013. Description of manufacturing process is inadequate. Also expecting response to IR regarding isolation process.
 - f. CMC (facilities) – Update of inspection of 11/12-16/2012 at GSK Jurong (API manufacturer). Waiting for response from the firm but it should be in before the final review.
 - g. Biopharmaceutics: Final review to be completed in January 2013.
 - h. Nonclinical: Review is ongoing
 - i. CDRH: Nothing to report at this time.
 - j. Regulatory
 - i. Sponsor withdrew their request for priority review on September 27, 2012. Review Schedule for this application – Standard 10-month review vs. **8½-month review** (targeting completion date of **April 15, 2012**). Refer to discussion for Agenda Item 1. Will this goal date be changed?
 - ii. DMEPA found Proprietary Name (b)(4) unacceptable. Sponsor submitted new Proprietary Name request – TAFINLAR and an alternative name request is (b)(4). To date, the Team has no issues or concerns with the requested names but prefers TAFINLAR. Response to be provided to DMEPA on 12.18.2012.

- iii. Received current SGE list from Caleb Briggs 10.17.2012. Marc to provide responses to Caleb's questions.

3. Upcoming Meetings:

Team Meetings

Team Meeting 5: January 9, 2013

Team Meeting 6: March 6, 2013

Mid-Cycle Meeting: Re-scheduled for January 4, 2013 (Friday). Mid-Cycle slides to CDTL by December 28, 2012 (Friday).

Wrap- Up Meeting: Per 8½-month clock, scheduled for February 7, 2013 (Thursday).

Labeling Meetings (suggested section groupings): Schedule for after mid-cycle; plan to have ~2 labeling meetings per week scheduled for after mid-cycle.

Labeling Mtg 1 January 22, 2013

Clinical Sections: Indications and Usage, Adverse Reactions, Warnings and Precautions

Labeling Mtg 2 January 25, 2013

Dosage Forms and Strengths, Description, How Supplied/Storage and Handling, Nonclinical Sections, Nonclinical Toxicology, Clinical Studies

**Include OSE/CMC during this labeling meeting to review carton and container.

Labeling Mtg 3 January 29, 2013

Clinical Sections: Dosage and Administration, Drug Interactions, Use in Specific Populations, Overdosage, Contraindications, Clinical Pharmacology,

Labeling Mtg 4 January 30, 2013

Highlights, Indications and Usage, Patient Counseling Information

Labeling Mtg 5 February 5, 2013

If needed, to follow up on any sections of the label as needed.

PMR/PMC Working Meetings: not needed

4. Milestone Dates:

Milestone	6-month review	8½-month review (targeted completion April 15, 2012)	Comments
Application Received	July 30, 2012		
Acknowledgment Letter			Issued August 15, 2012
Filing Action Letter	Due September 28, 2012 (Friday)		GSK submitted Withdrawal of Request for Priority Review – therefore this application was 'filed' as of September 28, 2012
Deficiencies Identified Letter (74	October 12, 2012 (Friday)		Issued October 15, 2012

Milestone	6-month review	8½-month review (targeted completion April 15, 2012)	Comments
Day Letter)			
Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner's Target date)	January 2, 2013 (Wednesday)	February 25, 2013 (Monday)	
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	January 9, 2013 (Wednesday)	March 4, 2013 (Monday)	
Review Target Due Dates: <i>Primary Review Due</i> <i>Secondary Review Due</i> <i>CDTL Review Due</i> <i>Division Director Review Due</i> <i>Office Director Review Due/Sign-Off</i>	January 2, 2013 January 4, 2013 January 9, 2013 January 18, 2013 By January 30, 2013	February 18, 2013 February 25, 2013 March 4, 2013 March 25, 2013 April 15, 2013	
Compile and circulate Action Letter and Action Package	January 9, 2013 (Wednesday)	March 4, 2013 (Monday)	
FINAL Action Letter Due	January 30, 2013 (Wednesday)	April 15, 2013 (Monday)	

5. Review Status

- Priority Review request withdrawn on September 27, 2012; will continue under an ~8 1/2-month review clock with targeted completion date of April 15, 2012.

6. Consults/Collaborative Reviewers:

OPDP	Carole Broadnax - professional reviewer Karen Munoz-Nero - consumer reviewer Olga Salis – RPM
OSE	Sue Kang-OSE RPM Sean Bradley-OSE RPM TL <u>DRISK</u> assigned to review Risk Management Plan Cynthia LaCivita (TL) <u>DMEPA</u> to review Proprietary Name Todd Bridges (TL) James Schlick <u>DMEPA/CMC/DDMAC</u> to review carton/container, and patient labeling <u>DPV</u> – Corrinne Kulick (TL) – invite to mid-cycle and wrap up or as requested by Team <u>DEPI</u> – 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)
Facility/OMPQ	
QT-IRT	**ClinPharm requested QT-IRT consult; per ClinPharm and QT-IRT, consult not needed.
OSI	Jean Mulinde
Pediatric Page/PeRC	Full Waiver Requested
Patient Labeling Team (Patient Information Leaflet included)	Brantley Dorch – Project Manager Latonia Ford – Reviewer Barbara Fuller – Team Leader
SEALD	Consult requested 9.18.2012 – 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	To determine if needed

7. **ODAC Needed/Not Needed:** Not needed - this drug/biologic is not the first in its class

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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 13, 2012
From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 202806; GlaxoSmithKline, LLC
Clinical Pharmacology (pharmacometrics) Comments

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

Dear Ms Cutler:

Please refer to your New Drug Application (NDA) NDA 202806 for product "(dabrafenib)" received on July 31, 2012.

Our Pharmacometrics Reviewer has the following comments and information request:

"Please submit the following data files from your metabolite population PK analysis datasets by the close of business on Monday, December 17th, 2012.

nonmemDataStudies1234_M7.csv
nonmemDataStudies1234_M4.csv
nonmemDataStudies1234_M8.csv"

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
12/13/2012



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

Memorandum

Date: December 5, 2012
From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 202806; GlaxoSmithKline, LLC
Clinical Pharmacology Comments

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

Dear Ms Cutler:

Please refer to your New Drug Application (NDA) NDA 202806 for product “(dabrafenib)” received on July 31, 2012.

We also refer to our Clinical Pharmacology Comments sent to you on September 6, 2012, and your response of November 14, 2012 for Comment #4. Our Clinical Pharmacology Reviewer has the following comments and request for information.

Clinical Pharmacology Comments:

FDA would like to re-state that a dedicated drug-drug interaction trial with a strong CYP3A4 inducer is necessary in order to provide guidance on dose adjustment for patients concomitantly taking CYP3A4 inducers. The observed exposure data from one patient does not provide sufficient basis regarding the magnitude of exposure changes for dabrafenib and its metabolites. Please propose PMR language and milestone timelines for a drug-drug interaction trial with a strong CYP3A4 inducer following the FDA 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>.

The study results should allow for a determination on how to dose dabrafenib with regard to CYP3A4 inducers.

Please provide your response to me via email by Wednesday, December 12, 2012 and follow that with a formal submission to the NDA. Please also note that I will be out of the office the week of December 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
12/05/2012



NDA 202806

**REQUEST FOR METHODS
VALIDATION MATERIALS**

GlaxoSmithKline LLC
Attention: Ellen S. Cutler
Senior Director, Regulatory Affairs
1250 South Collegeville Road
PA 19426
FAX: (610) 917-5772

Dear Ellen S. Cutler:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for (b) (4) (dabrafenib) capsules, 50 mg and 75 mg.

We will be performing methods validation studies on (b) (4) (dabrafenib) capsules, 50 mg and 75 mg, as described in NDA 202806.

In order to perform the necessary testing, we request the following sample materials and equipments:

Method, current version

- Determination of Dabrafenib Mesylate content and drug-related impurities content in Dabrafenib Mesylate drug substance by HPLC
- Identification and content determination of dabrafenib in dabrafenib capsules by HPLC
- Determination of drug-related impurities in dabrafenib capsules, 50 mg and 75 mg by HPLC
- Determination of dabrafenib release by dissolution of dabrafenib sapsules, 50 mg and 75 mg by UV

Samples and Reference Standards

- (b) (4) Dabrafenib Mesylate drug product
- (b) (4) Dabrafenib Mesylate reference drug standard
 - (b) (4) reference standard if available
- 50 (b) (4) (dabrafenib) capsules, 50 mg
- 50 (b) (4) (dabrafenib) capsules, 75 mg

Equipment

1
20

(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: Michael Trehy
1114 Market Street, Room 1002
St. Louis, MO 63101

Please notify me upon receipt of this FAX. 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, Ph.D.
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
12/03/2012

Team Meeting #3 Summary
November 15, 2012

NDA: 202806

Product: (b)(4) (dabrafenib)
Submission Date: July 29, 2012
Received Date: July 30, 2012
Sponsor: GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation

Meeting Participants:

Norma Griffin., Regulatory Health Project Manager
Suzanne Demko, Clinical TL and VDTL
Marc Theoret, M.D., Clinical Reviewer
Kun He, Ph.D., Statistics (TL)
Jian Wang., Clinical Pharmacology
Rosane Charlab-Orbach, Acting Genomics TL
Whitney Helms, Nonclinical (TL)
Alexander Putman, Nonclinical Reviewer
Liang Zhou, Ph.D., Product (TL)
Amit Mitra, Product Quality Reviewer
Gaetan Ladouceur, Product Quality Reviewer
Donna Roscoe, CDRH Consultant
Cathryn Lee, Safety RPM, DOP2
Amarilys Vega, DRISK

Discussion Items

1. Discuss by Primary Discipline:
 - a. Clinical: No new updates
 - i. Clinical Protocol/Site inspection (per Jean Mulinde 11.15.2012):
 - Inspections in France (Grob) scheduled for Nov 9 - Dec 1
 - Inspection in Russia (Demidov) scheduled for Nov 30 - Dec 15
 - GSK Sponsor inspection – underway, results pending
 - b. Statistics
 - i. Face-to-face STATS working meeting held Thursday, November 15, 2012.
 - c. Clinical Pharmacology: IR sent to Sponsor for proposed PMR language.
 - d. Genomics: No issues – review is on-going.
 - e. CMC: No issues to report – review is on-going.
 - f. CMC (facilities) – Inspection at GSK Jurong (API manufacturer) started on 11.12.2012 and will close 11.16.12.

- g. Biopharmaceutics: No issues reported.
- h. Nonclinical: No issues – review is on-going.
- i. CDRH: No issues to report
- j. Regulatory
 - i. Sponsor withdrew their request for priority review on September 27, 2012.
 - ii. 74-Day Deficiencies Letter signed and issued 10.12.2012. Sponsor response received on 10.24.2012 and 11.14.2012 (for Biopharmaceutics).
 - iii. Review Schedule for this application – Standard 10-month review vs. 8½-month review (targeting completion date of April 15, 2012).
 - iv. Due to issues with the STATS datasets, the mid-cycle meeting has been re-scheduled for January 4, 2013. Mid-cycle slides are due to Suzanne Demko by December 28, 2012 (all dates are around the holidays!)
 - v. Received current SGE list from Caleb Briggs 10.17.2012. Marc to provide responses to Caleb's questions.
 - vi. Proprietary Name – 10.18.2012; DMEPA **now finds the name unacceptable.**

5. **Upcoming Meetings:**

Team Meetings

Team Meeting 4: December 18, 2012

Team Meeting 5: January 9, 2013

Team Meeting 6: March 6, 2013

Mid-Cycle Meeting: Re-scheduled for January 4, 2013 (Friday).

Note: Need Mid-Cycle slides to CDTL by December 28, 2012 (Friday). Combine safety and efficacy slides (no more than 10).

Wrap- Up Meeting: Per 8½-month clock, scheduled for February 7, 2013 (Thursday).

Labeling Meetings (suggested section groupings): Schedule for after mid-cycle; plan to have ~2 labeling meetings per week; will schedule for after mid-cycle ~ mid to end of January.

PMR/PMC Working Meetings: To be scheduled as needed.

3. Milestone Dates:

Milestone	6-month review	8½-month review (targeted completion April 15, 2012)	Comments
Application Received	July 30, 2012		
Acknowledgment Letter			Issued August 15, 2012
Filing Action Letter	Due September 28, 2012 (Friday)		GSK submitted Withdrawal of Request for Priority Review – therefore this application was ‘filed’ as of September 28, 2012
Deficiencies Identified Letter (74 Day Letter)	October 12, 2012 (Friday)		Issued October 15, 2012
Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner’s Target date)	January 2, 2013 (Wednesday)	February 25, 2013 (Monday)	
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	January 9, 2013 (Wednesday)	March 4, 2013 (Monday)	
Review Target Due Dates: <i>Primary Review Due</i> <i>Secondary Review Due</i> <i>CDTL Review Due</i> <i>Division Director Review Due</i> <i>Office Director Review Due/Sign-Off</i>	January 2, 2013 January 4, 2013 January 9, 2013 January 18, 2013 By January 30, 2013	February 18, 2013 February 25, 2013 March 4, 2013 March 25, 2013 April 15, 2013	
Compile and circulate Action Letter and Action Package	January 9, 2013 (Wednesday)	March 4, 2013 (Monday)	
FINAL Action Letter Due	January 30, 2013 (Wednesday)	April 15, 2013 (Monday)	

4. Review Status

- Priority Review request withdrawn on September 27, 2012; will continue under an ~8 1/2-month review clock with targeted completion date of April 15, 2012.

5. Consults/Collaborative Reviewers:

OPDP	Carole Broadnax - professional reviewer Karen Munoz-Nero - consumer reviewer Olga Salis – RPM
OSE	Sue Kang-OSE RPM Sean Bradley-OSE RPM TL <u>DRISK</u> assigned to review Risk Management

	<p>Plan Cynthia LaCivita (TL)</p> <p><u>DMEPA</u> to review Proprietary Name Todd Bridges (TL) James Schlick</p> <p><u>DMEPA/CMC/DDMAC</u> to review carton/container, and patient labeling</p> <p><u>DPV</u> – Bob Pratt (TL) – invite to mid-cycle and wrap up or as requested by Team</p> <p><u>DEPI</u> – Cunlin Wang (TL) – invite to mid-cycle and wrap up or as requested by Team</p>
Maternal Health	Tammie Brent Howard (optional invitees: Carrie Ceresa and Melissa Tassinari)
QT-IRT	**ClinPharm requested QT-IRT consult; 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 Latonia Ford – Reviewer Barbara Fuller – Team Leader
SEALD	Consult requested 9.18.2012 – 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	To be determined if needed

6. **ODAC Needed/Not Needed:** Not needed - this drug/biologic is not the first in its class

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/s/

NORMA S GRIFFIN
04/17/2013



NDA 202806

**PROPRIETARY NAME REQUEST
UNACCEPTABLE**

GlaxoSmithKline
1250 South Collegeville Rd.
Collegeville, PA 19426

ATTENTION: Ellen Cutler
Senior Director, Regulatory Affairs, Oncology

Dear Ms. Cutler:

Please refer to your New Drug Application (NDA), dated and received on July 30, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Dabrafenib Capsules, 50 mg and 75mg.

We also refer to your correspondence, dated and received on July 30, 2012, requesting review of your proposed proprietary name, ^{(b) (4)} [redacted]. We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

[redacted] ^{(b) (4)}

[redacted] ^{(b) (4)}

(b) (4)

We acknowledge that the proposed proprietary name (b) (4) was previously found acceptable under IND 105032 and communicated via a conditionally acceptable letter dated April 13, 2012. However, participants in the FDA Name Simulation Studies during that review cycle did not misinterpret the (b) (4) prescription for a currently marketed product. Thus, the FDA Name Simulation Study results from this review cycle represent a new safety concern and this new information is why we have reached a different decision this cycle. (b) (4)

We acknowledge this conclusion differs from the (b) (4) external study submitted by the Applicant. However, the name (b) (4) was not evaluated in the study.

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Frances Fahnbulleh, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-0942. 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/

TODD D BRIDGES
10/27/2012

Team Meeting #2 Summary
October 16, 2012

NDA: 202806

Product: (b) (4) (dabrafenib)
Submission Date: July 29, 2012
Received Date: July 30, 2012
Sponsor: GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation

Meeting Participants:

Patricia Keegan, M.D., Director DOP2
Norma Griffin., Regulatory Health Project Manager
Suzanne Demko, Clinical TL and VDTL
Marc Theoret, M.D., Clinical Reviewer
Kun He, Ph.D., Statistics (TL)
Weishi (Vivian) Yuan, Statistics
Hong Zhao, Ph.D, Clinical Pharmacology (TL)
Alexander Putman, Nonclinical Reviewer
Gaetan Ladouceur, Product Quality Reviewer
Mahesh Ramanadham, OC (Facilities)
Derek Smith, OC (Facilities)
Jean Mulinde, OSI Reviewer
James Schlick, OSE Proprietary Name Reviewer
Donna Roscoe, CDRH Consultant
Cathryn Lee, Safety RPM, DOP2
Jeff Summers, Deputy Director for Safety, DOP2
Gregory Reaman, OHOP
Amarilys Vega, DRISK

Discussion Items

1. Discuss by Primary Discipline:
 - a. Clinical: Has one comment for 74-day letter.
 - i. Clinical Protocol/Site inspection (update per **J. Mulinde - OSI**):
 - All inspection results pending at this point.
 - BIMO inspections - GSK requested of field that they hold starting from this week until 10/29
 - Inspections in France (Grob and Roberts) scheduled for 11/9 – 12/1/2012
 - Inspections in Russia (Demidov) scheduled for Nov 30 - Dec 15
 - Scheduling last domestic CI pending, but anticipate within next 30 days

- b. Statistics: Updated on 9.21.2012 dataset submission. Verified a code for pike estimator with Cox. Still having trouble running Sponsor's macros. If there are still issues, FDA will run their own.
- c. Clinical Pharmacology: No issues, review on-going.
- d. Genomics: No update
- e. CMC: PQM memo will be uploaded 10/17/2012.
- f. CMC (facilities) – Update from M.Ramanadham
 - GSK Singapore - inspection scheduled for 11/12/2012 and will cover both NDA 204114 and NDA 202806. CDER/OC and ONDQA will be participating in this inspection.
- g. Biopharmaceutics: Review on-going.
- h. Nonclinical: No issues; review on-going.
- i. CDRH: Meeting this week with bioMerieux regarding PMA and co-approval.
- j. Regulatory
 - i. Sponsor withdrew their request for priority review on September 27, 2012.
 - ii. 74-Day Deficiencies Letter signed and issued 10.12.2012. Letter contained the following deficiencies: one clinical, two biopharmaceutics, and one regulatory (labeling).
 - iii. Review Schedule for this application – Standard 10-month review vs. 8½-month review (division target completion date of April 15, 2012).
 - iv. Working with Marc and Susan Lang to generate competing products list and will submit a request to screen for SGE.

2. Milestone Dates:

Milestone	6-month review	8½-month review (targeted completion April 15, 2012)	Comments
Application Received	July 30, 2012		
Acknowledgment Letter			Issued August 15, 2012
Filing Action Letter	Due September 28, 2012 (Friday)		GSK submitted Withdrawal of Request for Priority Review – therefore this application was 'filed' as of September 28, 2012
Deficiencies Identified Letter (74 Day Letter)	October 12, 2012 (Friday)		Issued October 15, 2012
Send proposed	January 2, 2013 (Wednesday)	February 25,	

Milestone	6-month review	8½-month review (targeted completion April 15, 2012)	Comments
labeling/PMR/PMC/REMS to applicant (Review Planner's Target date)		2013 (Monday)	
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	January 9, 2013 (Wednesday)	March 4, 2013 (Monday)	
Review Target Due Dates: <i>Primary Review Due</i> <i>Secondary Review Due</i> <i>CDTL Review Due</i> <i>Division Director Review Due</i> <i>Office Director Review Due/Sign-Off</i>	January 2, 2013 January 4, 2013 January 9, 2013 January 18, 2013 By January 30, 2013	February 18, 2013 February 25, 2013 March 4, 2013 March 25, 2013 April 15, 2013	
Compile and circulate Action Letter and Action Package	January 9, 2013 (Wednesday)	March 4, 2013 (Monday)	
FINAL Action Letter Due	January 30, 2013 (Wednesday)	April 15, 2013 (Monday)	

3. **Upcoming Meetings:**

Team Meetings

- Team Meeting 3: November 15, 2012
- Team Meeting 4: December 18, 2012
- Team Meeting 5: January 9, 2013
- Team Meeting 6: March 6, 2013

Mid-Cycle Meeting: Per 8½-month clock, scheduled for December 7, 2012 (Friday).

Note: Need Mid-Cycle slides to CDTL by November 30, 2012 (Friday)

Wrap- Up Meeting: Per 8½-month clock, scheduled for February 7, 2013 (Thursday).

Labeling Meetings (suggested section groupings): Schedule for after mid-cycle; plan to have ~2 labeling meetings per week; will schedule for after mid-cycle ~ mid to end January.

PMR/PMC Working Meetings: To be scheduled as needed.

Note: Dec. 4th is PEDS ODAC – Mekinist adolescent animal studies.

4. **Review Status**

- Priority Review request withdrawn on September 27, 2012; will continue under an ~8 1/2-month review clock with targeted completion date of April 15, 2012.

5. **Consults/Collaborative Reviewers:**

OPDP	Carole Broadnax - professional reviewer Karen Munoz-Nero - consumer reviewer Olga Salis – RPM
OSE	Sue Kang-OSE RPM Sean Bradley-OSE RPM TL <u>DRISK</u> assigned to review Risk Management Plan Cynthia LaCivita (TL) <u>DMEPA</u> to review Proprietary Name Todd Bridges (TL) James Schlick <u>DMEPA/CMC/DDMAC</u> to review carton/container, and patient labeling <u>DPV</u> – Bob Pratt (TL) – invite to mid-cycle and wrap up or as requested by Team <u>DEPI</u> – 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; 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 Latonia Ford – Reviewer Barbara Fuller – Team Leader
SEALD	Consult requested 9.18.2012 – 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. **ODAC Needed/Not Needed:** Not needed - this drug/biologic is not the first in its class

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/s/

NORMA S GRIFFIN
04/17/2013



NDA 202806

FILING COMMUNICATION

GlaxoSmithKline, LLC
Attention: Ellen S. Cutler
Senior Director, Regulatory Affairs, Oncology
1250 South Collegeville Road
Collegeville, PA 19426

Dear Ms. Cutler:

Please refer to your New Drug Application (NDA) dated July 29, 2012, received July 30, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for (b) (4) (dabrafenib) capsules, 50 mg and 75 mg.

We also refer to your amendments dated August 15, 2012, August 16, 2012, August 17, 2012, August 23, 2012, August 30, 2012, September 6, 2012, September 17, 2012, September 18, 2012, September 21, 2012, September 24, 2012, and September 27, 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 May 30, 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 11, 2013.

During our filing review of your application, we identified the following potential review issues:

Clinical Comments

1. Submit a dataset listing all subjects (identified by a USUBJID) included in the integrated safety analysis who received only the HPMC capsule formulation of dabrafenib.

Biopharmaceutics Comments

2. From the *in vitro* (dissolution) and *in vivo* data (relative bioavailability (BA) data) provided in the NDA, our understanding is that the *in vitro* dissolution and the pharmacokinetic (PK) parameters (b) (4) can impact the dissolution of the drug product. Therefore, provide additional dissolution profile data (b) (4).
3. Provide dissolution profile data from the batches manufactured at the high and low end of the following proposed encapsulation parameters:

Table 21 Process Parameters for Operation of (b) (4) Encapsulation Machine

(b) (4)

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.

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
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
10/12/2012



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

Memorandum

Date: September 20, 2012
From: Norma Griffin, RPM DOP2/OHOP/CDER/FDA
Subject: NDA 202806 – GlaxoSmithKline, LLC
Clinical Comments and Request for Information

GlaxoSmithKline LLC
Attention: Ellen Cutler
Global Regulatory Affairs
1250 S. Collegeville Road; UP4110
Collegeville, PA 19426

Dear Ms. Cutler:

In the analysis and raw datasets to be submitted to NDA 202806 on September 21, 2012—the date of submission as stated in your September 17, 2012, response to the September 6, 2012, FDA Clinical Information Request—please ensure that all safety datasets include the unique adverse event record identifier variable “AEREFID.” The BRF113683 analysis datasets “AE” and “AEANAL” submitted to NDA 202806 on July 30, 2012, do not contain this identifier.

Please submit your response by September 21, 2012.

If you have any questions or concerns please contact me at norma.griffin@fda.hhs.gov .

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/s/

NORMA S GRIFFIN
09/20/2012

Team Meeting #1 Summary
September 18, 2012

NDA: 202806

Product: (b) (4) (dabrafenib)

Submission Date: July 29, 2012

Received Date: July 30, 2012

Sponsor: GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation

Meeting Participants:

Patricia Keegan, M.D., Director DOP2

Anthony Murgo, M.D., Associate Director of Regulatory Science, OHOP

Norma Griffin., Regulatory Health Project Manager

Suzanne Demko, Clinical TL and VDTL

Marc Theoret, M.D., Clinical Reviewer

Kun He, Ph.D., Statistics (TL)

Weishi (Vivian) Yuan, Statistics

Hong Zhao, Ph.D, Clinical Pharmacology (TL)

Jian Wang., Clinical Pharmacology

Justin Earp, Pharmacometrics Reviewer

Rosane Charlab-Orbach, Acting Genomics TL

Christian Grimstein, Genomics Reviewer

Whitney Helms, Nonclinical (TL)

Alexander Putman, Nonclinical Reviewer

Nallaperumal Chidambaram, Acting Branch Chief

Liang Zhou, Ph.D., Product (TL)

Amit Mitra, Product Quality Reviewer

Gaetan Ladouceur, Product Quality Reviewer

Jewell Martin, Product (ONDQA RPM)

Akm Khairuzzaman, Biopharmaceutics Reviewer

Derek Smith, OC (Facilities)

James Schlick, OSE Proprietary Name Reviewer

Cathryn Lee, Safety RPM, DOP2

Jeff Summers, Deputy Director for Safety, DOP2

Katherine Coyle, OSE

Amarilys Vega, DRISK

Discussion Items

1. Ranjit Thomas provided brief introduction/overview of Panorama.
2. Discuss by Primary Discipline:
 - a. Clinical: Just beginning review process.
 - i. Clinical Protocol/Site inspection sites selected (Sites 87119 86744); working on the dates for inspections.
 - b. Statistics: Working (hands-on) meeting scheduled for 9.19.2012 with GSK STATS to work on issues with the datasets.
 - c. Clinical Pharmacology: IR sent out last week and propose one PMR.
 - d. Genomics: No updates at this time.
 - e. CMC: Need final SPL labeling.
 - f. CMC (facilities): Scheduled facility inspection in Singaport (Nov. 12th).
 - g. Biopharmaceutics: In-vitro dissolution deficiency. Comment (IR) to go out to Sponsor.
 - h. Nonclinical: No issues; review on-going.
 - i. CDRH: No update.
 - j. Regulatory
 - i. Per ClinPharm, QT-IRT Consult Request cancelled.
 - ii. Confirmed that GSK will not be submitting carton labeling.
 - iii. Need deficiencies / comments for 74 day letter from all disciplines.
 - iv. SGE or Patient Consults – obtain SGE list from Dianne Spillman / Caleb Briggs.
 - v. Filing Letter drafted – 9.18.2012
 - vi. Filing Reviews need to be complete by 9.27.2013.
3. Review Status: Priority Review requested - team agreed on standard review with a shortened division goal date (8 ½ month review schedule).
4. **Consults/Collaborative Reviewers:**

OPDP	???- professional reviewer ???- consumer reviewer Olga Salis – RPM Consult sent – 9.18.2012
OSE	Sue Kang-OSE RPM Sean Bradley-OSE RPM TL <u>DRISK</u> assigned to review Risk Management Plan

	<p>Cynthia LaCivita (TL)</p> <p><u>DMEPA</u> to review Proprietary Name Todd Bridges (TL) James Schlick</p> <p><u>DMEPA/CMC/DDMAC</u> to review carton/container, and patient labeling</p> <p><u>DPV</u> – Bob Pratt (TL) – invite to mid-cycle and wrap up or as requested by Team</p> <p><u>DEPI</u> – Cunlin Wang (TL) – invite to mid-cycle and wrap up or as requested by Team</p>
Maternal Health	Consult sent – 9.18.2012
OSI	Jean Mulinde/Paul Okwesili
Pediatric Page/PeRC	Full Waiver Requested
Patient Labeling Team	Patient Information Leaflet included
SEALD	Consult requested 9.18.2012 – 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	Obtain approved list from Caleb Briggs

5. Upcoming Meetings:

- **Team Meetings Scheduled**

Team Meeting 2: October 16, 2012

Team Meeting 3: November 15, 2012

Team Meeting 4: December 18, 2012

Team Meeting 5: January 9, 2013

- **Mid-Cycle Meeting:** Per 6-month clock, scheduled for October 30, 2012. Will need to reschedule per 8 ½ month review clock.
- **Wrap- Up Meeting:** Per 6-month clock, scheduled for January 3, 2013. Will need to reschedule per 8 ½ month review clock.
- **Labeling Meetings (suggested section groupings):** Schedule for after mid-cycle; plan to have ~2 labeling meetings per week; will schedule after review cycle has been determined.
- **PMR/PMC Working Meetings:** To be scheduled as needed.

6. ODAC Needed/Not Needed: Not needed - this drug/biologic is not the first in its class.

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/s/

NORMA S GRIFFIN
04/17/2013

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: 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: 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 documents 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

(b) (4) BRF113929 Independent Review Charter

(b) (4) 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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Reference ID: 3305747

file:///N:/...NDA 202806 GSK for Dabrafenib/IRs to Sponsor/9.14.2012 IRC Charters and IR for OSI/9.14.2012 NDA 202806 IRC charters htm[5/8/2013 3:46:25 PM]

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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 “(b) (4) (dabrafenib) and Mekinist (trametinib).”

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

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

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

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

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

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

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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 202806; GlaxoSmithKline, LLC
Clinical Comments and Information Request

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

Dear Ms Cutler:

We refer to your amendment to NDA 202806 submitted on July 30, 2012, which completed the rolling submission. On review of NDA 202806, we have the following comments and information request:

1. Submit the raw datasets, in SAS transport file format, for all supportive trials, i.e., BRF113710 and BRF113929.
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 BRF113683 do not appear to include the serious adverse event criteria met by the AE. Please identify the location of the dataset for trial 113683 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 BRF113683 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. In regard to the “Time and Events Schedule for Study: BRF113683_SV3” on Page 2 of the annotated CRF for trial BRF113683, please provide a detailed description of the information that is listed under each visit column for each row (CRF). For example, under the week 12 (WK12) [S] column, there is a “1” listed in the “Date of Visit/Assessment” row, a “9” listed in the “ECOG Performance Status Scale” row, an “11” listed in the Echocardiogram row, and “18-RF” listed in the EORTC QLQ-C30 (Version 3) 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



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 202806; GlaxoSmithKline, LLC
Clinical Pharmacology Comments

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

Dear Ms Cutler:

Please refer to your New Drug Application (NDA) NDA 202806 for product “(b) (4) (dabrafenib)” received on July 31, 2012.

Our Clinical Pharmacology Reviewer has the following comments and request for information.

Clinical Pharmacology Comments:

1. Provide the relevant data (e.g. calculated $[I]/K_i$ (or IC_{50}) ratio or net flux ratio) from *in vitro* studies to determine whether dabrafenib is a substrate or inhibitor of cytochrome P450 enzymes and transporters, and to determine the need to conduct PK drug interaction trial(s). Refer to the FDA 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>.
2. Propose PMR (post marketing requirement) language and provide a timeline for submitting the final study report for the DDI trial BRF113771 (with ketoconazole, warfarin and gemfibrozil).
3. Propose PMR language and provide milestone timelines for the renal and hepatic impairment trials.
4. Propose PMR language and milestone timelines for a drug-drug interaction trial with a strong CYP3A4 inducer.

5. Provide a timeline for submitting the final study report for the DDI trial BRF113220 (with trametinib).

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

Reference ID: 3184307

file:///N:/...for Dabrafenib/IRs to Sponsor/9.4.2012 Carton Labeling for D and T/Question for NDAs 204114 and 202806 - Carton Labeling htm[9/4/2012 4:02:29 PM]

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/s/

NORMA S GRIFFIN
09/04/2012

Filing Meeting Summary
August 31, 2012

NDA: 202806

Product: (b) (4) (dabrafenib)
Submission Date: July 29, 2012
Received Date: July 30, 2012
Sponsor: GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation

Participants:

Patricia Keegan, M.D., Director DOP2
Karen Jones (CPMS), DOP2
Norma Griffin., Regulatory Health Project Manager
Suzanne Demko, Clinical TL and CDTL
Marc Theoret, M.D., Clinical Reviewer
Kun He, Statistics (TL)
Weishi (Vivian) Yuan, Statistics
Hong Zhao, Clinical Pharmacology (TL)
Jian Wang, Clinical Pharmacology
Rosane Charlab-Orbach, Genomics Reviewer
Alexander Putman, Nonclinical Reviewer
Nallaperumal Chidambaram, Acting Branch Chief
Liang Zhou, Product (TL)
Amit Mitra, Product Quality Reviewer
Gaetan Ladouceur, Product Quality Reviewer
Jewell Martin, Product (ONDQA RPM)
Akm Khairuzzaman, Biopharmaceutics Reviewer
Mahesh Ramanadham, OC (Facilities)
Derek Smith, OC (Facilities)
Jean Mulinde, OSI Reviewer
Sue Kang, OSE, Safety RPM
Donna Roscoe, CDRH Consultant
Jeff Summers, OHOP Safety Deputy Director
Cathryn Lee, OHOP Safety RPM
Amarylis Vega, DRISK

Discussion Items

1. The review team agreed to review this submission as a standard review but will determine goal date of shortened review clock – justification to be drafted.
2. Mid-cycle meeting scheduled for October 30, 2012 (based on a 6-month review clock). Mid-cycle slides are due to CDTL by October 22, 2012
3. Standing monthly meetings were set up from September 2012 – January 2013.
4. Labeling meetings are to be scheduled.
5. Four 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.
 - a. Clinical: need a deadline for getting raw datasets and will request variable names.
 - b. STATS: see Clinical above
 - c. ClinPharm: potential PMRs
 - d. CMC: Had a TCON regarding stability at ‘alternate’ (b) (4) site – Sponsor will withdraw this site.
 - e. Biopharmaceutics: HPMC vs. capsules and exposure – need bridging study.
9. Need to verify if there is a Carton label.

Review Status

- Priority Review requested, team agreed to a standard 10-month review
- 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
- 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 12, 2012
- Risk Management Plan
- The clinical development of dabrafenib has been conducted under IND 105032.

Milestone Dates:

Milestone	6-month review	Comments
Application Received	July 30, 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.	Due September 28, 2012 (Friday)	
Deficiencies Identified Letter (74 Day Letter)	October 12, 2012 (Friday)	
Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner's Target date)	January 2, 2013 (Wednesday)	
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	January 9, 2013 (Wednesday)	
Review Target Due Dates: <i>Primary Review Due</i> <i>Secondary Review Due</i> <i>CDTL Review Due</i> <i>Division Director Review Due</i> <i>Office Director Review Due/Sign-Off</i>	January 2, 2013 January 4, 2013 January 9, 2013 January 18, 2013 By January 30, 2013	
Compile and circulate Action Letter and Action Package	January 9, 2013 (Wednesday)	
FINAL Action Letter Due	January 30, 2013 (Wednesday)	

Upcoming Meetings:

Applicant Orientation Presentation: Scheduled for Friday, September 7, 2012. Joint meeting with NDA 204114

Mid-Cycle Meeting: Per 6-month clock, scheduled for October 30, 2012. (Mid-Cycle slides to CDTL by October 22, 2012)

Labeling Meetings: To be scheduled - After mid-cycle; plan to have ~2 labeling meetings per week.

Labeling included: 50mg x 120 Container Label, 75mg x 120 Container Label, Draft Labeling (PI) with Patient Information Leaflet

Team Meetings Scheduled: Team Meeting 1: September 18, 2012, Team Meeting 2: October 16, 2012, Team Meeting 3: November 15, 2012, Team Meeting 4: December 18, 2012, Team Meeting 5: January 9, 2013

PMR/PMC Working Meetings: Scheduled as needed

Wrap- Up Meeting: Per 6-month clock, scheduled for January 3, 2013.

ODAC Not Needed: this drug is not the first in its class.

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/s/

NORMA S GRIFFIN
04/17/2013

Filing Meeting Minutes
August 31, 2012

NDA: 202806

Product: (b) (4) (dabrafenib)
Submission Date: July 29, 2012
Received Date: July 30, 2012
Sponsor: GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation

Meeting Participants:

Patricia Keegan, M.D., Director DOP2
Karen Jones (CPMS), DOP2
Norma Griffin., Regulatory Health Project Manager
Suzanne Demko, Clinical TL and VDTL
Marc Theoret, M.D., Clinical Reviewer
Kun He, Ph.D., Statistics (TL)
Weishi (Vivian) Yuan, Statistics
Hong Zhao, Ph.D, Clinical Pharmacology (TL)
Jian Wang., Clinical Pharmacology
Rosane Charlab-Orbach, Genomics Reviewer
Whitney Helms, Nonclinical (TL)
Alexander Putman, Nonclinical Reviewer
Nallaperum Chidambaram, Acting Branch Chief
Liang Zhou, Ph.D., Product (TL)
Amit Mitra, Product Quality Reviewer
Gaetan Ladouceur, Product Quality Reviewer
Jewell Martin, Product (ONDQA RPM)
Debasis Ghosh, QbD Liason
Angelica Dorantes, Ph.D., Biopharmaceutics TL
Akm Khairuzzaman, Biopharmaceutics Reviewer
Mahesh Ramanadham, OC (Facilities)
Derek Smith, OC (Facilities)
Jean Mulinde, OSI Reviewer
Sue Kang, OSE, Safety RPM
Donna Roscoe, CDRH Consultant
Jeff Summers, OHOP Safety Deputy Director
Cathryn Lee, OHOP Safety RPM
Amarylis Vega, DRISK

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 standard review.
3. A mid-cycle meeting was scheduled for October 30, 2012 (based on a 6-month review clock). Mid-cycle slides are due to CDTL by October 22, 2012
4. Standing monthly meetings were set up from September 2012 – January 2013.
5. Labeling meetings are 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 standard 10-month review
- 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
- 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 12, 2012
- Risk Management Plan
- The clinical development of dabrafenib has been conducted under IND 105032.

Milestone Dates:

Milestone	6-month review	Comments
Application Received	July 30, 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.	Due September 28, 2012 (Friday)	
Deficiencies Identified Letter (74 Day Letter)	October 12, 2012 (Friday)	
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Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	January 9, 2013 (Wednesday)	
Review Target Due Dates: <i>Primary Review Due</i> <i>Secondary Review Due</i> <i>CDTL Review Due</i> <i>Division Director Review Due</i> <i>Office Director Review Due/Sign-Off</i>	January 2, 2013 January 4, 2013 January 9, 2013 January 18, 2013 By January 30, 2013	
Compile and circulate Action Letter and Action Package	January 9, 2013 (Wednesday)	
FINAL Action Letter Due	January 30, 2013 (Wednesday)	

Consults/Collaborative Reviewers:

OPDP	<p>????- professional reviewer ????- consumer reviewer Olga Salis – RPM Consult to be sent -</p>
OSE	<p>Sue Kang-OSE RPM Sean Bradley-OSE RPM TL</p> <p><u>DRISK</u> assigned to review Risk Management Plan</p>

	<p>Cynthia LaCivita (TL)</p> <p><u>DMEPA</u> to review Proprietary Name Todd Bridges (TL) James Schlick</p> <p><u>DMEPA/CMC/DDMAC</u> to review carton/container, and patient labeling</p> <p><u>DPV</u> – Bob Pratt (TL) – invite to mid-cycle and wrap up or as requested by Team</p> <p><u>DEPI</u> – Cunlin Wang (TL) – invite to mid-cycle and wrap up or as requested by Team</p>
Maternal Health	Consult to be sent -
Facility/OMPQ	
QT-IRT	*To be determined???
OSI	Jean Mulinde/Paul Okwesili
Pediatric Page/PeRC	Full Waiver Requested
Patient Labeling Team	Patient Information Leaflet included
SEALD	Consult to be sent -
CDRH	<p>Donna Roscoe; (others Reena Philip, Yun-Fu, Hu, Maria Chan, Elizabeth Mansfield, Robert Becker)</p> <p>Tamika Allen (BIMO Reviewer)</p>
SGE's or Patient Representatives	Consult to be sent -

Upcoming Meetings:

- **Applicant Orientation Presentation:** Scheduled for Friday, September 7, 2012. Joint meeting with NDA 204114
- **Mid-Cycle Meeting:** Per 6-month clock, scheduled for October 30, 2012.
Note: Need Mid-Cycle slides to CDTL by October 22, 2012

- **Labeling Meetings (suggested section groupings): To be scheduled** - 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)

Labeling included: 50mg x 120 Container Label
75mg x 120 Container Label
Draft Labeling (PI) with Patient Information Leaflet

- **Team Meetings**
 - Team Meeting 1: September 18, 2012
 - Team Meeting 2: October 16, 2012
 - Team Meeting 3: November 15, 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

- *this drug/biologic is not the first in its class*

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/s/

NORMA S GRIFFIN
10/02/2012

MEMORANDUM OF MEETING MINUTES

MEETING DATE: August 30, 2012
TIME: 1:00PM -2:00PM (EST)
LOCATION: TCON/RM3560
APPLICATION: NDA 202806
DRUG NAME: Dabrafenib
TYPE OF MEETING: FDA initiated TCON
MEETING CHAIR: Nallaperumal Chidambaram, Acting Branch Chief
MEETING RECORDER: Jewell Martin, Regulatory Health Project Manager
MEETING PURPOSE: The purpose of the TCON was to discuss lack of CMC and Biopharm data for manufacturing site [REDACTED] provided in NDA.

FDA Attendees:

Nallaperumal Chidambaram, PhD, ONDQA Acting Branch Chief, Branch II
Liang Zhou, PhD, CMC Lead
Akm Khairuzzaman, PhD, ONDQA Biopharmceutics Reviewer
Amit Mitra, PhD, ONDQA Chemistry Reviewer
Gaetan Ladouceur, PhD, ONDQA Chemistry Reviewer
Jewell Martin, MA, MBA, PMP, ONDQA Regulatory Health Project Manager

GSK Attendees:

Kathleen Church, GlaxoSmithKline
Jim Zisek, GlaxoSmithKline
Ellen Cutler, GlaxoSmithKline
Giselle Limentani, GlaxoSmithKline
David Bronson, GlaxoSmithKline
Lara Knowles, GlaxoSmithKline
Girish Pande, GlaxoSmithKline
Kevin Lan, GlaxoSmithKline
Daniele Ouellet, GlaxoSmithKline
Buffy Hudson-Curtis, GlaxoSmithKline

Meeting Notes:

The Agency stated that there were two manufacturing sites [REDACTED] submitted for NDA 202806 and that the applicant only provided stability and dissolution data for the [REDACTED] site. The applicant stated that the equipment used is identical at both sites [REDACTED]. The applicant also stated that the equipment used for encapsulation is the same.

The Agency stated that the normal requirement would be to provide the following:

- Side by side comparison in process, equipment and batch size
- Appropriate in vitro dissolution data (including f_2 similarity comparison) as per the recommendation for the respective change outlined in the guidance for industry: SUPAC IR.
- At least 3 months of accelerated stability data including dissolution.

The Agency asked if the applicant intended to market product manufactured from both (b) (4) facilities. (b) (4)

The Agency made clear that if the applicant intends to market this product in the US, the applicant must provide the necessary data to support site equivalence. Additional stability data can be provided later, but may not be reviewed. The Agency cannot commit to evaluate stability data if submitted in 3 months.

(b) (4)

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/s/

JEWELL D MARTIN
09/11/2012

NALLAPERUM CHIDAMBARAM
09/11/2012

Initial Planning Meeting Summary
August 15, 2012

NDA: 202806

Product: (b) (4) (dabrafenib)
Submission Date: July 29, 2012
Received Date: July 30, 2012
Sponsor: GlaxoSmithKline (GSK), LLC

Proposed Indication: For the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation

Participants:

Norma Griffin., Regulatory Health Project Manager
Anthony Murgo, Associate Director for Regulatory Science, OHOP
Joseph Gootenber, M.D., Deputy Director DOP2
Jeff Summers, M.D., Deputy Director for Safety, DOP2
Karen Jones (CPMS), DOP2
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)
Liang Zhou, Ph.D., Product (TL)
Gaetan Ladouceur, Product Quality Reviewer
Jewell Martin, Product (ONDQA RPM)
Debasis Ghosh, QbD Liason
Akm Khairuzzaman, Biopharmaceutics Reviewer
Mahesh Ramanadham, OC (Facilities)
Jean Mulinde, OSI Reviewer
Paul Okwesili, OSI
Sue Kang, OSE, Safety RPM
Donna Roscoe, CDRH Consultant

Discussion Items:

The following Review Status items were reviewed:

- Priority Review requested, discussion to expedite review clock
- 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 (b) (4)

OSE noted that for the Risk Management Plan, they will review this. There is a heightened awareness but they don't anticipate this will rise to the level of a REMS.

Review Status: Discussion of the review status will continue.

Review Planner attached: 6-month planner attached.

Milestone Dates – Table of Milestone dates was reviewed. Regarding holding TCON(s) with Sponsor before the Filing Date, FDA has already talked with the Sponsor regarding derived dataset deficiencies. Sponsor indicated that they will provide response by Friday.

Milestone	6-month review
Application Received	July 30, 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.	September 28, 2012 (Friday)
Deficiencies Identified Letter (74 Day Letter)	October 12, 2012 (Friday)
Send proposed labeling/PMR/PMC/REMS to applicant (Review Planner's Target date)	January 2, 2013 (Wednesday)
Week after the proposed labeling has been sent, discuss the Labeling/PRM/PMC with Applicant	January 9, 2013 (Wednesday)
Review Target Due Dates: <i>Primary Review Due</i> <i>Secondary Review Due</i> <i>CDTL Review Due</i> <i>Division Director Review Due</i> <i>Office Director Review Due/Sign-Off</i>	January 2, 2013 January 6, 2013 January 9, 2013 January 20, 2013 By January 30, 2013
Compile and circulate Action Letter and Action Package	January 9, 2013 (Wednesday)
FINAL Action Letter Due	January 30, 2013 (Wednesday)

Potential Consults/Collaborative Reviewers Needed:

OPDP	<p>????- professional reviewer ????- consumer reviewer Olga Salis – RPM Consult to be sent -</p>
OSE	<p>Sue Kang-OSE RPM Sean Bradley-OSE RPM TL</p> <p><u>DRISK</u> assigned to review Risk Management Plan Cynthia LaCivita (TL)</p> <p><u>DMEPA</u> to review Proprietary Name Todd Bridges (TL) James Schlick</p> <p><u>DMEPA/CMC/DDMAC</u> to review carton/container, and patient labeling</p> <p><u>DPV</u> – Bob Pratt (TL) – invite to mid-cycle and wrap up or as requested by Team</p> <p><u>DEPI</u> – Cunlin Wang (TL) – invite to mid-cycle and wrap up or as requested by Team</p>
Maternal Health	Consult to be sent -
Facility/OMPQ	
QT-IRT	*To be determined???
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 -

Discussion: If it is determined that it is not going to ODAC, then may plan to get an SGE.

Internal Team Meetings: Schedule 1 per month

PMC/PMR Meetings: Will schedule as needed.

Filing Meeting: Scheduled for August 31, 2012.

Mid-Cycle Meeting: Per 6-month clock, scheduled for October 30, 2012. Note that the Office requests ONE set of slides.

Labeling Meetings (suggested section groupings): Schedule monthly beginning after mid-cycle.

Labeling included: 50mg x 120 Container Label; 75mg x 120 Container Label; Draft Labeling with Patient Information Leaflet

Wrap- Up Meeting: Per 6-month clock, scheduled for January 3, 2013.

Applicant Orientation Presentation: Scheduled for Friday, September 7, 2012.

ODAC Needed/Not Needed: Will discuss this again. Note: Target AC date: November-December 2012 (month 4-5)

Miscellaneous Items or Issues:

- 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. Clinical Reviewer to review data in more depth and confirm with OSI for the selected Sites.
Preclinical study site Audits are NOT needed.
- b. CMC/Jewell Martin will assist with the following consults:
 - Establishment (EES)/Coordinate Inspections
 - Environmental Analysis: Request for Categorical Exclusion
 - Labeling
 - Micro consult was submitted today.
- c. Nonproprietary name on label (dabrefenib vs. dabrafenib mesylate) – this is ok for now but CMC will review.
- d. 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).
- e. 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.
- f. Cross reference letters to the NDA submitted in the PMA to reference NDA 202806 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



NDA 202806

NDA ACKNOWLEDGMENT

GlaxoSmithKline, LLC
Attention: Ellen S. Cutler
Senior Director, Regulatory Affairs, Oncology
1250 South Collegeville Road
Collegeville, PA 19426

Dear Ms. Cutler:

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: (b) (4) (dabrafenib) capsules, 50 mg and 75 mg

Date of Application: July 29, 2012

Date of Receipt: July 30, 2012

Our Reference Number: NDA 202806

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 September 28, 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“(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



NDA 202806 and NDA 204114

GlaxoSmithKline, LLC
Attention: Eric Richards, M.S., M.P.H.
Director, Global Regulatory Affairs
1250 South Collegeville Road; UP4110
Collegeville, PA 19426

Dear Mr. Richards:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for “(b)(4) (dabrafenib)” and “Mekinist (trametinib)”.

We also refer to your July 24, 2012, email correspondence requesting an application orientation meeting to discuss for “(b)(4) (dabrafenib)” and “Mekinist (trametinib). Based on the statement of purpose, objectives, and proposed agenda, we will consider this an informal type C meeting. Meeting minutes will not be issued.

The meeting is scheduled as follows:

Date: Friday, September 7, 2012
Time: ~1:00 PM – 2:30 PM (ET)
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 2205
Silver Spring, Maryland 20903

CDER participants:

Patricia Keegan	Joseph Gootenberg	
Karen Jones	Norma Griffin	
Suzanne Demko	Marc Theoret	
Kun He	Weishi (Vivian) Yuan	Xiaoping (Janet) Jiang
Hong Zhao	Jian Wang	Ruby Leong
Whitney Helms	Alexander Putman	Sachia Khasar
Nallaperum Chidambaram	Amit Mitra	Jean Tang
Liang Zhou	Gaetan Ladouceru	Sue Ching Lin
Jewell Martin	Mahesh Ramanadham	
Angelica Dorantes	Minerva Hughes	John Duan
Jean Mulinde	Paul Okwesili	

Please provide me with a list of GSK's meeting participants so that their names can be entered into our LobbyGuard system.

Please submit desk copies and/or slides to me at the following address:

Norma Griffin
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 2369
10903 New Hampshire Avenue
Silver Spring, Maryland
*Use zip code **20903** if shipping via United States Postal Service (USPS).*
*Use zip code **20993** if sending via any carrier other than USPS (e.g., UPS, DHL, FedEx).*

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

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/s/

NORMA S GRIFFIN
08/01/2012



NDA 202806

NDA PRESUBMISSION ACKNOWLEDGEMENT

GlaxoSmithKline, LLC
Attention: Ellen S. Cutler
Senior Director, Regulatory Affairs, Oncology
1250 South Collegeville Road
Collegeville, PA 19426

Dear Ms. Cutler:

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: dabrafenib capsule; 50 mg and 75 mg

Date of Submission: June 21, 2012

Date of Receipt: June 21, 2012

Our Reference Number: NDA 202806

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



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

Memorandum

Date: July 2, 2012
From: Norma Griffin, RPM DOP 2/OHOP/CDER/FDA
Subject: NDA 202806; GlaxoSmithKline, LLC
Information Request – Datasets Information

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

Dear Ellen:

Please refer to your New Drug Application (NDA) for the investigational product “(b) (4)” (dabrafenib).”

We are currently reviewing your submission of June 29, 2012, (Part 2 of 3 Presubmission to Rolling Submission) containing Part 3 (Site Level Dataset) and have the following comments from OSI Review Team:

The datasets submitted for use in the clinical site selection tool are missing multiple of the requested data variables (LASTNAME, FRSTNAME, MINITAL, PHONE, FAX, EMAIL, SITEEFFE, SITEEFFS, FINLMAX, FINLDISC, COUNTRY, STATE, CITY, POSTAL, STREET, and TRTEFFS). We request that you submit a revised dataset. You can also include all studies in a single dataset, however, if you find it easier leaving as three separate datasets FDA can recombine here.

Please address the aforementioned comments and provide a response as soon as possible, via electronic (email) communication at Norma.Griffin@fda.hhs.gov and follow that 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
07/02/2012



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 “trametinib (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 [REDACTED] (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 (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) 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 (b) (4)

Considering the general similarity 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 previously 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 $\geq 99\%$ 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/m² administered intravenously (IV) once every 3 weeks
- paclitaxel 175 mg/m² 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 ^{(b) (4)} mutation-positive advanced and/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

(b) (4)

GSK states that the proposed indication, (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} mutation-positive advanced (Stage III) or 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/m² 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,c}		
% (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 as 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)

[REDACTED] ?

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 \pm 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) 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 (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 (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)

[Redacted] ?

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 safely 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 mutations, in terms of response rate and duration of response, across the studies.

[REDACTED] (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.

[REDACTED] (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 BRF113292 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 BRF113292 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 \pm 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/OfficeofMedicalPr
oductsandTobacco/CDER/ucm180482.htm](http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalPr
oductsandTobacco/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/GuidanceComplianceRegulatoryInf
ormation/Guidances/ucm072137.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInf
ormation/Guidances/ucm072137.pdf) and

[http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInf
ormation/Guidances/ucm072109.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInf
ormation/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) [REDACTED] for the dabrafenib NDA submission.

a) **Does the FDA agree with the proposed plans?**

FDA RESPONSE: No, the proposal [REDACTED] (b) (4) [REDACTED] 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 (b) (4)

(b) (4) assuming this data is compelling enough to warrant filing. This filing (b) (4) monotherapy (b) (4) would happen within the fourth quarter of this year.

This proximity of filling the mono-therapy data (b) (4) will better align with the anticipated usage of the drug (as single-agent (b) (4)), and facilitate greater efficiency in the crafting of submission documents and labeling. (b) (4)
(b) (4). 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 (b) (4) based on BRF113220: 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 (b) (4)

(b) (4)
(b) (4)
(b) (4)
(b) (4)

CDRH stated that whether a PMA supplement would be required for bridging data to support trametinib alone (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)

(b) (4)
(b) (4)

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

(b) (4)

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).
-

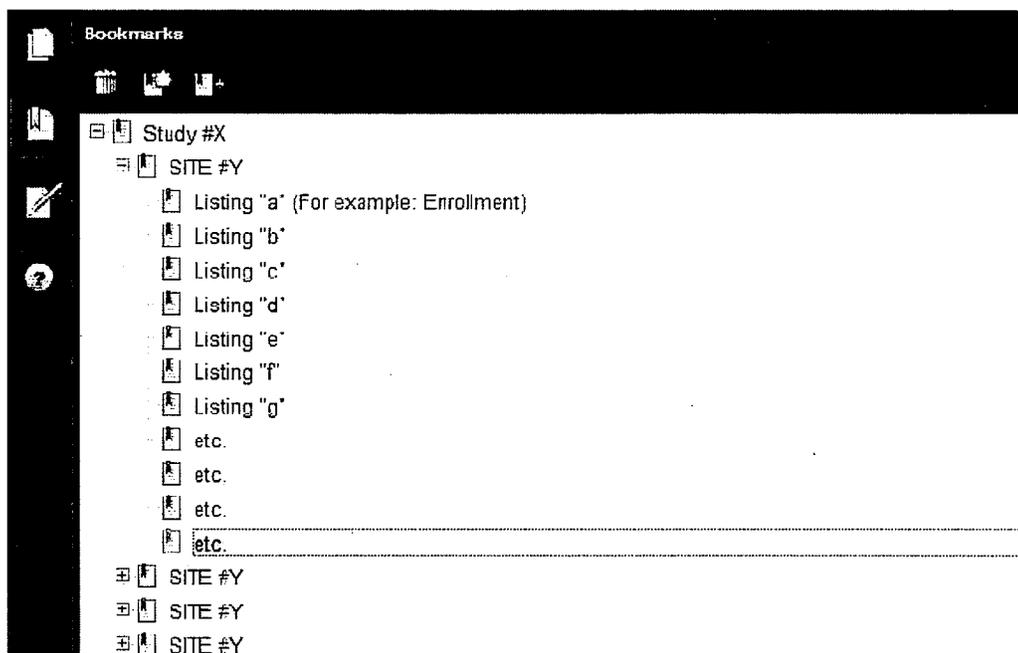
Appendix 1
OSI Pre-NDA Request

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:

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OSI Pre-NDA Request



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)

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- 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).

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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	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

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Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., <u>not limited to</u> only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount (\$USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount (\$USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parties. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00

Appendix 1
OSI Pre-NDA Request

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	MINITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

Appendix 1
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The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the 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	ENROLL	SCREEN	DISCONT
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

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OSI Pre-NDA Request

MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

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

Appendix 1
OSI Pre-NDA Request

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).
-

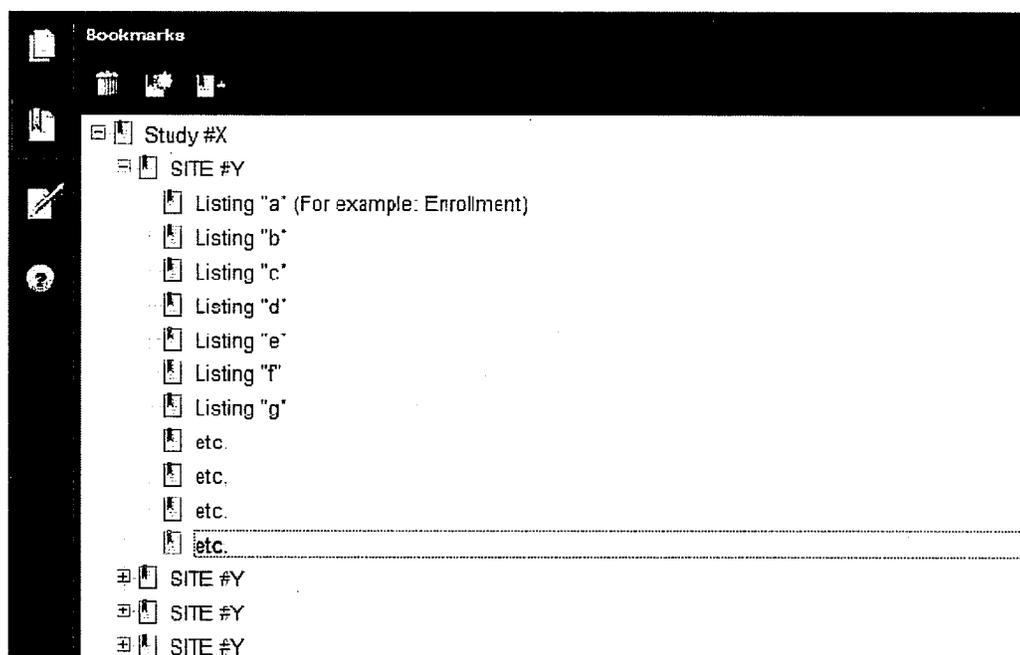
Appendix 2
OSI Pre-NDA Request

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:

Appendix 2 OSI Pre-NDA Request



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.

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)

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- 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).

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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	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100

Appendix 2
OSI Pre-NDA Request

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
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17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
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19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
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25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., not limited to only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount (\$USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860), if unable to obtain the information required to the corresponding statements, enter -1.	20000.00
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Appendix 2
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30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	MINITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

Appendix 2
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The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

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STUDY	STUDYTL	DOMAIN	SPONNO	SPONNAME	IND	UNDERIND	NDA	BLA	SUPPNUM	SITEID	ARM	ENROLL	SCREEN	DISCONT
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPOINT	ENDTYPE	TRTEFFR	TRTEFFS	SITEEFFE	SITEEFFS	CENSOR	NSAE	SAE	DEATH	PROTVIOL	FINLMAX	FINLDISC	LASTNAME	FRSTNAME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washington	George
Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

Appendix 2
OSI Pre-NDA Request

MINITIAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1. Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1. Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk.

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

Appendix 2
OSI Pre-NDA Request

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	ANTI-CANCER	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	--
	DSCAT	Category for Disposition Event	PROTOCOL MILESTONE	Yes	Perm	Char	DSCAT
	DSDECOD	Standardized Disposition Term	DEATH, RANDOMIZED, LOST TO FOLLOW-UP, ALIVE, ADVERSE EVENT, PROGRESSIVE DISEASE	Yes	Req	Char	NCOMPLT (Completion/Reason for Non-Completion)
	DSDTC	Date/Time of Collection	--	Yes	Perm	Char	ISO 8601

	DSSCAT	Subcategory for Disposition Event	STUDY DISCONTINUATION, TREATMENT DISCONTINUATION, STUDY TERMINATION	Yes	Perm	Char	--
	DSSTDTC	Start Date/Time of Disposition Event	--	Yes	Exp	Char	ISO 8601
	DSSTDY	Study Day of Start of Disposition Event	--	Yes	Perm	Num	--
	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 TGRES, NTGRES & 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	--
	ANCHDTC	Anchor date of assessment schedule	Variable in ADSL - no name determined	NEW		Char	
	MAXPRD	Maximum length of assessment schedule		NEW		Char	ISO 8601 Duration
	MINPRD	Minimum length of assessment schedule		NEW		Char	ISO 8601 Duration
	STOFFSET	Start time from anchor date		NEW		Char	ISO 8601 Duration
	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

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

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	VARIABLE	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	EXFRT	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	LBDFC	C
LB	LBDFY	N
MH	STUDYID	C
MH	USUBJID	C
MH	MHDECOD	C
MH	MHRODSVC	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 of 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. Eisenhauer*, P. Therasse, 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, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Code list or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	TU	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App.C2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
TUSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
TUGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TUREFID	Reference ID	Char		Identifier	Internal or external identifier. Example:	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TUSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TULINKID	Link ID	Char		Identifier	Identifier used to link identified tumors to the assessment results over the course of the study.	Exp	
TUTESTCD	Tumor Identification Short Name	Char	*	Topic	Short name of the TEST in TUTEST. TUTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: TUMIDENT, NEWTUMOR. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
TUTEST	Tumor Identification Test Name	Char	*	Synonym Qualifier	Verbatim name of the test for the tumor/lesion identification. The value in TUTEST cannot be longer than 40 characters. Examples: Tumor Identification, New Tumor Identified. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
TUCAT	Category for Tumor Identification	Char		Grouping Qualifier	Used to categorize tumors.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
TUSCAT	Sub-Category for Tumor Identification	Char		Grouping Qualifier	A further classification of the TUTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TUORRES	Tumor Identification Result	Char	*	Result Qualifier	Result of the Tumor identification. Examples: When TUTESTCD=TUMIDENT (Tumor Identification), values of TUORRES might be: TARGET or NON-TARGET. When TUTESTCD=NEWTUMOR the value of TUORRES might be: Y When TUTESTCD=BENIGNAB the value of TUORRES might be: BENIGN RENAL LESIONS Contains the result value for all findings copied from TUORRES.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TUSTRESC	Tumor Identification Result Std. Format	Char	*	Record Qualifier	The name or identifier of the vendor that performed the Tumor Identification.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TUNAM	Vendor Name	Char		Record Qualifier	Used to specify the anatomical location of the identified tumor. Example: Gastrointestinal Tract. Note: When anatomical location is broken down and collected as distinct pieces of data that when combined provide the overall location information (e.g. organ / laterality /location / sub-location) then the additional information should added as supplemental qualifiers. See Assumption 3	Perm	SDTM 2.2.3
TULOC	Location of the Tumor	CHAR	(LOC)	Record Qualifier	Method used to identify the tumor. Examples: X-ray, MRI, CT-Scan.	Exp	SDTMIG 2.2.3
TUMETHOD	Method of Identification		*	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST	Exp	SDTMIG 2.2.3
TUEVAL	Evaluator	Char	(EVAL)	Record Qualifier	This column can be left Null when the Investigator provides the complete set of data in the domain. However the column should contain no Null values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TUEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with TUEVAL to provide an additional level of detail. When multiple assessors play the role identified in TUEVAL, values of TUEVALID will attribute a row of data to a particular assessor. TUEVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The TUEVALID variable would not be subject to CDISC Controlled Terminology. See Assumption 5.	Perm	
TUACPTFL	Accepted Record Flag	Char	*	Record Qualifier	In cases where more than one independent assessor (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide independent assessments at the same timepoint this flag identifies the record that is considered to be the accepted assessment. 1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Perm	
VISITNUM	Visit Number	Num		Timing		Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISITDY	Planned Study Day of Visit	Num		Timing		Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TUDTC	Date/Time of Tumor Identification	Char	ISO 8601	Timing		Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TUDY	Study Day of Tumor Identification	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.1. ASSUMPTIONS FOR THE TUMOR IDENTIFICATION DOMAIN MODEL

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

1. The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). The --LINKID variable is used for values that support a relrec dataset to dataset relationship and to provide a unique code for each identified tumor.
2. The values of TUTESTCD and TUTEST will be relatively simple and will either represent that the Tumor is identified and categorized at screening or that the Tumor is identified as New (has appeared since the Screening assessment).

Proposed TUTESTCD / TUTEST values for this domain:

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

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

- a. The occurrence of a New Tumor is the sole piece of information that a sponsor collects because this is a sign of disease progression and no further details are required. In such cases a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y".
- b. The occurrence of a New Tumor and the anatomical location of that newly identified Tumor are the only collected pieces of information. In this case it is expected that a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y", and the TUOC variable would be populated with the anatomical location information (the additional location variables may be populated depending on the level of detail collected).
- c. A sponsor might record the occurrence of a New Tumor to the same level of detail as Target and Non-Target Tumors. In this case the occurrence of the new tumor and the anatomical location information, and also measure the New Tumor. In this case it is expected that a record would be created where TUTEST="New Tumor Identified" and TUORRES="Y", and the identifier, TULINKID, would all be populated. The measurement/assessment of the New Tumor would be recorded in the TR domain.

3. TUCAT and TUSCAT have been included as they are standard domain variables however these columns would generally not be needed and so the variables are not included in the accompanying examples.
4. Anatomical Location information might be collected in a number of ways the simplest way is as a long text string and in these cases the text string is captured in the TULOC variable. However, anatomical location might also be collected through a number of distinct and separate variables (that might possibly be subject to controlled terminology) and in such cases the additional information would be recorded in the following Supplemental Qualifiers:

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

5. The Acceptance Flag variable (TUACPTFL) identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.
6. The Evaluator Specified variable (TUEVALID) is used in conjunction with TUEVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the TUEVAL variable. For example TUEVAL="INDEPENDENT ASSESSOR" and TUEVALID="RADIOLOGIST 1". The TUEVALID variable is not subject to Controlled Terminology. TUEVAL must also be populated when TUEVALID is populated.
7. The following proposed supplemental Qualifiers would be used to represent information regarding previous irradiation of a tumor when that information is known:

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

TUMOR RESULTS - TR
tr.xpt, Tumor Results - Findings, Version 3..x.x One record per tumor measurement/assessment per tumor per visit per subject, Tabulation

Variable Name	Variable Label	Type	Controlled Terms, Code list or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	TR	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App, 2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
TRSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
TRGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TRREFID	Reference ID	Char		Identifier	Internal or external identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
TRSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4
TRLINKID	Link ID	Char		Identifier	Identifier used to link the assessment result records to the tumor identification record.	Exp	
TRTESTCD	Tumor Assessment Short Name	Char	*	Topic	Short name of the TEST in TRTEST. TRTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: LDIAM, DIAM. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
TRTEST	Tumor Assessment Test Name	Char	*	Synonym Qualifier	Verbatim name of the test or examination used to obtain the measurement or finding. The value in TRTEST cannot be longer than 40 characters. Examples: LONGEST DIAMETER, LONGEST PERPENDICULAR, AXIAL THICKNESS, VOLUME, AREA. See Assumption 2	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
TRCAT	Category for Tumor Assessment	Char	*	Grouping Qualifier	Used to categorize assessments. Examples: Measurement Categorical	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
TRSCAT	Sub-Category for Tumor Assessment	Char		Grouping Qualifier	A further classification of the TRTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Code list or Format	Role	CDISC Notes	Core	References
TORRES	Result or Finding in Original Units	Char		Result Qualifier	Result of the Tumor measurement/assessment as originally received or collected.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TORRESU	Original Units	Char	(UNIT)	Variable Qualifier	Original units in which the data were collected. The unit for TRORRES. Example: mm	Exp	SDTMIG 2.2.3 SDTMIG 4.1.3.2
TRSTRESC	Character Result/Finding in Std Format	Char		Record Qualifier	Contains the result value for all findings, copied or derived from TRORRES in a standard format or standard units. TRSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in TRSTRESN	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRSTRESN	Numeric Result/Finding in Standard Units	Num		Result Qualifier	Used for continuous or numeric results or findings in standard format; copied in numeric format from TRSTRESC. TRSTRESN should store all numeric test results or findings.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
TRSTRESU	Standard Units	Char	(UNIT)	Variable Qualifier	Standardized unit used for TRSTRESN.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.3.2 SDTMIG 4.1.5.1
TRSTAT	Tumor Assessment Status	Char	(ND)	Result Qualifier	Used to indicate a measurement was not done, or a tumor measurement was not taken. Should be Null if a result exists in TRORRES.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
TRREASND	Reason Tumor Measurement Not Performed	Char		Record Qualifier	Describes why a measurement or test was not performed. Examples: BROKEN EQUIPMENT or SUBJECT REFUSED. Used in conjunction with TRSTAT when value is NOT DONE.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
TRNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the Tumor measurement or assessment.	Perm	SDTM 2.2.3
TRMETHOD	Method used to identify the Tumor		*	Record Qualifier	Method used to measure the tumor. Examples: X-ray, MRI, CT-Scan.	Exp	SDTMIG 2.2.3

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TREVAL	Evaluator	Char	(EVAL)	Record Qualifier	<p>Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST</p> <p>This column can be left <i>Null</i> when the Investigator provides the complete set of data in the domain. However the column should contain no <i>Null</i> values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR</p>	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.4
TREVALID	Evaluator Specified	Char		Variable Qualifier	<p>The Evaluator Specified variable is used in conjunction with TREVAL to provide an additional level of detail. When multiple assessors play the role identified in TREVAL, values of TREVALID will attribute a row of data to a particular assessor. TREVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The TREVALID variable would not be subject to CDISC Controlled Terminology. Note TREVAL must also be populated when TREVALID is populated.</p> <p>See Assumption 4</p>	Perm	
TRACPTFL	Accepted Record Flag	Char	*	Record Qualifier	<p>In cases where more than one independent assessor (e.g. where TREVALID has values of "RADIOLOGIST 1" & "RADIOLOGIST 2") provide independent assessments at the same timepoint this flag identifies the record that is considered to be the accepted assessment.</p>	Perm	
VISITNUM	Visit Number	Num		Timing	<ol style="list-style-type: none"> Clinical encounter number. Numeric version of VISIT, used for sorting. 	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	<ol style="list-style-type: none"> Protocol-defined description of clinical encounter. May be used in addition to VISITNUM and/or VISITDY. 	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISITDY	Planned Study Day of Visit	Num		Timing		Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
TRDTC	Date/Time of Tumor Measurement	Char	ISO 8601	Timing		Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
TRDY	Study Day of Tumor Measurement	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.2. ASSUMPTIONS FOR THE TUMOR RESULTS DOMAIN MODEL

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

- The organization of data across the TU and TR domains requires a relrec relationship in order to link the data between the 2 domains. A dataset to dataset link would be the most appropriate linking mechanism. Utilizing one of the existing ID variables is not possible in this case because all three of the variables (GRPID, REFID & SPID) are needed (see examples). The --LINKID variable is used for values that support a relrec dataset to dataset relationship and to provide a unique code for each identified tumor. TRLINKID is a required variable as the records in the TR domain must relate back to an identification record in TU.
- TRTESTCD / TRTEST values for this domain (this is for illustration purposes these values will be published as Controlled Terminology):

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

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

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

3. The Acceptance Flag variable (TRACPTFL) identifies those records that have been determined to be the accepted assessments/measurements by an independent assessor. This flag should not be used by a sponsor for any other data censoring purpose. This would be used in cases where multiple assessors (e.g. RADIOLOGIST 1 & RADIOLOGIST 2) provide assessments or evaluations at the same timepoint or an overall evaluation.
4. The Evaluator Specified variable (TREVAlID) is used in conjunction with TREVAl to provide additional detail and allows for values that might deviate from the controlled terminology expected in the TREVAl variable. For example TREVAl="INDEPENDENT ASSESSOR" and TREVAlID="RADIOLOGIST 1". The TREVAlID variable is not subject to Controlled Terminology. TREVAl must also be populated when TREVAlID is populated.

RESPONSE – RS

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

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req	SDTMIG 2.2.4
DOMAIN	Domain Abbreviation	Char	RS	Identifier	Two-character abbreviation for the domain.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.2 SDTMIG App.C2
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req	SDTMIG 2.2.4 SDTMIG 4.1.2.3
RSSEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness within a dataset for a subject. May be any valid number.	Req	SDTMIG 2.2.4
RSGRPID	Group ID	Char		Identifier	Used to link together a block of related records within a subject in a domain.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
RSREFID	Reference ID	Char		Identifier	Internal or external identifier.	Perm	SDTMIG 2.2.4 SDTMIG 4.1.2.6
RSSPID	Sponsor ID	Char		Identifier	Sponsor-defined identifier.	Perm	SDTMIG 2.2.4
RSLINKID	Link ID	Char		Identifier	Used to link the response assessment to the appropriate measurement records (in TR) used to determine the response result.	Perm	
RSTESTCD	Response Assessment Short Name	Char	*	Topic	Short name of the TEST in RSTEST. RSTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: TRGRES, BESTRESP, SYMPTPD	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1
RSTEST	Response Assessment Name	Char	*	Synonym Qualifier	Verbatim name of the response assessment. The value in RSTEST cannot be longer than 40 characters. Examples: Target Response, Best Overall Response, Symptomatic deterioration	Req	SDTMIG 2.2.3 SDTMIG 4.1.2.1 SDTMIG 4.1.2.4
RSCAT	Category for Response Assessment	Char		Grouping Qualifier	Used to categorize tumors.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
RSSCAT	Sub-Category for Response Assessment	Char		Grouping Qualifier	A further classification of the RSTEST.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.2.6
RSORRES	Response Assessment Original Result	Char		Result Qualifier	Result of the Response assessment as originally received, collected, or calculated.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
RSSTRES	Response Assessment Result in Std Format	Char		Record Qualifier	Contains the result value for the response assessment, copied or derived from RSORRES in a standard format or standard units. RSSTRES should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in RSSTRES	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.1
RSSTAT	Response Assessment Status	Char	(ND)	Result Qualifier	Used to indicate the response assessment was not performed. Should be Null if a result exists in RSORRES.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
RSREASND	Reason Response Assessment Not Performed	Char		Record Qualifier	Describes why a response assessment was not performed. Examples: Subject does not have target lesions. Used in conjunction with TRSTAT when value is NOT DONE.	Perm	SDTMIG 2.2.3 SDTMIG 4.1.5.1.1
RSNAM	Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the response assessment.	Perm	SDTM 2.2.3
RSEVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Examples: INVESTIGATOR, RADIOLOGIST, ONCOLOGIST This column can be left Null when the Investigator provides the complete set of data in the domain. However the column should contain no Null values when data from one or more independent assessors is included meaning that the rows attributed to the Investigator rows should contain a value of INVESTIGATOR.	Exp	SDTMIG 2.2.3 SDTMIG 4.1.5.4

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format	Role	CDISC Notes	Core	References
RSEVALID	Evaluator Specified	Char		Variable Qualifier	The Evaluator Specified variable is used in conjunction with RSEVALID to provide an additional level of detail. When multiple assessors play the role identified in RSEVALID, values of RSEVALID will attribute a row of data to a particular assessor. RSEVALID should not contain the names of the assessors but should contain values such as RADIOLOGIST 1 or RADIOLOGIST 2. The RSEVALID variable would not be subject to CDISC Controlled Terminology. See Assumption 5	Perm	
RSACTFL	Accepted Record Flag	Char		Record Qualifier	In cases where more than one independent assessor (e.g. independent Oncologist) provides an evaluation of response this flag identifies the record that is considered to be the accepted evaluation.	Perm	
VISITNUM	Visit Number	Num		Timing	1. Clinical encounter number. 2. Numeric version of VISIT, used for sorting.	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
VISIT	Visit Name	Char		Timing	1. Protocol-defined description of clinical encounter. 2. May be used in addition to VISITNUM and/or VISITDY.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
RSDTC	Date/Time of Response Assessment	Char	ISO 8601	Timing	Date may be derived if based on multiple dates of scans Exception: derived data in RS needed for reviewer	Exp	SDTMIG 2.2.5, SDTMIG 4.1.4.5, SDTMIG 7.4
RSDY	Study Day of Response Assessment	Num		Timing	1. Study day of the Tumor measurement, measured as integer days. May be from rand date not first dose date 2. Algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in Demographics.	Perm	SDTMIG 2.2.5, SDTMIG 4.1.4.4, SDTMIG 4.1.4.6

1.1.3. ASSUMPTIONS FOR THE TUMOR RESPONSE DOMAIN MODEL

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

1. The RSLINKID variable is used for values that support a relrec dataset to dataset relationship. RSLINKID would be required when a response evaluation relates back to an individual tumor.
2. RSTESTCD / RSTEST values for this domain (this is for illustration purposes these values will be published as Controlled Terminology):

RSTESTCD	RSTEST	Definition
TRGRES	Target Response	
NTRGRES	Non-target Response	
OVLRRESP	Overall Response	
BESTRESP	Best Response	
LESNRESP	Lesion Response	
SYMPTPD	Symptomatic Deterioration	

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

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

4. *TS – TSPARIM/TSVAL needed to represent the Response Criteria used in the clinical trial.*
5. The Evaluator Specified variable (RSEVALID) is used in conjunction with RSEVAL to provide additional detail and allows for values that might deviate from the controlled terminology expected in the RSEVAL variable. For example RSEVAL="INDEPENDENT ASSESSOR" and RSEVALID="RADIOLOGIST 1". The RSEVALID variable is not subject to Controlled Terminology. RSEVAL must also be populated when RSEVALID is populated.

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
Elton Cutler	GSK
DANIELE QUELLET	GSK
Vicki Goodman	GSK
Rafael Amado	GSK
Jennifer Dudenak	GSK
Michael Streit	GSK
AMITA MAJUMDAR	GSK
ANNE-MARIE MARTIN	GSK
MARIA CHAN	FDA/CDRH/OVD
Hong Zhao	CDER/OTS/OC/DCPS
Ruby Leung	FDA/DCPS
KUN HU	FDA/OB/DBV
Whitney Helms	FDA/CDER/DOP1
Anthony MURGO	FDA - OHOP-IO
DONNA ROSCOE	FDA-CDRH-OND-DHAD
SALMA KHASAR	FDA/OHOP/DHOT
Jean Mulinde	FDA/CDER/OC/OST
Amarilis 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
Lillian Zhang	FDA/CDER/OTS/OC/DCPS
Jenny Zhang	FDA/CDER/OTS/OB/DBS
Eric Richards	GSK
MICHELLE CASEY	GSK

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/s/

DEANNE R VARNEY
05/23/2012



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.

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: Genotoxic impurity (b)(4) is controlled in the manufacturing process (b)(4)

Does the Agency agree with the above proposed control strategy?

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: Genotoxic impurity (b)(4) is controlled in the manufacturing process, (b)(4)

Does the Agency agree with the above proposed control strategy?

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) is a potential impurity in the dabrafenib mesylate manufacturing process (b)(4)

Does the Agency agree with the above proposed control strategy?

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 (b) (4) in the NDA. The adequacy of the justification will be a review issue.

Your proposals (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: (b) (4) Does the Agency agree with the proposed testing intervals?

FDA Response to Question 4: No, the Agency does not agree with the proposed testing intervals (Table 27 on page 67) (b) (4) as the proposal (b) (4) 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 (b) (4) the dissolution specification?

FDA Response to Question 5: No, we do not agree with the proposed drug product specification. It is not acceptable (b) (4). The description test should include the appearance of the capsule content. It is recommended that testing (b) (4) be included in the specifications (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 (b) (4).
FDA stated that GSK could propose (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 (b) (4) in addition to the appearance of capsules. FDA expressed concerns (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 (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 (b) (4) dissolution acceptance criteria. FDA indicated that (b) (4) dissolution acceptance criteria is viewed as (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 (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)

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}

Sarah Pope-Miksinski, Ph.D.
Branch Chief
Division of New Drug Quality Assessment 1
Office of New Drug Quality Assessment
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments, handouts or slides distributed for the teleconference.

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/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
Qiang (Casey) Xu, Ph.D., Mathematical Statistician, DB 5
Robert Dorsam, Ph.D., Pharmacologist/Acting supervisory Pharmacologist
Sarah J. Schrieber, PharmD. Clinical Pharmacology Reviewer, DCP5
Pengfei Song, Ph.D., Clinical Pharmacology Reviewer, DCP5
Maria M. Chan, Ph.D., DIHD, CDRH
Donna Roscoe, Ph.D., DIHD, CDRH
Jamila A. Mwidau, RN, BSN, MPH, Regulatory Project Manager
Kim J. Robertson, Consumer Safety Officer

INDs 102175 & 105032
Meeting Minutes
EOP1/Pre-Phase 3, Type B

OODP
DDOP

GLAXOSMITHKLINE ATTENDEES

Kiran Patel, M.D., Clinical Development
Rafael Amado, M.D., Clinical Development
Vicki Goodman, M.D., Clinical Development
Jeff Legos, Ph.D., Clinical Development
Michele Casey, Ph.D., Biostatistics
Agnes Westelinck, Pharm D., Regulatory Affairs
Ellen Cutler, Regulatory Affairs
Eric Richards, MS, MPH, Regulatory Affairs

1.0 BACKGROUND

(b) (4)

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.

(b) (4)

[Redacted text block]

(b) (4)

[Redacted text block]

2.0 DISCUSSION

(b) (4)

[Redacted text block]

Minutes Preparer:

{See appended electronic signature page}

Kim J. Robertson
Regulatory Health Project Manager

Meeting Adjourned:

11:40 AM

Meeting Chair:

{See appended electronic signature page}

V. Ellen Maher, M.D.
Clinical Team Leader

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/s/

KIM J ROBERTSON

03/03/2011

24February11 Sponsor Meeting Minutes MEK and BRAF INDs 102175 and 105032; GSK

VIRGINIA E MAHER

03/08/2011



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

MEETING MINUTES

DATE: July 6, 2010

TIME: 11:00AM

LOCATION: Room 1419

IND/NDA: IND: 105,032

Meeting Request Submission Date: April 14, 2010

FDA Response Date: May 4, 2010

Briefing Document Submission Date: June 3, 2010

DRUG: GSK2118436 BRAF Inhibitor; Capsules

SPONSOR/APPLICANT: GlaxoSmithKline

TYPE of MEETING: Type B, EOP1/Pre-Phase 3

Proposed Indication: Treatment of patients with BRAF V600E (b)(4) mutation positive advanced and/or metastatic melanoma.

FDA PARTICIPANTS:

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BACKGROUND:

GSK has submitted a proposal to conduct the following two clinical studies to support their proposed indication: Study BRF113710 is a Phase 2 single-arm, open label, study of GSK2118436 in patients with BRAF mutant metastatic melanoma (Stage IV) who received prior systemic therapy. The proposed study will enroll 100 patients that will receive 150 mg of GSK2118436 as a single agent twice daily and continue on treatment until disease progression, death, or unacceptable adverse event. The primary endpoint is Overall Response Rate (ORR). The secondary endpoints are Progression Free Survival (PFS), Duration of Response, and Overall Survival (OS). Study BRF113683 is a two-arm, open-label, randomized Phase 3 study comparing dacarbazine (DTIC) to the single agent GSK2118436. The proposed study will enroll 600 patients (300 per group) in order to observe 342 deaths. DTIC is to be administered intravenously (1000 mg/m² every 3 weeks, as labeled). Cross-over to GSK2118436 will not be permitted in the Phase 3 study. This study is designed to have co-primary endpoints and they are Progression Free Survival (PFS) and Overall Survival (OS). The secondary endpoints are Overall Response Rate (ORR) and Duration of Response.

As GSK2118436 is being developed specifically for the treatment of B-RAF mutant tumors, an in-vitro diagnostic (IVD) test is being co-developed to select patients for enrollment in the clinical trials. A melanoma tumor sample will be obtained from a superficial (skin) lesion or an invaded lymph node to perform the mutation assay that will determine the eligibility of the patient for the study. BRAF-WT (Wild Type) patients will not be enrolled in the proposed GSK2118436 clinical studies.

Attachment 2 **List of Questions**

Brief background

GSK plans to conduct the following two clinical studies to support the proposed indication:

- BRF113710: A phase 2 single-arm, open-label study of GSK2118436 in patients with BRAF mutant metastatic melanoma who have received prior systemic therapy.
- BRF113683: A randomized, open-label phase 3 study comparing GSK2118436 to dacarbazine in previously untreated patients with BRAF mutant metastatic melanoma.

It is anticipated that these studies will support the initial marketing application for GSK2118436 capsules for the treatment of patients with BRAF V600E^{(b)(4)} mutation positive metastatic melanoma. Co-development of an in vitro diagnostic (IVD) to select patients with the V600E/K^{(b)(4)} mutation is ongoing as described in Section 3.5. A meeting with FDA/CDRH/DIHD occurred on May 19, 2010 to discuss development of the IVD for screening patients for BRAF V600 mutations.

The briefing document includes a summary of the available safety and activity data from the ongoing Phase I study, dose rationale, Clinical Pharmacology plan, and detailed overviews of the proposed Phase 2 and 3 studies including the rationale for the studies and design details.

Clinical / Statistical

General

Question 1: As discussed in Section 2.5, dose selection for further monotherapy development is based on the exposure, safety profile, and clinical activity observed in the first-time-in-human study conducted in patients with BRAF mutant tumors. Does the Agency have any comments regarding the dose selected for further monotherapy development?

FDA Response: Yes. We recommend that you include the 35 mg BID dose of GSK2118436 in a randomized Phase 2 dose response study. The low dose arm can be terminated early for lack of activity. The 35 mg BID dose level had a high response rate (i.e., out of 5 patients, there was one CR and two PRs) and none of the patients on the 35 mg BID dose were reported to have developed squamous cell carcinomas (secondary malignancies) as described at the higher doses. The lower dose of 35 mg BID may inhibit ERK signaling in BRAF-mutant melanomas and spare “normal” skin tissue from increased ERK signaling.

Discussion Point: The sponsor provided rationale for the dose selection. Most of the patients on the 35 mg BID cohort were dose escalated and do not represent the 35 mg dose. The FDA recommends that a dose response study be performed.

Question 2: Does the Agency agree with the rationale provided in Section 3.2 for not enrolling subjects with Wild-type B-RAF in GSK2118436 clinical studies?

FDA Response: This is your decision.

Discussion Point: No further discussions were necessary.

The following question pertains to the proposed Phase 2 study in subjects with previously treated metastatic melanoma:

Question 3: As there is currently no FDA approved product indicated for the treatment of previously treated patients with metastatic melanoma, does the Agency agree with the potential for an accelerated approval based on a clinically meaningful response rate and duration of response in the Phase II study (Section 3.2)?

FDA Response: Possibly. This will be a review issue.

Discussion Point: No further discussions were necessary.

Are other efficacy measures needed to support an accelerated approval?

FDA Response: Response rate and duration can suffice as the primary endpoints for the study. Your Phase 2 study should also monitor for the appearance of squamous cell

carcinoma. You should also monitor other sites (i.e., head & neck, esophagus, lung, cervix, and anus) for squamous cell carcinomas.

Discussion Point: GSK indicated that secondary malignancies will be captured as SAEs and agreed to include baseline and end of study PE with rectal and pelvic exams.

The following questions pertain to the proposed Phase 3 study protocol in subjects with previously untreated metastatic melanoma (Section 3.3):

Question 4: Does the Agency agree there is sufficient evidence of clinical activity and an acceptable risk profile to allow proceeding to the proposed Phase 3 study that will include IDMC review of ongoing safety?

FDA Response: Yes.

Discussion Point: No further discussions were necessary.

Question 5: Does the Agency agree with the proposed patient population/eligibility criteria?

FDA Response: Yes.

Discussion Point: GSK indicated that they will also include unresectable Stage 3 patients. Stratification will be included in the protocol.

Question 6: Does the Agency agree with the proposed study design (dacarbazine comparator, open-label)?

FDA Response: Yes.

Discussion Point: No further discussions were necessary.

Question 7: With regard to the statistical plan:

- a. Does the Agency agree with the proposed co-primary endpoints of progression-free survival (PFS) and overall survival (OS) and the statistical plan for assessment of each outcome?

FDA Response: Yes. Whether approval could be granted based on PFS is a review issue and depends on the risk/benefit assessment.

Please provide justification for the assumptions used for the statistical analysis plan. We noted that the median PFS difference to be detected is 2 months. Given the response rate and duration observed to date, we would expect a bigger effect on PFS and OS.

Discussion Point: *GSK plans to re-evaluate their proposal for the Phase 3 protocol, including the effect size.*

- b. Does the Agency agree with GSK's proposal to use a hierarchical testing procedure to maintain the overall Type I error of the study?

FDA Response:

Yes, however the final analysis for PFS should be performed after enrollment has been completed and 60% events for survival have occurred.

Discussion Point: *No further discussions were necessary.*

- c. Does the Agency agree with the proposal for the definition, assessment schedule, and evaluation of PFS including use of central review as an audit of the results of the investigator evaluation?

FDA Response:

No information concerning PFS assessment or schedule of assessments is provided for the Phase 3 trial. Please provide a plan for blinded review of imaging studies to assess for potential bias.

Discussion Point: *The details will be provided (b)(4)
GSK proposed (b)(4)*

The sponsor will have all scans available in the event further review is needed. The FDA stated that this will be a review issue.

- d. Does the Agency agree with the proposal to file with the results from the final PFS analysis and interim survival analysis?

FDA Response: **We recommend a Pre NDA meeting when top-line data are available.**

Discussion Point: *No further discussions were necessary.*

Question 8: Does the Agency agree with the overall development plan, a Phase II study in previously treated patients to potentially support an accelerated approval and a Phase III study in previously untreated patients, to provide confirmatory evidence of clinical benefit for the proposed indication?

FDA Response: **See responses above.**

Discussion Point: *No further discussions were necessary.*

Clinical Pharmacology

Question 9: The Clinical Pharmacology program, including food effect, mass balance, drug-drug interaction, special populations, and QTc evaluation is summarized in Section 4.1 of the briefing document.

- a. Does the agency agree with the overall clinical pharmacology plan?

FDA Response:

No. Please also address the following issues:

- The effect of a strong CYP3A4 inducer (e.g, rifampin) on the pharmacokinetics and safety of GSK2118436 and major active metabolites

Discussion Point: The FDA indicated that this will be a review issue

- o Please see FDA response to question 9b below.

Depending on the human mass balance data, you may need to conduct the following studies in humans:

- o Hepatic impairment study
- o Renal impairment study

In addition, we recommend that you collect sparse PK samples from all patients that treated with GSK2118436 in your Phase 3 trial to explore exposure-response relationships for efficacy and safety.

- b. Does the agency agree ^{(b) (4)}

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FDA Response:

No. Though the static model on CYP inhibition (CYP2C8, CYP2C9, CYP2C19) by GSK2118436 is well presented, it can not adequately address the drug-drug interaction potential of GSK2118436 given the complexity associated with its disposition and drug interaction mechanisms. As the potential inhibitory effect of major metabolites (e.g., metabolites which have 2x exposure and longer t1/2) of GSK2118436 need to be considered, the lack of interactions on CYPs can not be concluded from your static model for GSK2118436 only. Similarly, though GSK2118436 may not show in vivo inhibition on OATP1B1 or 1B3 based on your in vitro data, the inhibitory effect of its major metabolites is unknown.

For the ongoing induction study with midazolam (Part B of study BRF112680, evaluating midazolam pharmacokinetics on Day-1 and Day 15), we recommend you

consider simultaneously evaluating the inhibitory effect of GSK2118436 on CYP3A4 by collecting the pharmacokinetics of midazolam on Day 1.

Depending on CYP3A inhibition data and in vitro inhibition by the metabolites of GSK2118436, you may need to consider additional in vivo studies for the other enzymes (CYP2C8, CYP2C9, CYP2C19) and OATP1B1/1B3.

We are interested in the mechanistic static model you developed for GSK2118436 on CYP2C8 though it oversimplified the complexity in your case. Please provide further information for the Figure 9 in your meeting package, particularly for the drugs that were under-predicted.

Discussion Point: This will be a review issue.

- c. Does the agency agree that ^{(b) (4)} is not required in the QTc study?

FDA Response: Possibly. Please submit your QT evaluation protocol for FDA/IRT review.

Discussion Point: This will be a review issue.

General / Regulatory

Question 10: As discussed in Section 4.2, metastatic melanoma, especially in patients with BRAF mutant tumors, currently represents a very rare disease in the pediatric population. Studies in this patient population are likely to be impossible or highly impracticable to perform. We therefore intend to request a full waiver under 505(a) of the Act for the requirement under the Pediatric Research and Equity Act (PREA). 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: That determination is made by PeRC. You should request a waiver with your application.

Discussion Point: No further discussions were necessary.

FDA QUESTIONS:

- **What was the RAS mutant status of the three BRAF WT melanoma patients, who you described on page 17 of the meeting package? Were there any other BRAF WT melanoma patients accrued to the study?**
- **Did the melanomas of any of the six patients, who you described with squamous cell carcinomas, have BRAF mutation negative and/or RAS mutation positive melanomas?**
- **Were the patients who responded also the ones who developed SCCs?**
- **What was the rationale for not stopping your drug when patients developed the drug-related secondary malignancy, squamous cell carcinoma?**

- **Have the investigators in all your studies with this drug been informed about the occurrence of SCCs? Have the patients on your studies been informed?**
- **In your Phase 1 study, at the time of progression and if accessible, tumor biopsies were to be performed. What results have these biopsies provided? Is pERK activated at progression? Is there enough tissue to re-do the BRAF mutation test?**
- **Your Phase 3 trial should include a secondary endpoint for the appearance of squamous cell carcinoma or other second malignancies.**
- **In your Phase 1 study, why did patient #3126 have a hemicolectomy on day 35?**
- **According to Poulikakos and co-authors (Nature. 464: 427-430, 2010), RAF inhibitors do not inhibit ERK signaling in cells that coexpress BRAF(V600E) and mutant RAS. What are your plans to also test for mutant RAS in the tumors of interest and exclude patients with mutant RAS tumors?**
- **Your recently submitted amended phase 1 protocol (dated 6/9/2010; serial #0065) should specifically exclude patients who are BRAF mutation negative. In the eligibility criteria (page 45 of the protocol, criterion #3), delete wording “or a tumor type with known BRAF mutations...”**
- **Please update the FDA on the results of HPV screening and genitourinary examinations that were performed in your Phase 1 study.**

Discussion Point: GSK will provide detailed responses to address the additional FDA questions.

Meeting Adjourned:
12:05PM

Meeting Chair:
John R. Johnson, M.D.
Clinical Team Leader

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

IND-105032

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GLAXO GROUP
LTD DBA
GLAXOSMITHKLIN
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GSK2118436 (BRAE Inhibitor)

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/s/

JOHN R JOHNSON

08/14/2010