CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202806Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

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

Memorandum

Date: May 2, 2013

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

Subject: NDA 202806: Clinical Pharmacology Review and Sign-Off

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The Clinical Pharmacology Review is combined in one cumulative review with signoff by Reviewers and Team Leaders on the same day. For the review completed on April 4, 2013, the following were the signatories:

Jian Wang
Justin Earp
Christian Grimstein
Nitin Mehrotra
Rosane Charlab Orbach
Michael Pacanowski
Hong Zhao
Nam Atiqur Rahman

Clinical Pharmacology NDA Review	
NDA	202806/3
Submission Date:	07/30/2012
PDUFA Date:	05/30/2013
Brand Name:	TAFINLAR
Generic Name:	Dabrafenib
Formulation:	Capsules: 50 mg, 75 mg
Submission Type; Code:	NME (Orphan, Fast-Track); Standard
Dosing regimen:	150 mg orally twice daily
Indication:	Unresectable or metastatic melanoma with BRAF V600E mutation by an FDA-approved test
Sponsor:	GlaxoSmithKline
OCP Reviewer:	Jian Wang, Ph.D.
OCP Team Leader:	Hong Zhao, Ph.D.
Pharmacometrics Reviewer	Justin Earp, Ph.D.
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1 EXECUTIVE SUMMARY

TAFINLAR (dabrafenib) is a small molecule inhibitor of RAF kinase activity. The applicant proposed indication of TAFINLAR is for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation. FDA recommended indication is for BRAF V600E mutation based on clinical data. The proposed dose regimen is 150 mg orally twice daily.

The efficacy and safety of TAFINLAR in previously untreated patients with BRAF V600E mutation positive advanced (Stage III unresectable) or metastatic (Stage IV) melanoma were evaluated in a randomized, open-label registration trial comparing TAFINLAR to dacarbazine (DTIC). Patients were randomized (3:1) to receive either oral TAFINLAR 150 mg twice daily under fasted condition or intravenous DTIC 1,000 mg/m^2 every 3 weeks. Treatment with TAFINLAR resulted in a statistically significant and clinically meaningful improvement in progression-free survival (PFS) compared to treatment with DTIC. Overall survival (OS) data were not mature at the time of the primary analysis. The most common adverse events (AE) reported in 20 to 37% of patients in the dabrafenib arm were hyperkeratosis, headache, pyrexia, arthralgia, skin papilloma, alopecia, and palmar-plantar erythrodysesthesia syndrome (PPES). Most frequent AE occurring at Grade 3 or higher was pyrexia (2%). Confirmation of BRAF V600E mutation-positive melanoma as detected by the bioMerieux THxID BRAF™ assay (or other FDA-approved test) is required for selection of patients for TAFINLAR therapy because these are the only patients studied and for whom benefit has been demonstrated.

The clinical pharmacology program of the NDA includes studies of food effect, mass balance, absolute bioavailability, and drug-drug interactions. Population pharmacokinetic (PK) and exposure-response (E-R) analyses using PK data from Phase 1-3 trials in patients did not identify significant covariates influencing dabrafenib PK or evident E-R relationships for effectiveness and safety.

1.1 Recommendation

This NDA is acceptable from a clinical pharmacology perspective provided that the Applicant and the Agency come to an agreement regarding the labeling language and the identified clinical pharmacology studies under the post-marketing requirements (PMRs) and the post-marketing commitment (PMC). The Office of Clinical Pharmacology recommends approval of this NDA.

See Section 3 for detailed labeling recommendations.

1.2 Post Marketing Requirements

Key questions	Rationale	PMRs
Does dabrafenib prolong QT/QTc intervals?	Inadequate data to rule out the possibility of QT prolongation potential	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. – Study population: patients with BRAF V600 mutation positive solid tumors – Study design: an open-label, dose-escalating safety lead-in study followed by a single-sequence, placebo-controlled, single-blind study. – Final protocol Submission: Submitted – Trial completion date: March, 2014 – Final report: December, 2015
Should the dose of dabrafenib be reduced in moderate and severe hepatic impairment?	Mass balance study: 71% of dose is excreted in feces	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*". – Study population: patients with BRAF V600 mutation positive solid tumors – Dose: 50 mg BID - 150 mg BID – Final protocol Submission: Submitted – Trial completion date: September, 2014 – Final report: June, 2015

Should the dose of dabrafenib be reduced in severe renal impairment?	Mass balance study: 23% dose excreted in urine	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"*. – Study population: patients with BRAF V600 mutation positive solid tumors – Dose: 50 mg BID - 150 mg BID – Final protocol Submission: Submitted – Trial completion date: September, 2014 – Final report: June, 2015
What are the effects of strong CYP3A4 inhibitors on dabrafenib pharmacokinetics *in vivo*?	*In vitro:* dabrafenib and active metabolites are substrates of CYP3A4	Complete a clinical trial evaluating the effects of repeat doses of oral ketoconazole 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 inhibitors. – Study population: patients with BRAF V600 mutation positive solid tumors – Dose: dabrafenib 75 mg BID on Days 1-22; ketoconazole 400 mg QD on Days 19-22) – Final protocol Submission: Submitted – Study/Trial Completion: Completed – Final report: May, 2013
What are the effects of strong 2C8 inhibitors on dabrafenib pharmacokinetics *in vivo*?	*In vitro:* dabrafenib is a substrate of CYP2C8	Complete a clinical trial evaluating the effects of repeat doses of oral gemfibrozil 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 CYP2C8 inhibitors. – Study population: patients with BRAF V600 mutation positive solid tumors – Dose: dabrafenib 75 mg BID on Days 1-22; gemfibrozil 600 mg BID on Days 19-22.

		– Final protocol Submission: Submitted – Study/Trial Completion: Completed – Final report: May, 2013
What are the effects of strong CYP3A4 and CYP2C8 inducers on dabrafenib pharmacokinetics *in vivo*?	*In vitro:* dabrafenib is a substrate of CYP2C8 and CYP3A4	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. – Study population: patients with BRAF V600 mutation positive solid tumors – Dose: dabrafenib 150 mg BID on Days 1-22; rifampin 600 mg QD on Days 8-22 – Final protocol submission: June, 2013 – Completion date: December, 2014 – Final report: June, 2015
What is the effect of dabrafenib on pharmacokinetics of CYP2C9 substrates in vivo?	*In vitro:* dabrafenib is an inducer of CYP2C9	Complete a clinical trial evaluating the effects of repeat doses of dabrafenib on the single dose pharmacokinetics of warfarin (CYP2C9 substrate) 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 sensitive CYP2C9 substrates and CYP2C9 substrates with a narrow therapeutic window. – Study population: patients with BRAF V600 mutation positive solid tumors – Dose: dabrafenib 150 mg BID on Days 8 to 29; warfarin: a 15 mg dose on Day 1 (alone) and on Day 22 (with dabrafenib) – Final protocol Submission: Submitted – Study/Trial Completion: Completed – Final report: May, 2013

1.3 Post Marketing Commitments

Key question	Rationale	PMC
What is the effect of gastric pH elevating agents on bioavailability of dabrafenib?	Solubility in simulated gastric fluid (pH=1.2) is 6-fold higher than in simulated intestinal fluids (pH=4.9).	Conduct a clinical trial to evaluate if proton pump inhibitors, H_2 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. – Final Protocol Submission: June 2013 – Trial Completion Date: December 2015 – Final Report: December 2016

1.4 Summary of Clinical Pharmacology Findings

Proposed Dose and Indication: TAFINLAR (Dabrafenib) is a potent, selective, ATP-competitive inhibitor of RAF kinases. The applicant proposed indication of TAFINLAR is for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation. FDA recommended indication is for BRAF V600E mutation based on clinical data. The proposed dose regimen is 150 mg orally twice daily (BID).

ADME *Absorption:* After oral administration of dabrafenib, the median time to achieve peak plasma concentration is 2 hours. Mean absolute bioavailability of oral dabrafenib is 95%. Dabrafenib exposure (C_{max} and AUC) increased in a dose proportional manner between 12 and 300 mg following single-dose administrations, but the increase was less than dose-proportional after repeat twice daily dosing. This observed decrease in exposure with repeat dosing is likely due to induction of its own metabolism. Mean accumulation ($AUC_{Day18/Day1}$) ratios averaged 0.73. Following administration of 150 mg dabrafenib twice daily, geometric mean (CV%) C_{max}, $AUC_{(0-\tau)}$, and predose concentration values were 1,478 ng/mL (37%), 4,341 ng*hr/mL (38%), and 26 ng/mL (119%), respectively.

Food effect: Administration of a single 150 mg dose of dabrafenib capsules with a high-fat meal decreased its C_{max} and AUC by 51% and 31%, respectively, when compared to the fasted state.

Distribution: The apparent volume of distribution at steady-state is 70.3 L. Dabrafenib is 99.7% bound to human plasma proteins.

Metabolism: The metabolism of dabrafenib is primarily mediated by CYP2C8 and CYP3A4 to form hydroxy-dabrafenib, which is further oxidized via CYP3A4 to form carboxy-dabrafenib and is excreted in bile and urine. Carboxy-dabrafenib can be decarboxylated via a non-enzymatic process in the gut to form desmethyl-dabrafenib and reabsorbed. Desmethyl-dabrafenib is metabolized by CYP3A4 to oxidative metabolites. Hydroxy-dabrafenib terminal half-life parallels that of the parent drug with a half-life of 10 hours while the carboxy- and desmethyl-metabolites exhibited longer half-lives (21 to 22 hours). Mean metabolite to parent AUC ratios following repeat-dose administration were 0.9, 11, and 0.7 for hydroxy-, carboxy-, and desmethyl-dabrafenib, respectively. Based on exposure, relative potency and pharmacokinetic properties, both hydroxy- and desmethyl-dabrafenib are likely to contribute to the clinical activity of dabrafenib; the activity of carboxy-dabrafenib is not likely to be clinically meaningful.

Elimination: The elimination half-life of dabrafenib is 8 hours after oral administration and 2.6 hours following intravenous microdose with plasma clearance of 12 L/hr. Fecal excretion is the major route of elimination accounting for 71% of radioactive dose while urinary excretion accounts for 23% of radioactivity.

Drug Interactions: Dabrafenib induces cytochrome P450 isoenzyme (CYP) 3A4-mediated metabolism and may induce other enyzmes including CYP2B6, CYP2C8, CYP2C9, and CYP2C19. A decrease in single-dose midazolam exposure with mean (90% CI) ratios of 0.39 (0.25, 0.63) for C_{max} and 0.26 (0.21, 0.32) for AUC, respectively, was observed with repeat

dosing of dabrafenib 150 mg BID, indicating that dabrafenib induces CYP3A4-mediated metabolism.

Dabrafenib and its active metabolites are primarily metabolized by CYP2C8 and CYP3A4. Strong inhibitors or inducers of CYP3A4 or CYP2C8 may increase or decrease, respectively, systemic exposure to dabrafenib. The effects of strong inhibitors or inducers of CYP3A4 or CYP2C8 on pharmacokinetics of dabrafenib *in vivo* are to be studied under PMRs.

E-R Relationship: Exposure-response analyses were unable to identify any relationships for efficacy or safety at 150 mg BID dose.

There are several ongoing trials including: (1) drug-drug interaction trials to evaluate the effects of repeat doses of dabrafenib on the single dose pharmacokinetics (PK) of warfarin, the effects of repeat oral doses of ketoconazole and oral doses of gemfibrozil on the repeat dose PK of dabrafenib; (2) PK trials of dabrafenib in patients with moderate and severe hepatic impairment or in patients with severe renal impairment; and (3) a QTc trial to evaluate the effect of repeat oral dosing of dabrafenib on cardiac repolarization. Additional drug interaction trials with concomitant strong CYP3A4/2C8 inducers as a PMR and with concomitant gastric pH elevating agents as a PMC are requested.

Signatures:

Reviewer: Jian Wang, Ph.D. Division of Clinical Pharmacology 5	Team Leader: Hong Zhao, Ph.D. Division of Clinical Pharmacology V
PM reviewer: Justin Earp, Ph.D. Division of Pharmacometrics	Acting PM Team Leader: Nitin Mehrotra, Ph.D., Division of Pharmacometrics
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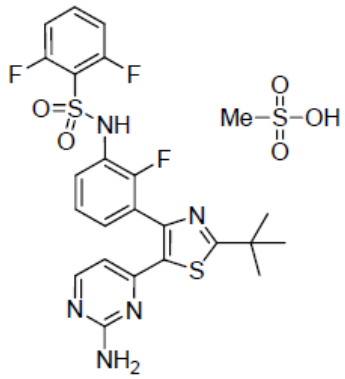
Cc: DOP2: CSO - N Griffin; MTL - S Demko; MO - M Theoret DCP-V: Reviewer - J Wang; TL- H Zhao; DDD - B Booth; DD - A Rahman	

2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review? (Do not include full details of formulation here. Details go in Biopharmaceutics section.)

Dabrafenib mesylate is a nitrogen and sulfur containing heterocycle possessing an aromatic sulfonamide. The chemical name for dabrafenib mesylate is N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzene sulfonamide, methane sulfonate salt. It has the molecular formula $C_{23}H_{20}F_3N_5O_2S_2 \bullet CH_4O_3S$ and a molecular weight of 615.68. Dabrafenib mesylate has the following chemical structure:



Dabrafenib mesylate is a white to slightly colored solid with three pK_as: 6.6, 2.2, 1.5. It is very slightly soluble at pH 1 and practically insoluble above pH 4 in aqueous media. The to-be-marketed formulation for TAFINLAR is hydroxypropyl methylcellulose (HPMC) capsule. TAFINLAR Capsules are supplied as 50 mg and 75 mg dose strengths for oral administration. Each 50 mg capsule contains 59.25 mg dabrafenib mesylate equivalent to 50 mg of dabrafenib free base. Each 75 mg capsule contains 88.88 mg dabrafenib mesylate equivalent to 75 mg of dabrafenib free base.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Dabrafenib is an inhibitor of some mutated forms of BRAF kinases with *in vitro* IC_{50} values of 0.65, 0.5, and 1.84 nM for $BRAF^{V600E}$, $BRAF^{V600K}$, and $BRAF^{V600D}$ enzymes, respectively. Dabrafenib also inhibits wild-type BRAF and CRAF kinases with IC_{50} values of 3.2 and 5.0 nM, respectively. Some mutations in the BRAF gene, including those that result in $BRAF^{V600E}$, can result in constitutively activated BRAF kinases that may stimulate tumor cell growth. BRAF mutations have been identified at a high frequency in specific cancers, including approximately 50% of melanoma.

The applicant proposed indication of TAFINLAR is for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation. FDA recommended indication is for BRAF V600E mutation based on clinical data.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The proposed dose of TAFINLAR is 150 mg (two 75 mg capsules) given orally twice daily. The applicant proposes that TAFINLAR should be administered one hour before or two hours after meals. FDA recommends that do not administer TAFINLAR with high-fat meals. Refer to Section 2.5.3 for details.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Table 1 summarizes clinical studies included in this NDA.

Table 1: Studies Included Supporting the Clinical Pharmacology Evaluation of Dabrafenib

Protocol	Type of Study	Formulation	No. of Subjects
BRF112680	FIH (Single and Repeat Dose PK)	Gelatin Capsules Daily dose ranged from 12-600 mg	184
BRF113468	Food Effect/Particle Size (Relative Bioavailability)	Gelatin and HPMC Capsules 150 mg	28
BRF113463	ADME (mass balance)	Suspension 95 mg	4
BRF113479	Absolute Bioavailability	HPMC Capsules and IV solution 150 mg oral; 50 µg IV infusion	4
BRF113771	Drug-drug Interaction (DDI) and PK	HPMC Capsules 75 mg BID	ongoing
BRF113220	Combination with Trametinib	Gelatin Capsules 75 mg dabrafenib + 2 mg trametinib	ongoing
BRF113710 (BREAK-II)	Phase II	Gelatin Capsules 150 mg BID	92
BRF113929 (BREAK-MB)	Phase II (with brain metastases)	HPMC Capsules 150 mg BID	172
BRF113683 (BREAK-III)	Phase III	HPMC Capsules 150 mg BID	250

Overall, the above studies provide the following clinical pharmacology results:

- The PK of dabrafenib and its 3 major circulating metabolites, hydroxy-dabrafenib (GSK2285403), carboxy-dabrafenib (GSK2298683), and desmethyl-dabrafenib (GSK2167542), after single and repeated oral dose administration in patients with solid tumors, with the majority of patients having metastatic V600 mutant melanoma;

- The disposition of [14C]-labelled-dabrafenib following administration of a single suspension dose;
- The PK of dabrafenib after an IV microdose;
- The PK drug interaction profile of dabrafenib, and its effect on single dose midazolam;
- A population PK analysis identifying the factors that have significantly influences on dabrafenib exposure;
- The exposure-response of dabrafenib on measures of efficacy and safety endpoints in patients with BRAF V600 mutation positive melanoma.

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

Biomarkers

Tumor biopsies were collected in Study BRF112680 for immunohistochemistry (IHC) staining analysis at baseline and 1 to 2 weeks of dosing in 8 evaluable subjects who received doses of 70 to 200 mg BID of dabrafenib. Changes in pERK, a downstream biomarker of the RAS/RAF/MEK/ERK pathway, have been shown to be associated with clinical response in BRAF mutant tumor models. The median decrease in pERK expression from baseline was 83.9% ranging from 38.0% to 93.3% in subjects with BRAF V600 mutation-positive metastatic melanoma, indicating significant inhibition of the enzymatic pathway. Six out of 8 subjects showed ≥80% inhibition of the pERK pathway.

Clinical Endpoints

The clinical efficacy endpoints include progression-free survival (PFS) as a primary endpoint, and overall survival (OS), overall response rate (ORR) and duration of response (DoR) as secondary endpoints.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships? (If yes, refer to 2.6, Analytical Section; if no, describe the reasons.)

Yes. Dabrafenib and its three major circulating metabolites, hydroxy-dabrafenib (GSK2285403), carboxy-dabrafenib (GSK2298683), and desmethyl-dabrafenib (GSK2167542) are appropriately identified and measured to assess their PK parameters. Refer to 2.6, Analytical Section for details.

2.2.4 Exposure-response

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

Within the studied exposure range, there does not appear to be a trend for increasing PFS with increasing exposure (Figure 1). However, because a statistical difference in PFS was observed between the dabrafenib treatment arm and placebo treatment arm, it is likely that a relationship exists; but the lower exposures need to reveal this relationship was not studied.

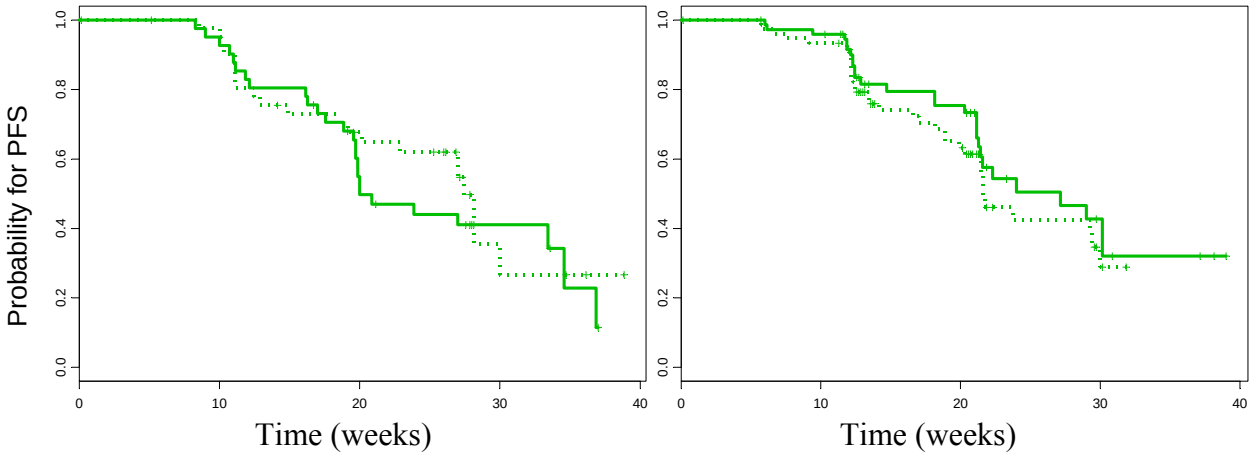
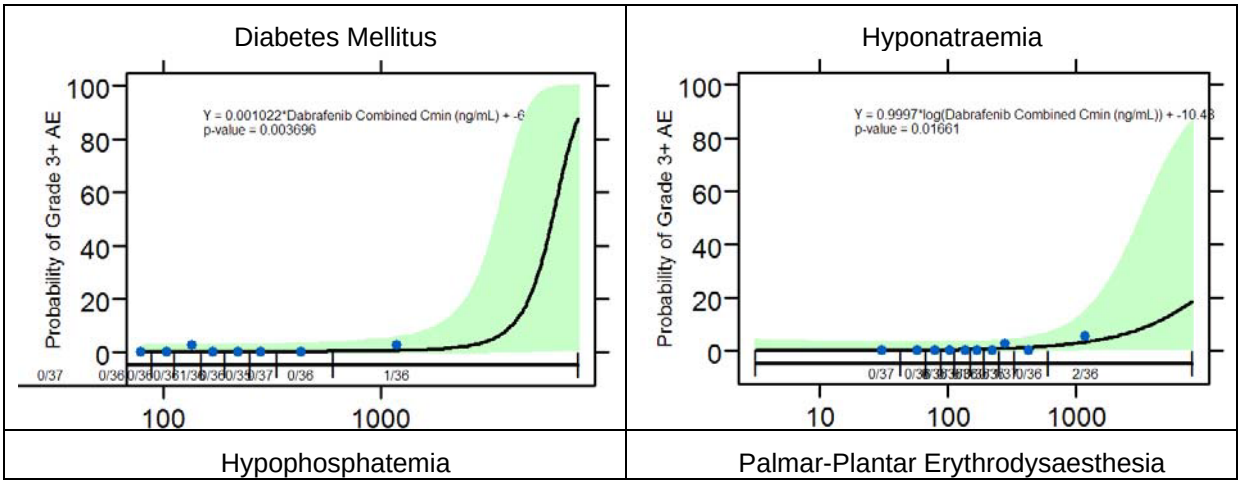


Figure 1. Kaplan Meier plots of PFS by Dabrafenib ($C_{min,parent}$ + $C_{min,met}$.) for the Phase II (BRF113710, Left Plot) and Phase III (BRF113683, Right Plot) Studies. Short dashed/dotted lines indicate probability of PFS from patients with exposures greater than the median active concentration (99.6 ng/mL). Solid lines indicate data from patients with exposures less than the median active concentration.

2.2.4.2 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the undesirable pharmacological response or clinical endpoint.

There is no evidence to suggest that the proposed dosing regimen is unacceptable from a safety perspective. Figure 2 shows the adverse events that were considered to have a significant relationship; however the number of these events is too small to make this conclusion, given the very shallow slope and uncertainty in the data at the higher exposures (>1000 ng/mL). No correlation was noted for pyrexia for grade 2 or higher and grade 3 or higher events. Further, because after dose interruptions or reductions the dose can potentially be increased upon establishing tolerability, this mitigates concerns associated with loss of efficacy with reductions to lower doses.



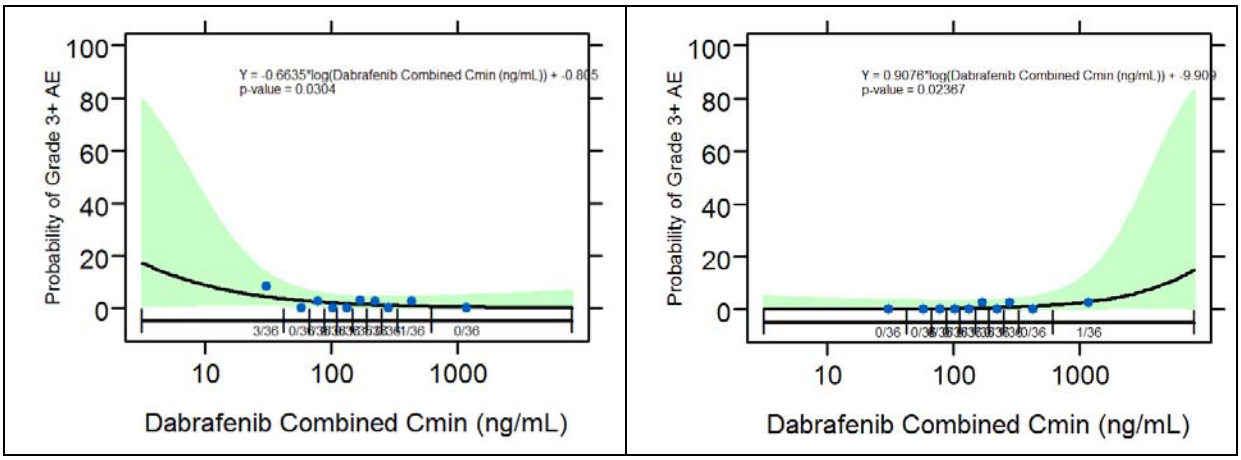


Figure 2. Plots of adverse events where a significant relationship was detected using logistic regression between the probability of the grade 3+ adverse event and the active concentration of dabrafenib plus hydroxy-dabrafenib. Dabrafenib Combined $C_{min} = C_{min,parent} + C_{min,hydroxy\text{-}metabolite}$. Points display the observed probability of the event in 1/10th of the evaluable population.

2.2.4.3 Does this drug prolong the QT or QTc interval? (You must answer this question, unless this is addressed in the question above.)

There is an ongoing clinical trial evaluating the potential for dabrafenib to prolong the QT/QTc interval. The final study report for the dedicated cardiovascular safety study will be submitted post-marketing under a PMR.

2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent with the known relationship between dose-concentration-response? Are there any unresolved dosing or administration issues? (In some cases, it may be possible to combine this with 2.2.4.2 and 2.2.4.3.)

Yes. The proposed starting dose is supported by the lack of difference between PFS results in patients below the median exposure from this dose versus patients with exposures above the median. Safety events are to be managed with dose interruptions and dose reductions. A total of 27% of the patients required one or more dose reductions in the registration trial. The proposed regimen allows for re-escalation based on tolerability. Based on the lack of exposure-response relationships for safety at the 150 mg BID and similar benefit from all exposures achieved with the 150 mg BID dose, the proposed dosing regimen appears acceptable and there is no unresolved dosing or administration issues.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters? (Provide tables to refer to in subsequent questions in this section.)

<u>Single dose PK</u>

In Trial BRF113468, 14 melanoma patients with BRAF mutation received a single dose of dabrafenib as HPMC capsules under fasted conditions (Figure 3). The single dose PK parameter estimates are summarized in Table 2.

Table 2: Summary of Dabrafenib, Hydroxy-Dabrafenib, Carboxy-Dabrafenib, and Desmethyl-Dabrafenib PK Parameters after a Single Dose Administration of 150 mg Dabrafenib

Parameter1	Dabrafenib	Hydroxy-Dabrafenib	Carboxy-Dabrafenib	Desmethyl-Dabrafenib
T_{max} (hr)	2.0 (1.0, 4.0)	4.0 (2.0, 10.0)	10.0 (6.0, 24.0)	36.2 (10.0, 72.2)
C_{max} (ng/mL)	2160 (56)	1009 (58)	2394 (64)	114 (54)
$AUC_{(0-t)}$ (ng*hr/mL)	11843 (49)	10390 (54)	77667 (53)	5871 (58)
$AUC_{(0-\infty)}$ (ng*hr/mL)	12120 (49)[1]	10812 (54)[1]	83346 (54)	6721 (32)[2]
$t_{½}$ (hr)	8.4 (113)[1]	9.7 (85)[1]	20.9 (29)	22.2 (43)[2]
AUC Ratio M:P[3]	NA	0.9 (23)[1]	7.0 (71)[1]	0.5 (65)

PK parameters are reported as geometric mean (CV %). T_{max} is reported as median (range). N=14 unless: [1]. N=13; [2]. N=6; [3]. Reported as $AUC_{(0-\infty)}$ for hydroxy- and carboxy-dabrafenib and $AUC_{(0-t)}$ for desmethyl-dabrafenib.

The half-life of hydroxy-dabrafenib metabolite is similar to the parent, whereas the half-lives of carboxy-dabrafenib and desmethyl-dabrafenib metabolites are longer (approximately 20 hours).

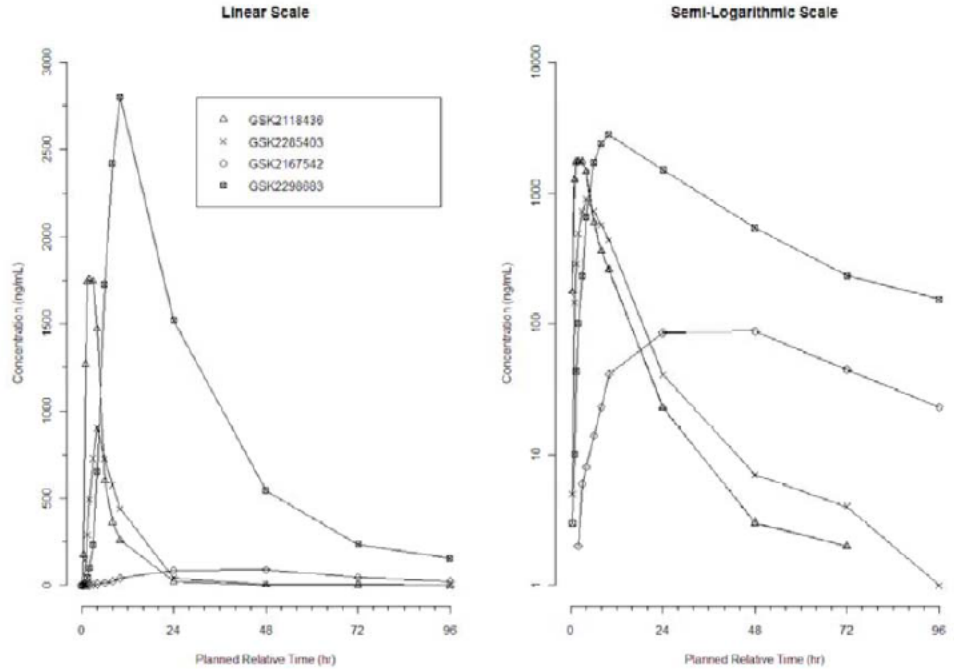


Figure 3: Median Plasma Dabrafenib, Hydroxy-Dabrafenib, Carboxy-Dabrafenib, and Desmethyl-Dabrafenib Concentration-Time Profile after Administration of a Single Dose of 150 mg Dabrafenib (HPMC Capsules) under Fasted Conditions (Linear and Semi-Log)

Note: In the applicant's reports: i) hydroxy-dabrafenib was known as GSK2285403 and/or M7; ii) carboxy-dabrafenib was known as GSK2298683 and/or M4; and iii) desmethyl-dabrafenib was known as GSK2167452 and/or M8

Multiple dose PK

Multiple dose PK was characterized in melanoma patients with BRAF mutation. Following repeat dosing of dabrafenib at 150 mg BID as HPMC capsules, geometric mean C_{max}, $AUC_{(0-\tau)}$, and predose concentration Cτ were 1,478 ng/mL, 4,341 ng*hr/mL, and 26.1 ng/mL, respectively. Inter-subject variability was 37% for C_{max}, 38% for $AUC_{(0-\tau)}$ and 119% for Cτ. The metabolite to parent AUC ratios following multiple dose administration of dabrafenib 150 mg (HPMC capsules) BID under fasted conditions were 0.9 for hydroxy-dabrafenib, 11 for carboxy-dabrafenib and 0.7, for desmethyl-dabrafenib (Table 3).

Table 3: Summary of Derived Dabrafenib, Hydroxy-Dabrafenib, Carboxy-Dabrafenib, and Desmethyl-Dabrafenib PK Parameters at Steady State (Week 6)

Parameter	Dabrafenib	Hydroxy-Dabrafenib	Carboxy-Dabrafenib	Desmethyl-Dabrafenib
$AUC_{(0-\tau)}$ (hr*ng/mL)	4,341 (38)	4,067 (38)	51,485 (39)	3,068 (35)
C_{max} (ng/mL)	1,478 (37)	1,009 (36)	6,153 (33)	347 (40)
Cτ (ng/mL)	26.1 (119)	46.3 (124)	2,805 (46)	235 (45)
T_{max} (hr)	1.93 (0.92, 6.00)	2.00 (1.00, 6.00)	5.93 (2.00, 8.00)	4.00 (0.00, 8.00)
Ratio of $AUC_{(0-\tau)}$ M:P	NA	0.911 (24)	11.2 (43)	0.726 (38)

Note: PK parameters are reported as geometric mean (CV%). T_{max} is reported as median (range).

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Dabrafenib PK has not been studied in healthy volunteers.

2.2.5.3 What are the characteristics of drug absorption?

- After oral administration of a single oral dose dabrafenib as HPMC capsules under fasted conditions, median time to achieve peak plasma concentration (T_{max}) is 2 hours.
- Oral absorption of dabrafenib HPMC capsules is nearly complete with a least squares (LS) mean (90% confidence interval [CI]) absolute bioavailability of 94.5% (81.3%, 109.7%).
- A high-fat, high-calorie meal reduced the relative bioavailability of dabrafenib HPMC capsules when compared to the fasted state, with least squares (LS) mean ratio (90% CI) of 0.49 (0.35, 0.69) and 0.69 (0.57, 0.85) for C_{max} and $AUC_{(0-\infty)}$, respectively. See Section 2.5.3 for details.

2.2.5.4 What are the characteristics of drug distribution? (Include protein binding.)

- *In vitro*, dabrafenib and its metabolites (hydroxy-, carboxy-, and desmethyl-dabrafenib), are highly bound to plasma proteins with percent bound of 99.7, 96.3, 99.5, and 99.9%, respectively.
- *In vitro* blood: plasma partitioning is 0.54 and is independent of dabrafenib concentrations.
- Following intravenous (IV) microdose administration, dabrafenib had a steady-state volume of distribution (Vdss) of 45.5 L. After oral dosing, the apparent volume of distribution at steady-state is 70.3 L.
- Preclinical data suggested that dabrafenib and desmethyl-dabrafenib may cross intact blood brain barrier.

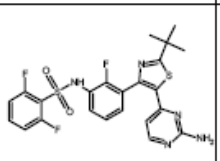
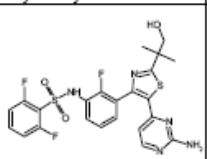
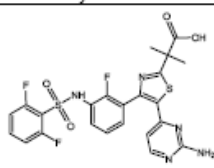
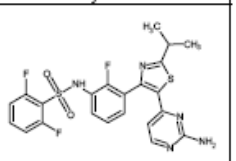
2.2.5.5 What are the characteristics of drug metabolism?

- Dabrafenib is metabolized via cytochrome P450 (CYP) 2C8/CYP3A4-mediated oxidation of the t-butyl group to form the mono-oxygenated product hydroxy-dabrafenib, which is further oxidized to the carboxylic acid derivative (carboxy-dabrafenib) via CYP3A4. The carboxy-metabolite can be decarboxylated via a nonenzymatic process to form desmethyl-dabrafenib. Carboxy-dabrafenib is excreted in bile and urine. Desmethyl-dabrafenib is likely formed in the gut and reabsorbed. Desmethyl-dabrafenib is metabolized via CYP3A4 to oxidative metabolites.

- The terminal half-lives of parent drug and hydroxy-dabrafenib are 8.4 and 9.7 hours, respectively, while the carboxy- and desmethyl-metabolites exhibited longer half-lives (21- 22 hours). Carboxy- and desmethyl-dabrafenib accumulate with repeat dosing. Metabolite to parent AUC ratios after repeat-dose administration of dabrafenib 150 mg BID are 0.9, 11.2 and 0.7 for hydroxy-, carboxy-, and desmethyl-dabrafenib, respectively.

- Based on systemic exposure, potency, and PK characteristics, both hydroxy- and desmethyl-dabrafenib are likely to contribute to the clinical activity of dabrafenib; while the activity of carboxy-dabrafenib is not likely significant (Table 4).

Table 4: Characteristics of Dabrafenib and Its Metabolites

Analyte	Dabrafenib	Hydroxy-Dabrafenib	Carboxy-Dabrafenib	Desmethyl-Dabrafenib
Structure				
Clinical Pharmacokinetics				
Tmax (SD) (hr)	2.0 (1.0, 4.0)	4.0 (2.0, 10.0)	10.0 (6.0, 24.0)	36.2 (10.0, 72.2)
t1/2 (SD) (hr)	8.4 (113)	9.7 (85)	20.9 (29)	22.2 (43)
AUCm/p Ratio, SD	NA	0.9 (23)	7.0 (71)	0.5 (65)
Cmax, RD (ng/mL)	1478 (37)	1009 (36)	6153 (33)	347 (40)
AUC(0-τ), RD (ng*hr/mL)	4341 (38)	4067 (38)	51485 (39)	3068 (35)
Cτ, RD (ng/mL)	26.1 (119)	46.3 (124)	2805 (46)	235 (45)
AUCm/p Ratio, RD	NA	0.9	11.2	0.7
Metabolism Data				
Metabolism	CYP2C8, CYP3A4	CYP3A4, glucuronidation	Biliary, Urinary Excretion	CYP3A4
Effect of CYP3A4 inhibition	↑ (57%)	↑ (48%)	↓ (33%)	↑ (61%)
Protein Binding (%)	99.7	96.3	99.5	99.9
Pharmacology Data (reported as IC50/gIC50 [nM] and fold relative to parent)				
BRAFV600E	0.65 (NA)	1.9 (2.9-fold)	16.6 (25.5-fold)	1.1 (1.7-fold)
pERK	9 (NA)	7 (0.8-fold)	156 (17.3-fold)	8 (0.9-fold)
Colo205 (10% FBS)	6 (NA)	23 (3.8-fold)	320 (53.3-fold)	23 (3.8-fold)
Colo205 (70% Human Serum)	518 (NA)	401 (0.8-fold)	11544 (22.3-fold)	6167 (11.9-fold)

2.2.5.6 Does the mass balance study suggest renal or hepatic as the major route of elimination? (This may include table with results of mass balance study.)

Fecal excretion is the major route of elimination after oral suspension dose, accounting for 71.1% of radioactive dose while urinary excretion accounted for 22.7 % of radioactivity.

2.2.5.7 What are the characteristics of drug excretion?

Terminal half-life following IV microdose of dabrafenib is 2.6 hours. After oral administration, dabrafenib terminal half-life is 8.4 hours possibly due to a prolonged terminal phase after oral administration. Fecal excretion is the major route of elimination accounting for 71% of radioactive dose while urinary excretion accounted for 23% of radioactivity.

IV plasma clearance (12.0 L/hr) of dabrafenib is low relative to liver blood flow, suggesting that dabrafenib is a low hepatic extraction ratio drug. The apparent clearance of dabrafenib is 17.0 L/hr after single dosing and 34.4 L/hr after two-weeks of twice daily dosing.

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Plasma dabrafenib exposure (C_{max} and $AUC_{(0-\infty)}$) increases in a dose proportional manner following single-dose administration of dabrafenib in the dose range of 35 to 300 mg (gelatin capsules). The increase is less than dose-proportional after repeat BID dosing. There is no significant increase in exposure after repeat dosing of 200 mg BID compared with 150 mg BID. Assessment of dose-proportionality on Day 1 and at steady state is shown in Figure 4.

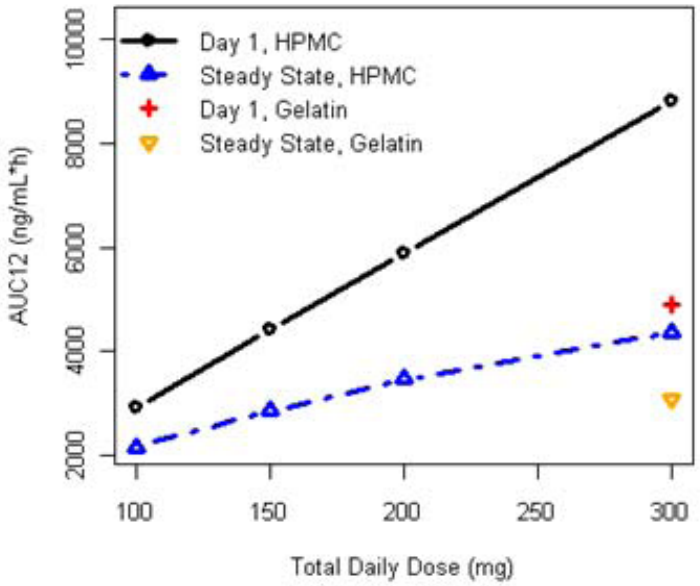


Figure 4: Relationship between AUC and Different Daily Doses of Dabrafenib

Dabrafenib oral clearance (CL/F) is shown as a function of total daily dose (administered as BID doses) in Figure 5. On Day 1, CL/F is similar across 75 to 300 mg BID Doses. CL/F on Day 15 is higher than the values on Day 1, and is higher after 300 mg BID repeat doses relative to lower doses.

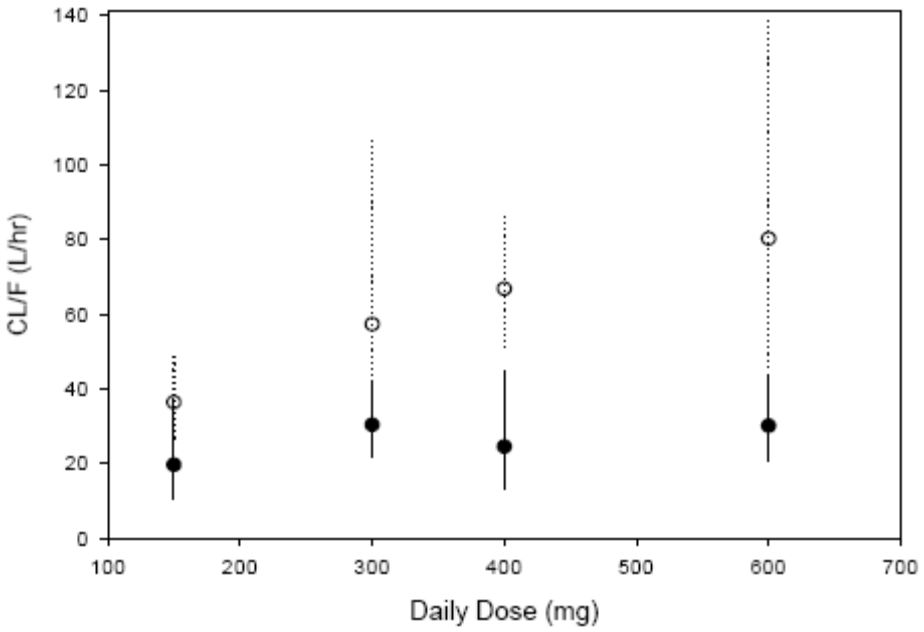


Figure 5: Dabrafenib Oral Clearance (CL/F) Geometric Mean (symbols) and 95% Confidence Intervals (bars) by Total Daily Dose on Day 1 (closed circles) and Day 15 (open circles).

2.2.5.9 How do the PK parameters change with time following chronic dosing? (This may include time to steady-state; single dose prediction of multiple dose PK; accumulation ratio.)

There is no accumulation with BID dosing; the Day 18 / Day 1 $AUC_{(0\text{-}12h)}$ ratio is 0.73 (0.62, 0.85) following administration of dabrafenib 150 mg BID (HPMC capsules). The decrease in exposure noted with repeat dosing of dabrafenib is likely due to induction of its own metabolism.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

At steady state, the inter-patient variability is 37% for C_{max} and 38% for $AUC_{(0\text{-}\tau)}$. Based on the population PK analysis, the inter-patient variability for CL/F and Vc/F is 59% and 53%, respectively.

2.3 Intrinsic Factors

2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

Body weight and gender are significant covariates in the population PK model. However, neither affects the value of clearance sufficiently to warrant dose adjustments. The inter-subject variability (CV%) on clearance is 58% with a fixed dose regimen. Gender does not decrease clearance by more than 10% for females compared to males. Additionally, no difference is noted in the median PFS between those with the lowest half of the exposures versus those with the highest half of

exposures after 150 mg BID. Race is not evaluated as a covariate in the population PK analysis because all the patients in the registration trial are Caucasians.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations (examples shown below), what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

There is no evident exposure-response relationship for efficacy or safety at 150 mg BID dose regimen. A decrement of 50 or 25 mg dabrafenib is recommended based on toxicity. Dose level reductions resulting in a dose below 50 mg twice daily are not recommended. See 2.1 for details.

2.3.2.1 Elderly

Age is not identified as a covariate on the PK of dabrafenib using a population PK analysis. See Figure 9 in the Pharmacometric Review.

2.3.2.2 What is the status of pediatric studies and/or any pediatric plan for study?

The pharmacokinetics, safety and effectiveness in pediatric patients have not been studied. The pediatric studies are not required based on the orphan drug designation for debrafenib.

2.3.2.3 Gender and Weight

Based on the population PK analysis, gender and weight are found to influence dabrafenib oral clearance; weight also affects oral volume of distribution and distributional clearance. These PK differences are not considered clinically relevant.

Gender is identified as a significant covariate on dabrafenib clearance. However the effect (8.9% reduction in clearance for females) is not clinically meaningful given the 58% inter-subject variability for dabrafenib and lack of exposure-response relationships.

2.3.2.4 Race, in particular differences in exposure and/or response in Caucasians, African-Americans, and/or Asians

Race is not evaluated as a covariate in the population PK analysis. All the patients enrolled in the registration trial are Caucasians.

2.3.2.5 Renal impairment

No formal PK study in patients with renal impairment has been conducted. The PK of dabrafenib is evaluated using a population analysis in 233 patients with mild renal impairment (GFR 60-89 mL/min/1.73 m^2) and in 30 patients with moderate renal impairment (GFR 30-59 mL/min/1.73 m^2) enrolled in clinical trials. Mild or moderate renal impairment has no effect on systemic exposures to dabrafenib and its metabolites. No data are available in patients with severe renal impairment. See Figure 9 in the Pharmacometric Review for further details. As urinary excretion accounts for 23% of the total drug, a post-marketing requirement (PMR) is recommended for a PK study of dabrafenib to determine the appropriate dose in patients with severe renal impairment.

2.3.2.6 Hepatic impairment

No formal PK study in patients with hepatic impairment has been conducted. The PK of dabrafenib is evaluated using a population analysis in 65 patients with mild hepatic impairment enrolled in clinical trials. The effect of mild hepatic impairment (as defined by bilirubin ≤ upper limit of normal [ULN], aspartate aminotransferase [AST] >ULN, or bilirubin >1 to 1.5 times ULN; AST: any value), has no effect on systemic exposures to dabrafenib and its metabolites. No data are available in patients with moderate to severe hepatic impairment. See Figure 10 in the Pharmacometric Review for further details. As fecal excretion accounts for 71% of the total drug, a post-marketing requirement is recommended for a PK study of dabrafenib to determine the appropriate doses in patients with moderate or severe hepatic impairment.

2.3.2.7 Genetics

The applicant restricted the Phase 3 registration trial (BREAK-3) to patients with the BRAF V600E mutation and only limited Phase 2 efficacy data are available for patients with BRAF V600K mutation. BRAF V600-mutated melanoma may be further classified in specific disease subtypes with distinct clinicopathologic features among BRAF mutant genotypes.

The Genomics reviewer assessed whether in Phase 2 studies BREAK-MB and BREAK-2, BRAF V600E and V600K mutations are associated with distinct clinicopathologic features and whether tumor responses in patients with metastatic melanoma differ by the specific BRAF V600 mutation. The analysis showed an association between BRAF mutation status and age at screening and gender. A greater proportion of patients with BRAF V600K mutation were male and older at screening compared to patients with the V600E mutation suggesting that mutant genotypes may define a subgroup of patients with distinct phenotypes. Although pre-clinical data show similar IC50 values for the V600E and V600K mutations, limited clinical data from Phase 2 studies BREAK-MB and BREAK-2 suggest marginal dabrafenib activity in patients with the BRAF V600K mutation compared to patients harboring the V600E mutation.

Because (1) limited antitumor activity was observed in V600K patients in Phase 2 trials, (2) V600K patients were excluded from Phase 3, and (3) V600K patients may represent a distinct subset of melanoma patients with distinct clinicopathologic features, it is reasonable at this point to exclude V600K patients and have the indication revised for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test, provided clinical and statistical reviews concur with demonstration of a favorable risk-benefit profile. (See Genomics review by Christian Grimstein in the Appendix)

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

Drugs that are strong inhibitors or inducers of CYP3A4 and CYP2C8 may increase or decrease dabrafenib exposure. See the following for details.

2.4.1.1 Based upon what are known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.

There is no evident exposure-response relationship for efficacy and safety; therefore, no dose adjustment is recommended based on the exposure-response analysis. Substitution of strong inhibitors or strong inducers of CYP3A4 or CYP2C8 is recommended during treatment with TAFINLAR. If concomitant use of strong inhibitors (e.g., ketoconazole, nefazodone, clarithromycin, gemfibrozil, grapefruit juice) or strong inducers (e.g., rifampin, phenytoin, carbamazepine, phenobarbital, St John's wort) of CYP3A4 or CYP2C8 is unavoidable, monitor patients closely for adverse reactions when taking strong inhibitors or for loss of efficacy when taking strong inducers.

2.4.2 Drug-drug interactions

2.4.2.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

Yes. See below for details.

2.4.2.2 Is the drug a substrate of CYP enzymes?

Yes. CYP2C8 is the predominant enzyme responsible for the formation of hydroxy-dabrafenib from dabrafenib with contributions from CYP3A4 and to a lesser extent from CYP2C9 and CYP2C19.

Hydroxy-dabrafenib is metabolized by CYP3A4 and desmethyl-dabrafenib is primarily metabolized by CYP3A4, with some involvement of CYP2C9 and CYP2C19. Carboxy-dabrafenib is not metabolized by any of the CYPs.

2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?

CYP induction:

The effects of dabrafenib on the mRNA levels of CYP genes (CYP1A2, 2B6 and 3A4) were evaluated at concentrations from 0.1 to 50 μM in cultured human hepatocytes from 3 donors. At 30 μM dabrafenib, maximal increases in CYP2B6 and CYP3A4 mRNA levels to a mean ratio of dabrafenib treated over control of 32 and 30, respectively were observed, , corresponding to 320% and 150% increases relative to their prototypic inducers (50 μM omeprazole (CYP1A2), 50 μM phenytoin (CYP2B6), 10 μM rifampicin (CYP3A4) (Table 5).

Table 5: Mean Effects of Dabrafenib and Prototypical CYP Inducers on the mRNA Levels of Cytochrome P450s

	Mean Effect on mRNA Level*					
Gene	**CYP1A2**		**CYP2B6**		**CYP3A4**	
Treatment	**Ratio**	**%**	**Ratio**	**%**	**Ratio**	**%**
0.1% DMSO	1.00	0.0	1.0	0.0	1.0	0.0
Dabrafenib						
0.1 µM	0.82	<1	1.1	2.5	2.2	7.7
0.3 µM	0.70	<1	1.1	<1	2.5	8.8
1.0 µM	0.84	<1	2.6	18	8.1	33
3.0 µM	0.54	<1	5.3	49	16	69
10 µM	0.48	<1	8.9	80	19	85
30 µM	1.1	<1	32	320	30	150
50 µM	1.7	1.8	30	320	23	90
Prototypical inducer	70	100	15	100	27	100

* Mean Ratio of Treated Over Control and % Induction Relative to the Prototypic Inducer

CYP2B6 and CYP3A4 mRNA induction is indicative of an interaction of dabrafenib with the pregnane X receptor (PXR) and constitutive androstane receptor (CAR) nuclear receptors, a family of transcription factors that function as modulators of gene expression. Therefore, it is possible that under these circumstances, the CYP2C family of enzymes could be induced as well, because expression of CYP2C enzymes also can result from drug binding to the PXR and CAR receptors. Based on *in vitro* results, dedicated drug-drug interaction trials to evaluate dabrafenib induction potential on CYP enzymes are warranted and requested as PMR studies.

CYP inhibition

In vitro studies in pooled human liver microsomes (PHLM) indicated that dabrafenib inhibited CYPs 2C8, 2C9, 2C19 and 3A4; hydroxy-dabrafenib and desmethyl-dabrafenib inhibited CYP2C9. No inhibition was indicated for carboxy-dabrafenib based on [I]/K_i ratio (Table 6).

Table 6: Direct and Metabolism-Dependent Cytochrome P450 Inhibition for Dabrafenib and Metabolites

CYP	Dabrafenib (2.84μM)			Hydroxy-dabrafenib (1.88μM)		Desmethyl-dabrafenib (0.69μM)		
	IC_{50}	[I]/Ki	Kinact/Ki	IC_{50}	[I]/Ki	IC_{50}	[I]/Ki	Kinact/Ki
1A2	87	0.07		83	0.05	*No Inhibition Obs.*		
2A6	*No Inhibition Obs.*			*No Inhibition Obs.*		*No Inhibition Obs.*		
2B6	*No Inhibition Obs.*			*No Inhibition Obs.*		78	0.02	
2C8	8.2	**0.69**		*No Inhibition Obs.*		49.3	0.03	
2C9	7.2	**0.79**		28.6	**0.13**	6.3	**0.22**	
2C19	22	**0.26**		*No Inhibition Obs.*		35.9	0.04	
2D6	*No Inhibition Obs.*			*No Inhibition Obs.*		*No Inhibition Obs.*		
3A4a	16	**0.36**		*No Inhibition Obs.*		19.6	0.07	
3A4b	*No Inhibition Obs.*		0.001	47	0.08	16.7	0.08	ND
3A4c	32	0.18		*No Inhibition Obs.*		27.5	0.05	

a = atorvastatin. b = midazolam. c = nifedipine. ND = not determined

Based on a drug-drug interaction study in humans, it appears that the CYP induction by dabrafenib prevail CYP inhibition *in vivo*. See Section 2.4.2.7 for details.

2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein and other drug transporters?

Substrates of transporters

Dabrafenib is a substrate of human P-glycoprotein (Pgp) and of murine BCRP1 (murine breast cancer resistant protein 1) *in vitro*. Given the high oral bioavailability (94.5%) and high metabolic clearance, these efflux transporters appear to have minimal impact on bioavailability and contribution to the parent drug elimination. The potential impact of Pgp and/or BCRP inhibitors on the elimination of dabrafenib is considered low.

Inhibitors of transporters

Dabrafenib, hydroxy-dabrafenib, desmethyl-dabrafenib and carboxy-dabrafenib did not inhibit human Pgp. *In vitro*, dabrafenib and desmethyl-dabrafenib were shown to be inhibitors of BCRP, while hydroxy-dabrafenib and carboxy-dabrafenib did not demonstrate inhibition of BCRP. The $[I]_1/K_i$ for dabrafenib and carboxy-dabrafenib could not be determined since an *in vitro* IC_{50} could not be calculated based on the FDA Drug Interaction Draft Guidance (Table 7). For hydroxy-dabrafenib and desmethyl-dabrafenib there was no risk identified (i.e., $[I]_1/K_i \leq 0.1$). When considering maximal gut concentration ($[I]_2$), only dabrafenib was evaluated as it is orally administered; however, $[I]_2/K_i$ could not be determined for dabrafenib since an *in vitro* IC_{50} could not be calculated.

Based on calculations described in the FDA Drug Interaction draft guidance (2012), an *in vivo* transporter drug interaction study is not warranted. Based on a static mathematical model analysis, the predicted transporter drug interaction potential of dabrafenib, with contributions from the metabolites, is minimal.

Table 7: Assessment of Dabrafenib and Metabolites as Inhibitors of BCRP & Pgp

	Transporter Inhibition					
	$[I]_1$ Cmax (μM)	$[I]_2$	BCRP IC_{50} (μM)	$[I]_1$/Ki	$[I]_2$/Ki	Pgp
Dabrafenib	2.84	0.0012	ND	NA	NA	*No Inhibition Obs.*
Hydroxy-dabrafenib	1.88	0.0011	82	0.023	NA	*No Inhibition Obs.*
Carboxy-dabrafenib	11.2	0.0011	ND	NA	NA	*No Inhibition Obs.*
Desmethyl-dabrafenib	0.69	0.0012	5.4	0.13	NA	*No Inhibition Obs.*

$[I]_1$: Mean steady-state total (free and bound) Cmax
$[I]_2$: Dose of inhibitor (in mol) / 250mL
ND : not determined; data insufficient to calculate IC_{50}.
NA: not applicable

Analysis of the OATP1B1 and OATP1B3 inhibition data for dabrafenib and its major circulating metabolites (Table 8) indicates that further risk assessments should be conducted (i.e., $[I]/IC_{50} \geq 0.1$). The applicant evaluated the perpetrator risk of dabrafenib and its circulating metabolites on OATP1B1 and OATP1B3 using static mathematical models (R-value approach) as described in the FDA Guidance. When surrogates of dabrafenib maximum inhibitor concentration at the inlet to the liver and maximum systemic plasma concentrations of contributing metabolites were corrected for plasma protein binding, the extrapolation for OATP1B1 and OATP1B3 yields an R value of 1.0 for both transporters, suggesting that the drug interaction potential of dabrafenib, with contributions from the metabolites, is minimal. Therefore, a drug-drug interaction study to evaluate the clinical significance of OATP inhibition is not warranted.

Table 8: Assessment of Dabrafenib and Metabolites as Inhibitors of OATP1B1 and OATP1B3

	Transporter Inhibition				
	C_{max} (μM)	OATP1B1 IC_{50} (μM)	$[I]/IC_{50}$	OATP1B3 IC_{50} (μM)	$[I]/IC_{50}$
Dabrafenib	2.84	1.4	2.03	4.7	0.60
Hydroxy-dabrafenib	1.88	4.3	0.44	23	0.08
Carboxy-dabrafenib	11.2	18	0.62	20	0.56
Desmethyl-dabrafenib	0.69	0.83	0.83	4.3	0.16

To assess the inhibition potential for OAT1 and OAT3, unbound surrogate concentrations of dabrafenib and unbound systemic concentrations of contributing metabolites (hydroxy-dabrafenib and desmethyl-dabrafenib) were incorporated into a static mathematical model as described in the FDA Guidance, the predicted drug interaction potential does not warrant an *in vivo* investigation (i.e., $fu[I]/IC_{50} < 0.1$). For carboxy-dabrafenib, the fu[I]/Ki could not be determined since the IC_{50} for OAT1 could not be calculated (Table 9).

Table 9: Assessment of Dabrafenib and Metabolites as Inhibitors of OAT1 & OAT3

	Transporter Inhibition					
	C_{max} (μM)	fu	OAT1 IC_{50} (μM)	fu[I]/ IC_{50}	OAT3 IC_{50} (μM)	fu[I]/ IC_{50}
Dabrafenib	2.84	0.003	6.9	0.0012	3.4	0.0025
Hydroxy-dabrafenib	1.88	0.005	29	0.0003	7.3	0.0013
Carboxy-dabrafenib	11.2	0.037	ND	NA	9.0	0.046
Desmethyl-dabrafenib	0.69	0.001	10	0.0001	3.4	0.0002

2.4.2.5 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and, if so, has the interaction potential between these drugs been evaluated?

Dabrafenib is used as monotherapy in the proposed indication. (b) (4) The drug interaction trial between dabrafenib and trametinib is ongoing.

2.4.2.6 What other co-medications are likely to be administered to the target patient population?

Gastric pH elevating agents such as proton pump inhibitors, H_2 antagonists and antacids are likely to be administered to the target patient population. Concomitant use of gastric pH elevating agents may alter the bioavailability of dabrafenib due to its property of pH-dependent solubility. Post-marketing commitment is recommended to evaluate if proton pump inhibitors, H_2 antagonists and antacids alter the bioavailability of dabrafenib (See Section 1.3).

2.4.2.7 Are there any *in vivo* drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

Effects of Other Drugs on Dabrafenib

- Dabrafenib metabolism is mediated by CYP2C8 and CYP3A4 while both hydroxy- and desmethyl-dabrafenib are CYP3A4 substrates. Interim data showed that dabrafenib $AUC_{(0-\tau)}$ increased by 57% in the presence of **ketoconazole, a potent CYP3A4 inhibitor** (Table 10). The magnitude of the increase in dabrafenib exposure was similar to the magnitude observed with hydroxy- and desmethyl-dabrafenib (48-61%), which are both themselves metabolized by CYP3A4. A 33% decrease in $AUC_{(0-\tau)}$ was noted for carboxy-dabrafenib.

Table 10: Summary of Interim PK Parameters of Dabrafenib and Its Metabolites after Repeat Dose of Dabrafenib 75 mg BID Alone and with Ketoconazole 400 mg Once Daily

PK Parameter	Day 18 (n=8) Repeat Dose without Inhibitor	Day 22 (n=7) Repeat Dose with Inhibitor
Dabrafenib		
T_{max} (hr)	1.1 (1.0 – 3.0)	2.0 (2.0 – 2.0)
Cmax (ng/mL)	1068 (45)	1348 (23)
$AUC_{(0-\tau)}$ (hr·ng/mL)	3262 (36)	5111 (31)
Cτ (ng/mL)	17.6 (120)	48.5 (73)
Hydroxy-Dabrafenib		
Tmax (hr)	1.6 (0, 3.0)	4.0 (2.0, 4.2)
Cmax (ng/mL)	500 (52)	583 (21)
$AUC_{(0-\tau)}$ (hr·ng/mL)	2442 (53)	3607 (38)
Cτ (ng/mL)	31.9 (123)	107 (77)
Ratio M:P $AUC_{(0-\tau)}$	0.77 (38)	0.73 (31)
Carboxy-Dabrafenib		
Tmax (hr)	5.0 (3.0 – 8.0)	8.0 (6.0 – 10.0)
Cmax (ng/mL)	4191 (75)	2749 (53)
$AUC_{(0-\tau)}$ (hr·ng/mL)	39791 (76)	27045 (51)
Ratio M:P $AUC_{(0-\tau)}$	12.91 (69)	5.60 (64)
Cτ (ng/mL)	2486 (84)	2252 (54)
Desmethyl-Dabrafenib		
Tmax (hr)	5.0 (0 – 12.0)	3.0 (1.0 – 12.0)
Cmax (ng/mL)	254 (76)	390 (103)
$AUC_{(0-\tau)}$ (hr·ng/mL)	1915 (85)	3092 (108)
Cτ (ng/mL)	129 (187)	297 (76)
Ratio M:P $AUC_{(0-\tau)}$	0.57 (92)	0.59 (104)

Note: PK parameters are reported as geometric mean (CV%). T_{max} is reported as median (range).

In Study BRF113220 (Part B), one patient (Subject 270) received phenytoin 300 mg BID, **a strong inducer of CYP3A4**, during dabrafenib administration. Dabrafenib $AUC_{(0-\tau)}$ decreased by 62% in the presence of phenytoin. The magnitude of the decrease of dabrafenib exposure was similar to the magnitude observed with hydroxy- and desmethyl-dabrafenib with decrease of 31% and 63%, respectively.

Table 11 : Plasma Dabrafenib and Metabolites C_{max} and $AUC_{(0-\tau)}$ following Repeat Dosing of Dabrafenib 150 mg BID (Day 21) in a Patient Receiving Phenytoin Compared to Other Patients

	Subject 270 (with phenytoin)	Geometric Mean (95% CI) (n=8)	Ratio
Dabrafenib			
C_{max} (ng/mL)	290	1263 (863, 1848)	0.23
$AUC_{(0-\tau)}$ (ng*hr/mL)	1778	4656 (3901, 5557)	0.38
Hydroxy-dabrafenib			
C_{max} (ng/mL)	301	775 (441, 1364)	0.39
$AUC_{(0-\tau)}$ (ng*hr/mL)	2251	3257 (2162, 4907)	0.69
Carboxy-dabrafenib			
C_{max} (ng/mL)	4406	5301 (3392, 8286)	0.83
$AUC_{(0-\tau)}$ (ng*hr/mL)	41096	47911 (30643, 74,909)	0.86
Desmethyl-dabrafenib			
C_{max} (ng/mL)	146	543 (298, 989)	0.27
$AUC_{(0-\tau)}$ (ng*hr/mL)	1350	3609 (2279, 5714)	0.37

It should be noted that the observed exposure data from one patient does not provide sufficient basis regarding the magnitude of exposure changes for dabrafenib and its metabolites. A dedicated drug-drug interaction trial with a strong CYP3A4/2C8 inducer (e.g. rifampin) should be conducted and the study results should allow for a determination on how to dose dabrafenib with regard to concomitant CYP3A4/2C8 inducers.

Effects of Dabrafenib on Other Drugs

- A decrease in single dose midazolam C_{max} and $AUC_{(0-\infty)}$ was observed with repeat dosing of dabrafenib 150 mg BID, with a mean ratio (90% CI) of 0.39 (0.24, 0.63) for C_{max} and 0.26 (0.21, 0.32) for $AUC_{(0-\infty)}$, indicating that dabrafenib induces CYP3A4-mediated metabolism (Table 12). Based on this result, dabrafenib appears to be a moderate inducer of CYP3A4 *in vivo*.

- The effect of dabrafenib on dexamethasone, a CYP3A4 substrate, was planned as part of Study BRF113929, but subjects for that cohort could not be recruited. PK data in the only 2 subjects enrolled showed a decrease in dexamethasone concentrations with dabrafenib, consistent with CYP3A4 induction.

- Dabrafenib also induced its own metabolism with a decrease in exposure with repeat dosing, with accumulation ratio of 0.73 (BRF113771).

- Based on *in vitro* results, other enzymes such as CYP2B6, CYP2C8, CYP2C9, and CYP2C19 may also be affected. Co-administration of dabrafenib and medications which are affected by the induction of these enzymes may result in loss of efficacy of these medications. A study (BRF113771, Part A) of the effect of repeat dose dabrafenib on single dose warfarin, a **CYP2C9** substrate, is ongoing. This study will provide a more definitive assessment of the inhibitory or induction risk of dabrafenib on a CYP2C9 substrate (warfarin).

Table 12: Results of Midazolam PK When Administered Alone and With Dabrafenib (n=12)

Parameter	Geometric Least Squares Mean		Midazolam + Dabrafenib / Midazolam Alone Ratio	
	Midazolam 3 mg Alone	Midazolam 3 mg + Dabrafenib 150mg BID	Estimate	90% Confidence Interval
$AUC_{(0-\infty)}$ (hr·ng/mL)	49.4	12.8	0.258	(0.210, 0.318)
$AUC_{(0-t)}$ (hr·ng/mL)	46.8	11.0	0.234	(0.183, 0.300)
C_{max} (ng/mL)	16.4	6.38	0.388	(0.241, 0.626)

2.5 General Biopharmaceutics

2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility, permeability, and dissolution data support this classification?

Based on the low solubility and high permeability determination, dabrafenib is likely a Biopharmaceutics Classification System (BCS) Class 2 compound (low solubility, high permeability).

Solubility in simulated gastric fluid (pH=1.2) is 43 µg/mL, which is 6-fold higher than 6.8 µg/mL in simulated intestinal fluids under fed (pH=4.9) and 7-fold higher that 6.2 µg/mL under fasted (pH=6.3) states. The *in vitro* permeability category for dabrafenib was determined in MDCKII-MDR1 cells following the BCS guidance. Dabrafenib permeability was measured at 0.019, 0.0095, 0.0019 and 0.00019 mg/mL (equivalent to 30, 15, 3 and 0.3 µM, respectively) at pH 5.5 and pH 7.4 over 4 time points (20, 45, 90 and 120 minutes). The *in vitro* permeability of dabrafenib at pH 7.4 and 5.5 exceeded that of the high permeability reference marker, labetalol. Oral absorption of dabrafenib HPMC capsules is nearly complete with a least squares (LS) mean (90% CI) absolute bioavailability of 94.5% (81.3%, 109.7%). Therefore, dabrafenib is a highly permeable compound.

Concomitant use of gastric pH elevating agents may alter the bioavailability of dabrafenib. Post-marketing commitment study is recommended to evaluate if proton pump inhibitors, H_2 antagonists and antacids alter the bioavailability of dabrafenib (See Section 1.3).

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial formulation?

The intended commercial product is in an immediate release HPMC Capsule formulation with 50 mg and 75 mg dose strengths, which is the same formulation used in the registration trial BRF113683 and Phase 2 trial BRF113929.

An initial gelatin capsule formulation of dabrafenib was developed to support the early clinical studies. The relative bioavailability of dabrafenib is higher following a single dose

administration as HPMC capsules compared to gelatin capsules, with a geometric LS mean ratio (90% CI) of 2.02 (1.42, 2.87) and 1.80 (1.32, 2.46) for C_{max} and $AUC_{(0-\infty)}$, respectively.

The applicant states that the difference between HPMC and gelatin formulation is smaller after repeat dosing relative to single dose with ratios of 1.66 and 1.42 for C_{max} and $AUC_{(0-\tau)}$, respectively, as estimated in the population PK analysis.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

A high-fat, high-calorie meal delayed absorption and reduced the relative bioavailability of dabrafenib HPMC capsules when compared to the fasted state, with LS mean ratio (90% CI) of 0.49 (0.35, 0.69) and 0.69 (0.57, 0.85) for C_{max} and $AUC_{(0-\infty)}$, respectively (Table 13). The median difference in the time of occurrence of C_{max} (t_{max}) between the high-fat meal and fasted states (90% CI) was 3.65 hours (2.39, 5.01).

Table 13: The Food Effect on Dabrafenib Exposure

PK Parameter	Fasting	Fed	Ratio (90% CI)
C_{max} (ng/mL)	2160	1066	0.49 (0.35,0.69)
$AUC_{(0-t)}$ (ng*hr/mL)	11843	8329	0.70 (0.58,0.85)
$AUC_{(0-\infty)}$ (ng*hr/mL)	12126	8415	0.69 (0.57,0.85)

Note: C_{max} and AUC are reported as geometric LS mean.

The applicant proposed labeling states that dabrafenib is recommended to be administered under fasted conditions, either 1 hour before or 2 hours after a meal, which is consistent with how dabrafenib was administered in clinical trials.

Since a single dose dabrafenib taking with a high fat meal resulted in a 30% decrease in AUC and 50% decrease in C_{max} and the clinical efficacy was established based on dabrafenib administration under fasted conditions, the review team recommends that do not administer dabrafenib with a high fat meal.

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Plasma concentrations of dabrafenib and its metabolites including the hydroxy-, carboxy- and desmethyl-metabolites, were measured in the clinical pharmacology studies using the validated UHPLC-MS/MS methodology. See the following sections for details.

2.6.2 Which metabolites have been selected for analysis?

Dabrafenib and its major metabolites including hydroxy-dabrafenib (GSK2285403, M7), desmethyl-dabrafenib (GSK2167542; M8) and carboxy-dabrafenib (GSK2298683; M4) were measured.

2.6.3 What bioanalytical methods are used to assess concentrations?

Dabrafenib and its major metabolites including hydroxy-dabrafenib (GSK2285403, M7) and desmethyl-dabrafenib (GSK2167542; M8) were extracted from 50 µL human plasma by liquid-liquid extraction using ethyl acetate after the addition of isotopically labeled internal standards [2H9]-GSK2118436, [2H6 13C2]-GSK2285403, and [2H6 13C2]-GSK2167542. Extracts were analyzed by UHPLC-MS/MS using a TurboIonspray interface with positive ion multiple reaction monitoring over two separate injections (Table 14).

Table 14: Summary of In-process Performance of the Analytical Methods Used for the Measurement of Dabrafenib, Hydroxy-dabrafenib and Desmethyl-dabrafenib

Analyte	Dabrafenib	Hydroxy-dabrafenib	Desmethyl-dabrafenib
Calibration Model	Linear weighted 1/x2		
Validated Range	1 to 1000 ng/mL		
QC Samples	1, 3, 50, 800, 1000 ng/mL		
Within Run Precision (%CV)	6.3%	8.3%	9.7%
Between Run Precision	6.9%	5.7%	11.0%
Accuracy (%bias)	-12.5% < Bias < 5.9%	-9.9% < Bias < 5.3%	-15.0% < Bias < 5.4%
Freeze-Thaw Stability	At least 3 cycles from -20°C to ambient temperature		
Processed Sample Stability	At least 72 hours at ambient temperature		
Short Term Stability in Plasma	At least 24 hours at ambient temperature		
Short Term Stability in Blood	At least 4 hours at 37°C		
Recovery	110.0 - 117.0%	100.0 - 117.1%	112.5 - 117.9%
Matrix Dilution	10-Fold in human plasma		

Carboxy-dabrafenib (GSK2298683; M4) was extracted from 25 µL human plasma by protein precipitation using 80/20 ethyl alcohol/Millipore water containing an isotopically labeled internal standard [2H6 13C2]-GSK2298683. Extracts were analyzed by UHPLC-MS/MS using a TurboIonspray interface and multiple reaction monitoring (Table 15).

Table 15: Summary of In-process Performance of the Analytical Methods Used for the Measurement of Carboxy-dabrafenib in Trial 113683

Analyte	Carboxy-dabrafenib
Calibration Model	Linear weighted 1/x2
Validated Range	5 to 5000 ng/mL
QC Samples	5, 15, 250, 4000, 5000 ng/mL
Within Run Precision (%CV)	8.0%
Between Run Precision	4.6%
Accuracy (%bias)	0.8% < Bias < 14.9%
Freeze-Thaw Stability	At least 4 cycles from -20°C to ambient temperature
Processed Sample Stability	At least 96 hours at 8 - 10°C
Short Term Stability in Plasma	At least 24 hours at ambient temperature
Short Term Stability in Blood	At least 4 hours at 37°C
Recovery	101.3 - 105.6%
Matrix Dilution	10-Fold in human plasma

2.6.4 What is the range of the standard curve?

The range of the standard curve for dabrafenib, hydroxy-dabrafenib, and desmethyl-dabrafenib is 1 to 1000 ng/mL. The range of the standard curve for carboxy- dabrafenib is 5 to 5000 ng/mL.

2.6.5 What are the lower and upper limits of quantification (LLOQ/ULOQ)?

	LLOQ (ng/mL)	ULOQ (ng/mL)
dabrafenib	1	1000
hydroxy-dabrafenib	1	1000
desmethyl-dabrafenib	1	1000
carboxy- dabrafenib	5	5000

2.6.6 What are the accuracy, precision, and selectivity at these limits?

Please refer to Table 14 and Table 15.

2.6.7 What is the sample stability under the conditions used in the study?

Please refer to Table 14 and Table 15.

3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included. . The segments which were removed by the reviewer are ~~strikethrough~~, and sections added by the reviewer are underlined.

2.1 Recommended Dosing

(b) (4)

7 DRUG INTERACTIONS

(b) (4)

7.2 Effects of (b) (4) Dabrafenib on Other Drugs

(b) (4)

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4 Appendices

4.1 Pharmacometric Review

OFFICE OF CLINICAL PHARMACOLOGY:
Pharmacometric Review

1 Summary of Findings

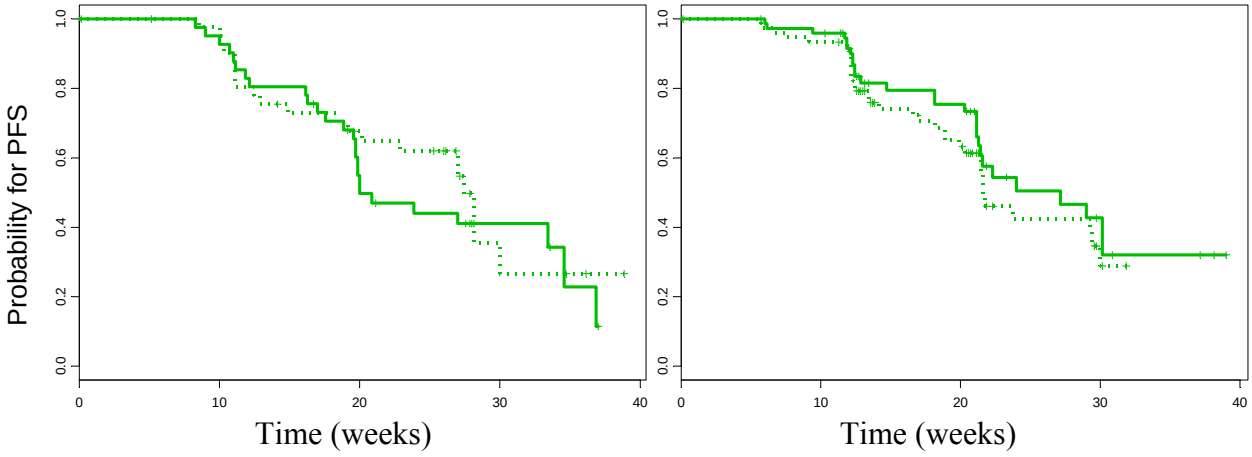
1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is there evidence of exposure-response for effectiveness?

No, there is no evidence of an exposure-response relationship for effectiveness. Within the studied exposure range (median = 374 ng/mL, 95% CI = 240, 502 ng/mL), with 72% of patients receiving 150 mg BID without dose reductions, there does not appear to be a trend for increasing progression free survival with increasing exposure (Figure 6). An insufficient number of patients received 50 or 75 mg BID for evaluating the relationship at the lowest doses the sponsor proposes be administered in order to manage adverse events.

Figure 6. Kaplan Meier plots of PFS by Dabrafenib ($C_{min,parent}$ + $C_{min,met}$.) for the Phase II (BRF113710, Left Plot) and Phase III (BRF113683, Right Plot) Studies. Short dashed/dotted Lines indicate probability of PFS from patients with exposures greater than the median active concentration (99.6 ng/mL). Solid lines indicate data from patients with exposures less than the median active concentration.

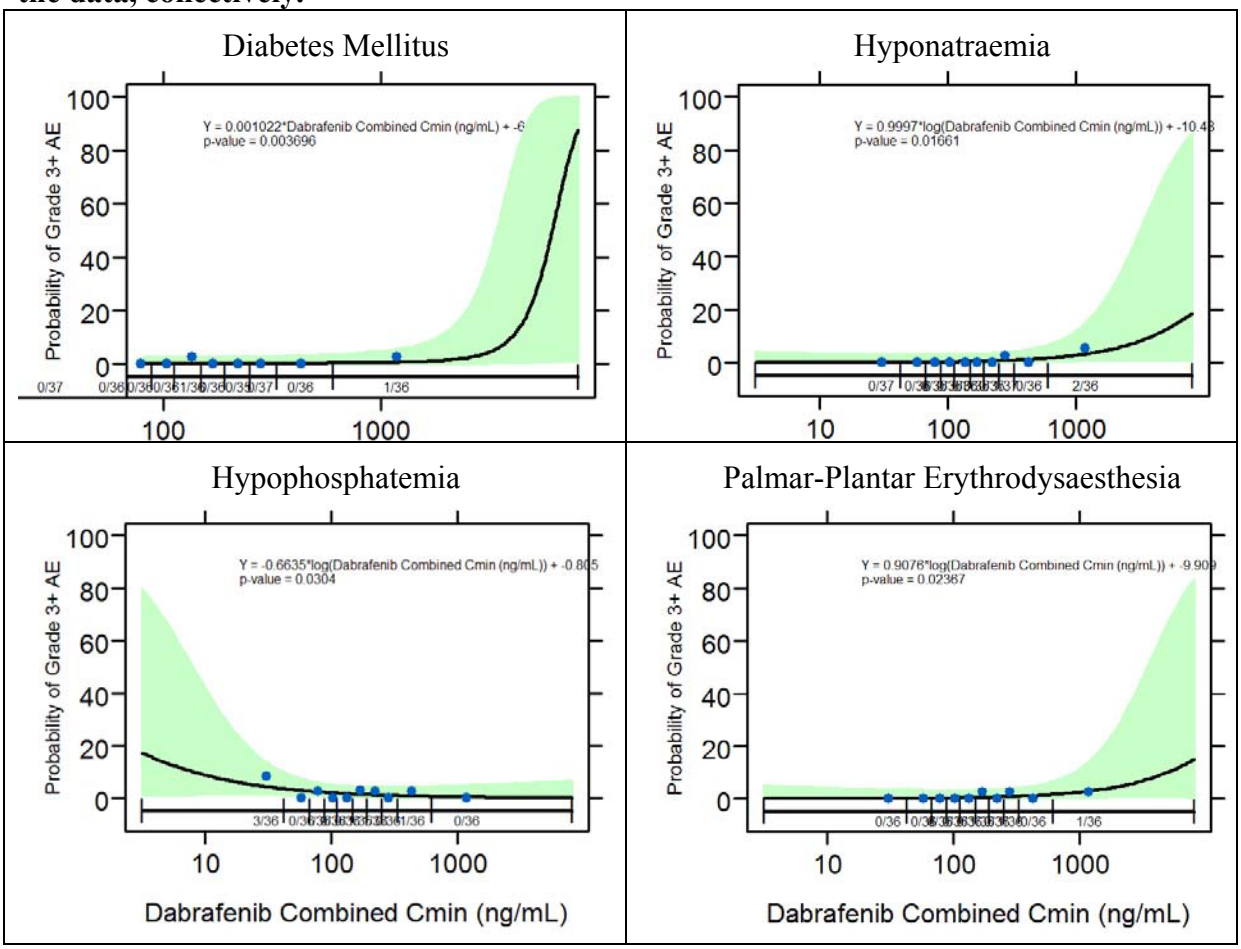


1.1.2 Is the dose reduction scheme proposed by the sponsor justified based on the exposure-response for Safety?

There is no evidence to suggest that the proposed dosing regimen is unacceptable from a safety perspective. Figure 7 shows the adverse events that were considered to have a significant relationship, however the number of these events is too small to make this conclusion, given the very shallow slope and uncertainty in the data at the higher exposures (>1000 ng/mL). No correlation was noted for pyrexia for grade 2 or higher and grade 3 or higher events. Further, because after dose interruptions or reductions the dose can potentially be increased upon

establishing tolerability, this mitigates concerns associated with of loss of efficacy with reductions to lower doses.

Figure 7. Plots of adverse events where a signification relationship was detected using logistic regression between the probability of the grade 3+ adverse event and the active concentration of dabrafenib plus hydroxy-dabrafenib. Dabrafenib Combined $C_{min} = C_{min,parent} + C_{min,hydroxy\text{-}metabolite}$. Points display the observed probability of the event in 1/10th of the evaluable population. Whereas, the logistic regression was performed on all the data, collectively.



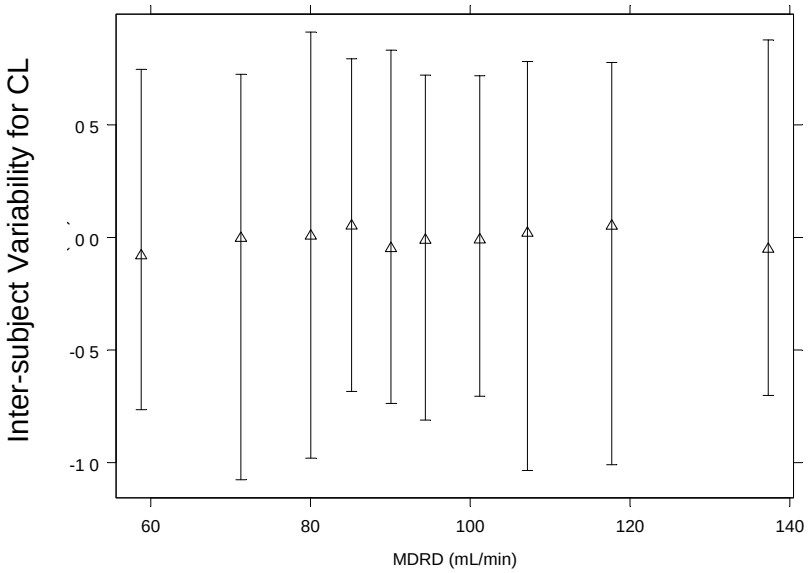
1.1.3 Do the exposure-efficacy and exposure-safety analyses support the proposed dose?

Yes. The proposed starting dose is supported by the lack of difference between PFS results in patients below the median exposure from this dose versus patients with exposures above the median. However, this analysis is limited in that the majority of the data come from the same starting dose of 150 mg BID. Safety events are to be managed with dose interruptions and dose reductions. The proposed regimen allows for re-escalation provided tolerability to the drug is be established. Based on the lack of exposure-response relationships for Safety at the 150 mg BID and similar benefit from all exposures achieved with the 150 mg BID dose, the proposed dosing regimen appears acceptable.

1.1.4 Is there a need for dose adjustment for mild, moderate or severe renal impairment?

No. No significant relationship was found between MDRD and dabrafenib clearance (Figure 8). Data were not available from patients with severe renal impairment.

Figure 8. Renal impairment, as assessed by MDRD, is not correlated with dabrafenib clearance.



See the reviewer's analysis of the sponsor's population PK model for more details regarding other covariate effects.

1.2 Recommendations

The Office of Clinical Pharmacology Division of Pharmacometrics has reviewed this application and finds the NDA approvable.

1.3 Label Statements

See the labeling section of the clinical pharmacology review.

2 Pertinent regulatory background

GlaxoSmithKline is seeking approval of dabrafenib for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600 mutation. Dabrafenib is an new molecular entity. It is an oral and selective RAF kinase inhibitor of the mutated forms BRAF V600E, BRAF V600K and BRAF V600D as well as human wild type BRAF and CRAF enzymes. If approved dabrafenib will be the second in this class of drugs approved for BRAF mutation positive metastatic melanoma. The sponsor is basing their evidence of effectiveness for dabrafenib on their phase III trial results that suggest an improvement in progression-free survival of 2.4 months after administration of dabrafenib compared to DTIC.

3 Results of Sponsor's Analysis

3.1 Clinical Trials used in Analysis

The exposure-response analyses of dabrafenib on efficacy endpoints in subjects with V600 mutation positive melanoma were based on 3 studies:

- **BRF112680:** A Phase I, Open-Label, Multiple-Dose, Dose-Escalation Study to Investigate the Safety, Pharmacokinetics, and Pharmacodynamics of the BRAF Inhibitor dabrafenib in Subjects with Solid Tumors. Doses ranged from 35 to 300 mg BID (gelatin capsules)
- **BRF113710:** A Phase II single-arm, open-label study of dabrafenib in BRAF mutant metastatic melanoma. Dabrafenib 150 mg BID (twice daily) (gelatin capsule) was administered.
- **BRF113683:** A Phase III randomized, open-label study comparing dabrafenib to DTIC in previously untreated subjects with BRAF mutation positive advanced (Stage III) or metastatic (Stage IV) melanoma. Dabrafenib 150 mg BID (HPMC capsule) was administered.

The exploratory analyses of AEs were conducted using the Phase II and III studies above in addition to the following study:

- **BRF113929:** A Phase II Open-Label, Two-Cohort, Multicentre Study of dabrafenib as a Single Agent in Treatment Naïve and Previously Treated Subjects with BRAF Mutation-Positive Metastatic Melanoma to the Brain. Dabrafenib 150 mg BID (HPMC capsule) was administered.

3.2 Exposure-response for Efficacy & Safety

Exposure was expressed as observed or predicted C_{min} (C_{min} or $C_{min,pred}$), predicted average concentration (C_{avg}) and average dose for dabrafenib. C_{avg} was used instead of AUC to be able to compare to *in vitro* IC50 values. The basic population PK model of dabrafenib was used to predict exposure based on individual Bayesian posthoc estimate of CL/F and other relevant PK parameters. In addition, the average observed C_{min} for each metabolite was also used. In all analyses, all measures of exposure were tested and the best measure was kept in the model. In the analysis of PFS, the effect was analyzed by splitting data around median exposure value (estimate HR for subjects who were above and below the median value) to ensure even sample size.

3.2.1 Progression Free-Survival

Cox proportional hazards model regression analysis was used to describe the relationship of individual measures of exposure to PFS during treatment with dabrafenib and relevant covariates. The semi-parametric Cox proportional hazards model was developed using a stepwise procedure. Demographic and disease covariates of interest were tested individually and ranked by significance level. For the full covariate model, demographic and/or disease covariates meeting the criteria of a significance level of at least 0.05 were included in order of significance.
The results of Cox proportional hazards analysis are shown in Table 16 and Figure 9 for dabrafenib C_{avg} and metabolites C_{min}. There was no association between PFS and exposure (expressed as above or below median value) in the Phase II (n=87 subjects) and III (n=182 subjects) studies, as the majority of subjects are likely at the top of the exposure-response relationship. Lactate dehydrogenase (LDH) and BRAF V600 mutation type (V600E vs. V600K, Phase II) are known predictors of PFS and were significant in the model.

Table 16. Cox Proportional Hazards Analysis using Different Measures of Exposure with LDH and BRAF V600 K (phase II) and LDH only (Phase III) as covariates.

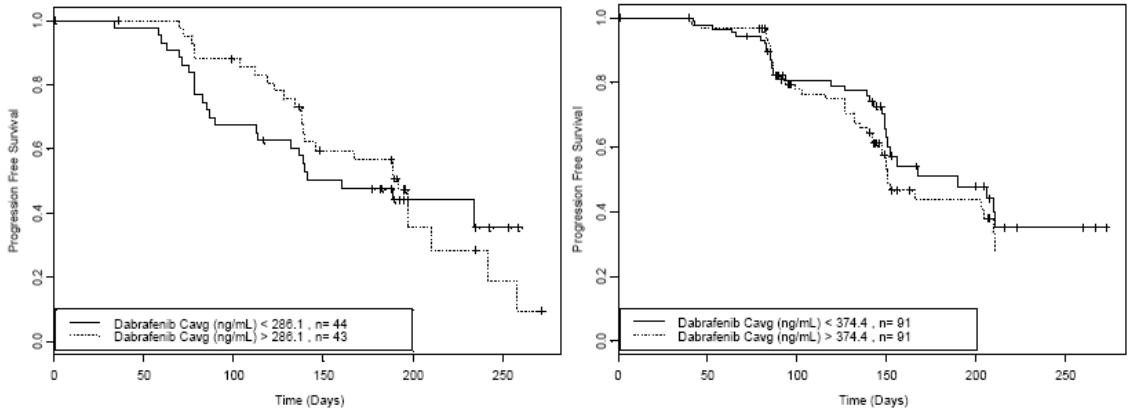
	BRF113710 (Phase II)		BRF113683 (Phase III)	
Exposure[1]	HR	95% CI	HR	95% CI
Average Dose (150 mg BID vs. <150 mg BID)	1.04	0.59-1.85	1.13	0.69-1.86
Dabrafenib Cavg (Above vs. Below Median)	0.81	0.45-1.46	1.36	0.86-2.17
Hydroxy-Dabrafenib Cmin (Above vs. Below Median)	0.97	0.53-1.75	1.21	0.73-2.00
Carboxy-Dabrafenib Cmin (Above vs. Below Median)	0.67	0.36-1.26	1.27	0.76-2.11
Desmethyl-Dabrafenib Cmin (Above vs. Below Median)	0.92	0.50-1.69	1.08	0.65-1.78

HR: Hazards Ratio; CI: Confidence Intervals

1. Analysis conducted by categorizing each subject as above or below the median exposure value determined in all subjects.

(Source: Sponsor's PK/PD Report, Page 35)

Figure 9. Kaplan Meier Estimates of PFS by Dabrafenib Cavg for the Phase II (BRF113710, Left) and Phase III (BRG113683, Right) Studies.



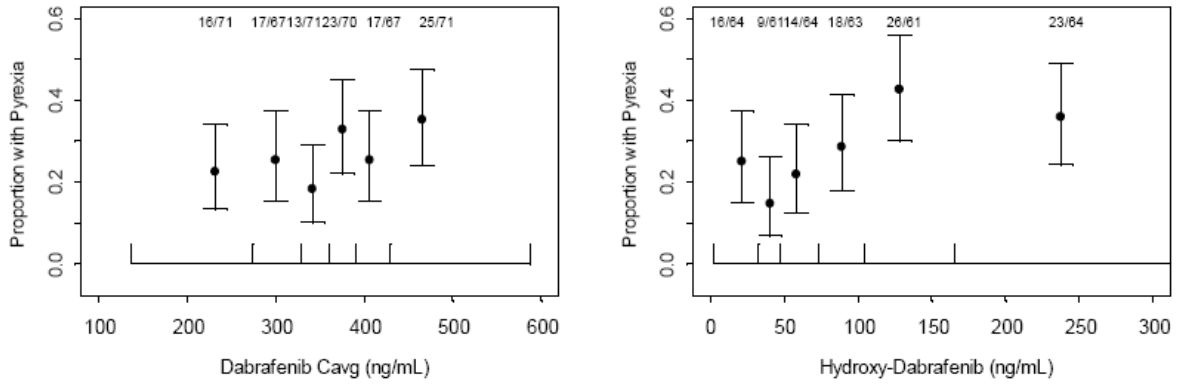
(Source: Sponsor's PK/PD Report, Figure 1)

Reviewer's Comment: *The sponsor's analysis is reasonable as it attempts not only to correlate dabrafenib concentrations to PFS, but also evaluates the concentrations of the metabolites and other factors as covariates in the Cox proportional hazards analysis. The sponsor's model does not attempt to evaluate the relationship with a combination of parent and metabolite concentrations, representative of the total active moiety.*

3.2.2 Safety

No strong relationships were noted between AEs and exposure, with the exception of pyrexia, where higher rate of pyrexia was noted with higher exposure (predose dabrafenib or hydroxy-dabrafenib concentrations). There was a weak association between PPE and exposure.

Figure 10. Proportion of Subjects with Pyrexia versus Dabrafenib Cavg (Left) and Hydroxy-dabrafenib Cmin (Right) for Pooled Data from Studies BRF113710, BRF113929, BRF113683.



(Source: Sponsor's PK/PD Report, Figure 7)

Reviewer's Comment: *The sponsor's safety analysis appears reasonable and focused on the events with a higher rate of incidence (e.g. pyrexia). However, the sponsor used average concentrations for the individual regardless of whether or not they had dose reduction due to an adverse event. The inclusion of dabrafenib PK exposures after dose reductions may bias the analysis. The sponsor's analysis also only uses one molecule as part of the independent variable. The reviewer's analysis aims to determine if these factors affect the results.*

3.3 Sponsor's Conclusions Regarding the Exposure-Response Analyses:

- There was no relationship between measures of exposure (above or below median) and PFS, as response is likely at the top of the exposure-response curve.
- Exploratory exposure-AE analysis showed that higher dabrafenib exposure was associated with higher fraction of subjects with pyrexia. A weaker relationship was noted between exposure and PPE. No exposure response was noted for arthralgia, SCC, and hyperkeratosis.
- Overall, the exposure-response analysis supports the recommended dose of 150 mg BID.

3.4 Population PK Analysis

3.4.1 Methods:

GSK2118436 concentration-time, dosing, demographics and covariate data from the First-Time-in-Human Study (BRF112680), Phase II studies (BRF113710 and BRF113929), and Phase III study (BRF113683) were used in the analysis. The population PK model was developed using a non-linear mixed-effect modeling approach; the NONMEM 7.2.0 software with the first order conditional estimation method with interaction (FOCEI) was used. The data from study BRF112680 were used to establish the preliminary semi-mechanistic base model. The model was then simplified to make it more feasible for exploration of covariates and to adapt to mostly sparse sampling of the other studies. Following availability of the final data for all 4 studies, data were combined and used to finalize the base model and to establish the covariate model. A full model approach was used to evaluate covariates. Covariates were included on oral clearance (CL/F), oral volume of distribution of central (Vc/F) and peripheral compartments (Vp/F), distributional clearance (Q/F), relative bioavailability (F), and absorption rate constant (Ka) as follows:

- CL/F: Effects of body weight (continuous), sex, age groups (<65, 65 to <75, ≥75 years), mild hepatic impairment (as defined by bilirubin ≤ upper limit of normal [ULN], aspartate aminotransferase [AST] >ULN, or bilirubin >1 to 1.5 times ULN; AST: any value), mild and moderate renal impairment (glomerular filtration rate [GFR] ≥90, 60≤ GFR <90, GFR <60 mL/min/1.73m2), concomitant CYP3A4 inhibitors or inducers and capsule shell;
- Vc/F: Effects of body weight (continuous) and sex;
- Vp/F, Q/F: Effect of body weight (continuous);
- F, Ka: Effect of capsule shell.

Other covariates were examined graphically. Once the final population PK model was developed, the ability of the model to describe the observed data was evaluated graphically and investigated using predictive check procedures and bootstrap analysis. Simulations were performed to quantify and illustrate the GSK2118436 concentrations over time at different doses and the effects of identified covariates. Estimates of individual PK parameters of GSK2118436 were obtained.

The final dataset for the analysis included 3787 GSK2118436 plasma concentrations of 595 subjects as follows: 1931 samples from 181 subjects in study BRF112680, 443 samples of 87 subjects in study BRF113710, 508 samples of 148 subjects in study BRF113929, and 905 samples of 179 subjects in study BRF113683. Patient demographics are shown in Table 17.

Table 17. Patient Demographics of Data used in Dabrafenib Population PK Analysis.

	Statistic or category	All Studies	BRF112680 Study 1	BRF113710 Study 2	BRF113929 Study 3	BRF113683 Study 4
Total Number of patients		595	181	87	148	179
Weight (kg)	Mean (SD) [Range]	79.8 (18.3) [36.2 - 149.5]	79.9 (20)	78 (17.9)	80.7 (17.7)	79.9 (17.1)
Age (yrs)	Mean (SD) [Range]	52.8 (14.2) [20 - 93]	52.2 (15.3)	54.3 (14.5)	52 (13.1)	53.3 (13.7)
Body mass index (kg/m2)	Mean (SD) [Range]	26.9 (5.9) [10.6 - 75.3]	27.4 (7.2)	26.3 (4.8)	26.8 (5.1)	26.9 (5.6)
Albumin (g/L)	Mean (SD) [Range]	39.7 (5.8) [18 - 51]	39.9 (5.8)	NA[a]	NA[a]	NA[a]
Alanine aminotransferase (IU/L)	Mean (SD) [Range]	24.7 (21.2) [0 - 292]	24.2 (23.9)[b]	20.1 (12.5)	27.2 (16)	25.3 (24.9)
Aspartate aminotransferase (IU/L)	Mean (SD) [Range]	25.8 (17.2) [8 - 225]	32.9 (24.8)	23 (13.1)	21.8 (10.2)	23.1 (11.1)
Total bilirubin (umol/L)	Mean (SD) [Range]	7.5 (4.7) [0 - 44.5]	8.7 (6.3)[c]	6.8 (3.7)[c]	6.7 (3.3)[c]	7.4 (4)[c]
Creatinine clearance (mL/min)	Mean (SD) [Range]	110.4 (36.8) [31.8 - 286.8]	112.2 (39.5)	104.9 (36.6)	115.6 (39.4)	106.8 (31.1)
GFR (mL/min/1.73 m²)	Mean (SD) [Range]	95 (24.7) [39.7 - 247.6]	95.9 (22.9)	94.1 (32.6)	98.5 (25.9)	91.7 (20.5)
Sex N (%)	Male Female	363 (61.0%) 232 (39.0%)	107 (59.1%) 74 (40.9%)	47 (54.0%) 40 (46.0%)	102 (68.9%) 46 (31.1%)	107 (59.8%) 72 (40.2%)
Race N (%)	Caucasian Non-Caucasian Missing	586 (98.5%) 7 (1.2%) 2 (0.3%)	177 (97.8%) 4 (2.2%) 0	86 (98.9%) 1 (1.1%) 0	147 (99.3%) 0 1 (0.7%)	176 (98.3%) 2 (1.1%) 1 (0.6%)
Age Group N (%)	< 65 yrs ≥ 65 but <75 yrs ≥ 75 but <85 yrs ≥ 85 yrs	468 (78.7%) 95 (16.0%) 30 (5.0%) 2 (0.3%)	141 (77.9%) 29 (16%) 11 (6.1%) 0	61 (70.1%) 21 (24.1%) 5 (5.7%) 0	125 (84.5%) 17 (11.5%) 5 (3.4%) 1 (0.7%)	141 (78.8%) 28 (15.6%) 9 (5%) 1 (0.6%)
Renal impairment N (%)	None Mild Moderate	332 (55.8%) 233 (39.2%) 30 (5.0%)	104 (57.5%) 71 (39.2%) 6 (3.3%)	46 (52.9%) 33 (37.9%) 8 (9.2%)	93 (62.8%) 47 (31.8%) 8 (5.4%)	89 (49.7%) 82 (45.8%) 8 (4.5%)
Hepatic impairment N (%)	None Mild Moderate	527 (88.6%) 65 (10.9%) 3 (0.5%)	151 (83.4%) 27 (14.9%) 3 (1.7%)	78 (89.7%) 9 (10.3%) 0	135 (91.2%) 13 (8.8%) 0	163 (91.1%) 16 (8.9%) 0
Mild 3A4 Inducers	N (%)	92 (15.5%)	11 (6.1%)	8 (9.2%)	59 (39.9%)	14 (7.8%)
Mild 3A4 Inhibitors	N (%)	148 (24.9%)	52 (28.7%)	20 (23%)	38 (25.7%)	38 (21.2%)
Strong 3A4 Inhibitors	N (%)	8 (1.3%)	1 (0.6%)	0	2 (1.4%)	5 (2.8%)
PgP inhibitors	N (%)	24 (4%)	8 (4.4%)	2 (2.3%)	5 (3.4%)	9 (5%)
Strong 2C8 Inhibitors	N (%)	1 (0.2%)	0	0	1 (0.7%)	0
Total Number of samples		3787	268+1663[d]	443+0[d]	498+10[d]	708+197[d]

a. Values for only 1, 3, and 2 subjects in studies 2, 3, and 4, respectively, were available;
b. 19 BLQ values assigned zero values;
c. 5, 6, 7, and 8 BLQ values assigned zero values in studies 1, 2, 3, and 4, respectively;
d. Number of samples from subjects with only sparse sampling + samples from subjects with serial and sparse sampling, respectively.

(Source: Sponsor's Population PK Report, Synopsis & Table 3)

3.4.2 Sponsor's Final Population Population PK Model:

The pharmacokinetics of GSK2118436 following oral administration to subjects with solid tumors were adequately described by a two-compartment model with first order absorption (Ka), absorption delay (T_{lag}), Vc/F, Vp/F, Q/F, and with elimination successfully described by non-inducible apparent clearance (CL0/F), and an inducible apparent clearance ($CL_{ind,ss}/F$) that increased almost linearly with dose and increased with time until it reached steady-state, with a half-life of induction of T50:

$$CL_{ind}=CL_{ind,SS}*(D*F_{GEL}/D_{Ref})^{\gamma}*(1-\exp(-0.693*TIME/T_{50})),$$

where D_{Ref} is the reference dose.

Continuous covariates were included in the model using a power function:

$$TVP_i = \theta_1*(COV_i/COV_{ref})^{\theta_2}$$

where TVP_i is the typical value of a PK parameter (P) for an individual i with a COV_i value of the covariate, while θ_1 is the typical value for an individual with a reference covariate value of *COVref*.

Categorical covariates were included in the model according to the following equation:

$$TVP_i = \theta_1 * \theta_2^{IND_i}$$

where TVP_i is the typical value of a PK parameter (P) for an individual i, θ_1 is the typical value for an individual in the absence of the covariate ($IND_i = 0$), and θ_2 is the fractional change in the typical value if the covariate is present and $IND_i = 1$.

The sponsor's final model estimates are shown in Table 18.

Table 18. Population Pharmacokinetic Parameter Estimates for Dabrafenib

Parameter		Estimate	%RSE	95%CI	Variability	Shrinkage
CL_0/F (L/hr)	θ_1	17.0	6.00	15 - 19		
V_C/F (L)	θ_2	70.3	5.48	62.7 - 77.8		
V_p/F (L)	θ_3	154	9.55	125 - 183		
Q/F (L/hr)	θ_4	3.30	7.32	2.82 - 3.77		
K_a (1/hr)	θ_5	1.88	10.2	1.5 - 2.25		
Tlag (hr)	θ_6	0.482	0.451	0.478 - 0.486		
$CL_{IND, SS}/F$ (L/hr)	θ_7	17.3	3.05	16.2 - 18.3		
Alpha	θ_8	0.927	4.67	0.842 - 1.01		
T_{50} (hr)	θ_9	67.3	15.2	47.2 - 87.3		
F_{GEL}	θ_{10}	0.555	6.14	0.488 - 0.622		
CL_{WT}	θ_{11}	0.331	22.1	0.188 - 0.474		
CL_{SEX}	θ_{12}	0.914	2.24	0.874 - 0.954		
Vc_{WT}	θ_{13}	0.384	31.1	0.15 - 0.617		
Q_{WT}	θ_{14}	1.22	24.4	0.637 - 1.8		
ω^2_{CL0}	$\Omega(1,1)$	0.343	11.1	0.268 - 0.418	CV=58.6%	24.5%
Covar ω_{CL}, ω_{Vc}	$\Omega(1,2)$	0.292	11.5	0.226 - 0.358	R =0.941	
ω^2_{Vc}	$\Omega(2,2)$	0.281	13.0	0.209 - 0.352	CV=53.0%	28.7%
ω^2_{Q}	$\Omega(3,3)$	0.980	13.0	0.729 - 1.23	CV=99.0%	32.6%
ω^2_{Ka}	$\Omega(4,4)$	2.57	9.74	2.08 - 3.06	CV=160%	29.4%
σ^2_{prop}	$\Sigma(1,1)$	0.28	3.27	0.262 - 0.298	CV=53.0%	9.6%
σ^2_{add} (ng/mL)	$\Sigma(2,2)$	17.6	13.5	13 - 22.3	SD=4.2	9.3%

Abbreviations: PE=Parameter Estimate; SE=Standard Error: %RSE= Relative Standard Error, %RSE=100·SE/PE; 95% CI= 95% confidence interval; SD=Standard Deviation computed as square root of the variance (=ω or =σ); CV= coefficient of variation, CV = 100*SD%; R = correlation coefficient; CL_0/F = apparent initial clearance; Vc/F = apparent volume of central compartment; Vp/F = apparent volume of peripheral compartment; Q/F = apparent inter-compartmental clearance; Ka = absorption rate constant; Tlag = absorption lag-time; $CL_{IND,SS}/F$ = apparent inducible clearance at steady state; Alpha = power of dependence of $CL_{IND,SS}$ on absorbed dose (LDOS*F_{GEL}); LDOS = last administered dose; F_{GEL} = relative bioavailability of gelatin capsule to HPMC capsule; T_{50} = half-life of clearance induction; ω^2_{CL0}, ω^2_{Vc}, $\omega^2_{Vp\_Part1}$, ω^2_{Q}, ω^2_{Ka} = variances of the respective inter-individual random effects; Covar = covariance; σ^2_{prop} = variance of the proportional component of the residual error model; σ^2_{add} = variance of the additive component of the residual error model.

(Source: Sponsor's Population PK Report, Table 4)

3.4.3 Reviewer Comments:

The sponsor's final PK model appears to be acceptable for the labeling statements. Additional details can be found in the reviewer's analysis.

4 Reviewer's Analysis

4.1 Introduction

The reviewer's analysis cross-checks the sponsor's exposure-response and safety analyses by using different metrics of exposure for the efficacy and safety analyses. The exposure-efficacy analysis was reviewed combining the metabolite and parent exposures into one metric and with different cut-points (e.g. 25th percentile) that define the exposure bins for the Kaplan-Meier curves. This helps evaluate the linearity of any potential relationship. The exposure-safety analysis was re-conducted using only dabrafenib exposure data prior to the occurrence of the event. This removes any bias that may be incorporated from dose reductions resulting from the adverse event.

4.2 Objectives

Analysis objectives are:

1. Evaluate if Exposure Response relationships for safety and effectiveness support the proposed dosing regimen?
2. Determine if the labeled population PK results are acceptable?
3. Determine if a PMR for renal impairment is necessary, based on the population PK results?

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 19.

Table 19. Analysis Data Sets

Study	Name	Link to EDR
multip	ae.xpt, exposure.xpt	\\cdsesub1\evsprod\NDA202806\0003\m5\datasets\iss\analysis\legacy\datasets\
multip	pfsex683.xpt, pfsex710.xpt, nonmemp.xpt, nonmemm7.xpt	\\cdsesub1\evsprod\NDA202806\0003\m5\datasets\pkpd\analysis\legacy\datasets\

4.3.2 Software

NONMEM VI (Icon, Ellicott City, MD) was used to review the sponsor's Population pharmacokinetic analysis and test model covariates. The statistical software R (www.r-project.org) and S-plus (Tibco, Palo Alto, CA) were used to generate all plots.

4.3.3 Models

No original models were developed and applied as part of this review. Evaluation of the sponsor's final population PK model is discussed on page 51.

4.4 Results

Exposure-response analyses for both efficacy and safety were performed by the reviewer to incorporate active metabolite concentrations into the exposure metric and cross-check these results with the sponsor's results which only considered one active molecule at a time. The predicted trough concentrations for each individual was used since corresponding hydroxy-metabolite concentrations were also available and trough concentrations for drug exhibiting linear pharmacokinetics can be indicative of clearance and overall exposure to the drug.

The exposure metric for these analyses is defined as:

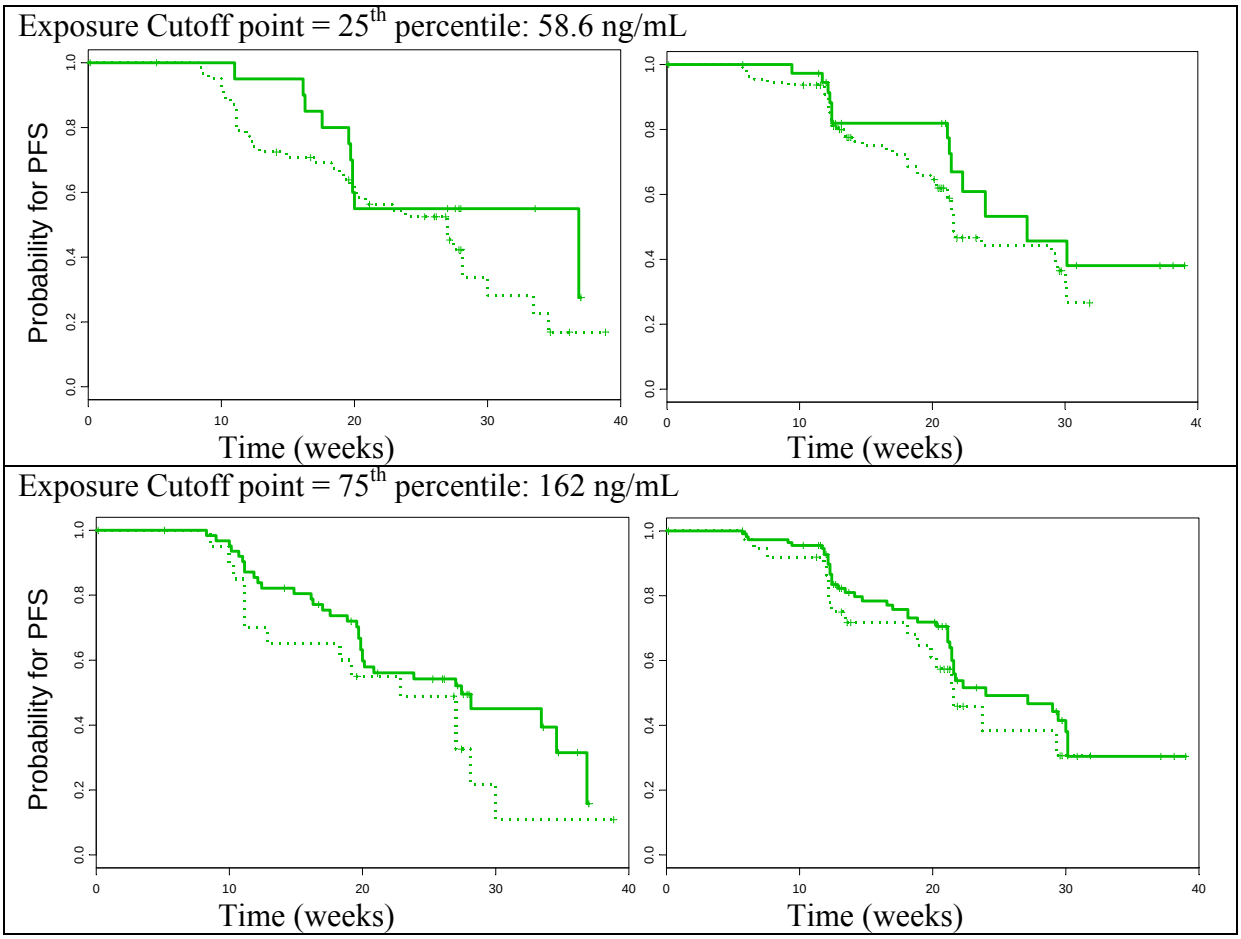
$$\text{Active-}C_{min} = C_{min,parent} + C_{min,met}$$

This equation assumes equal potency based on non-clinical assay data that indicates IC_{50} values for dabrafenib and hydroxy-dabrafenib in 70% human serum were 518 and 401 nM respectively (Source: Sponsor's Pharmacology Summary, page 26).

4.4.1 Exposure-Response for Progression Free Survival

In addition to Kaplan Meier plots of PFS by exposures split at the median (Figure 6). Cutoffs for the exposures at the 25^{th} and 75^{th} percentiles were also evaluated (Figure 11). No exposure-response relationships were evident at either the lower or upper end of concentrations achieved from the 150 mg BID dose.

Figure 11. Kaplan Meier plots of PFS by Dabrafenib ($C_{min,parent} + C_{min,met}$.) for the Phase II (BRF113710, Left Plots) and Phase III (BRF113683, Right Plots) Studies. The top panel and bottom panels indicates results for exposure cutpoints at the 25^{th} and 75^{th} percentiles. Short dashed/dotted lines indicate, exposures greater than the cutoff point. Solid lines indicate exposures less than the cutoff point.



4.4.2 Exposure-Response for Safety

Exposure-response analyses for safety were evaluated to determine whether increases or decreases in the starting dose could improve the benefit-risk ratio. Logistic regression analyses were performed for all adverse events listed in the ISS dataset for patients with PK exposures. Analyses were performed for grade 1 events or higher, grade 2 events or higher, or grade 3 events or higher. However, because of the number of plots generated (n=345, for those events where 2 or more instances occurred) was large, only grade 3+ adverse events correlations are plotted for their relevance in affecting dosing, and only those plots with significant logistic regression results are shown (Figure 7). No clinically meaningful correlations were detected.

For this safety analysis, only the active concentrations ($C_{min,parent}$ + $C_{min,metabolite}$) before the safety event occurred were used. This was to avoid bias introduced by dose reductions to manage adverse events.

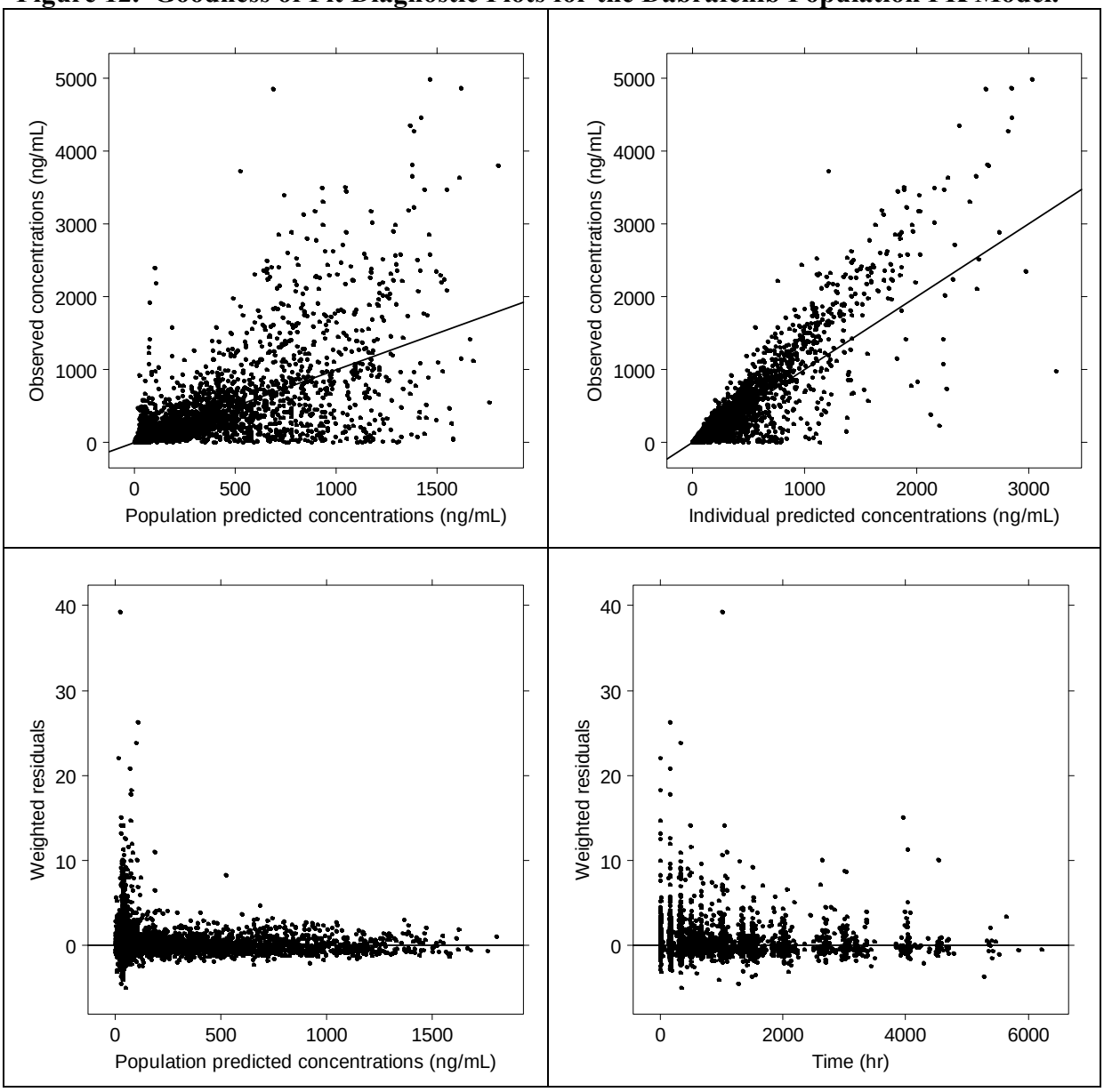
4.4.3 Population PK Analysis

The sponsor's population PK analysis was reviewed for goodness of fit, and relevance of covariates indicated in the labeling.

Reviewer generated diagnostic plots for the sponsor's final model are shown in Figure 12. Based on this it appears that the C_{max} values are being underpredicted by the model. This is fairly common and is particularly the case when the PK sampling is not dense enough to support a higher number of compartments in the model without over-parameterization. As C_{max} values are not reported in the

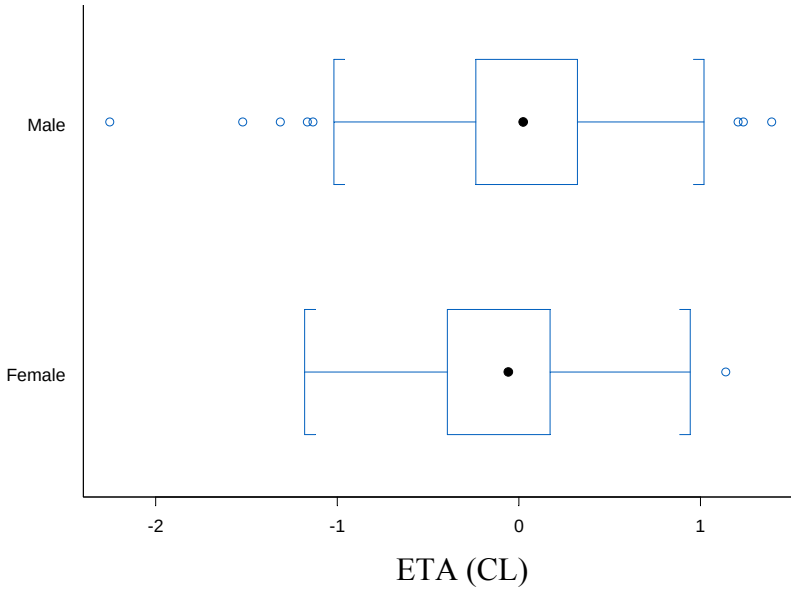
label nor were they used in the exposure-response analyses, this bias in the individual predicted concentrations is acceptable.

Figure 12. Goodness of Fit Diagnostic Plots for the Dabrafenib Population PK Model.



Body weight and Gender were found to be significant covariates in the population PK model. However gender does not appear to have a clinically meaningful effect on the PK of dabrafenib as the inclusion of gender as a covariate only reduced the between subject variability in clearance by 1.4%. Removing gender from the model yielded the following eta values, after correcting for body weight .

Figure 13. Gender effects on dabrafenib clearance are not clinically significant.



Age (Figure 13) mild hepatic impairment status (NCI classification) (Figure 15), and renal impairment (Figure 14) were not found to be significant covariates in the population PK model. Differences between model estimates and individual values do not evidence a trend with these covariates.

Figure 14. Dabrafenib CL does not correlate with Age.

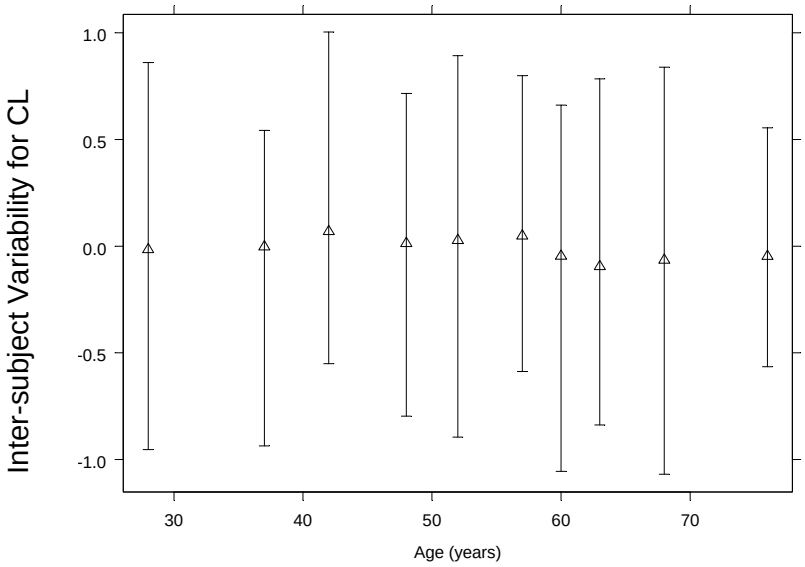
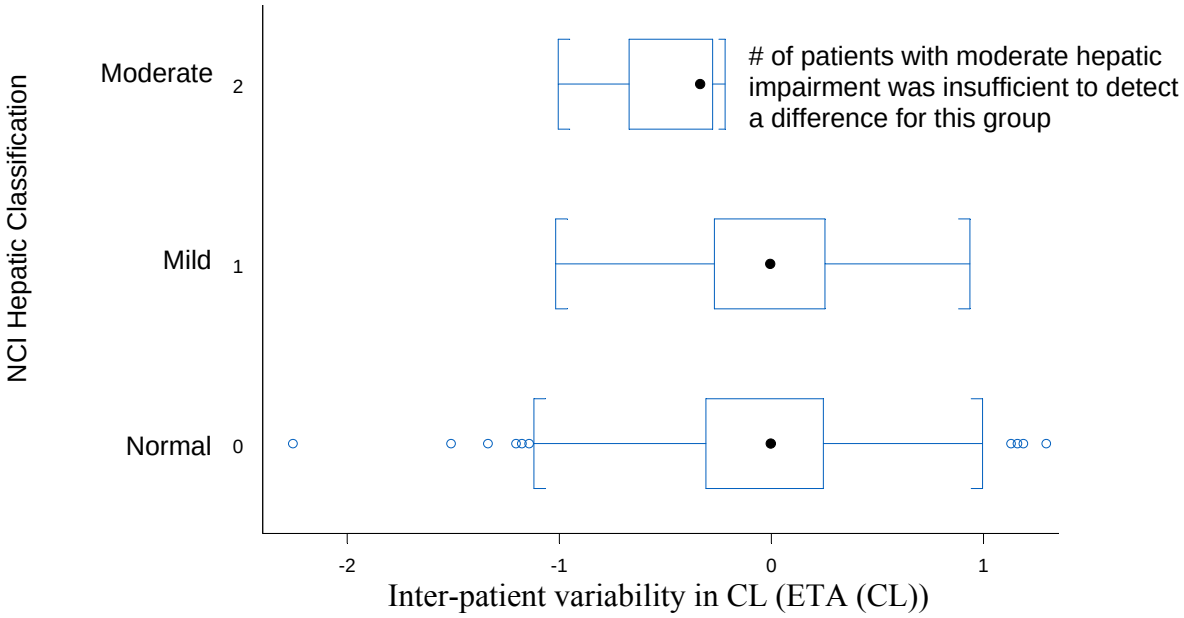


Figure 15. Hepatic impairment effects were not significant in the population PK model.



Race was not evaluated as a covariate in the population PK analysis.

5 Listing of Analyses Codes and Output Files

File Name	Description	Location in \\cdsnas\pharmacometrics\
EtaPlots.ssc	Diagnostic PK Plots for time-dependent PK Parameters	PM Review Archive\2013\Dabrafenib_NDA202806_JCE\F Analyses
.	Folder of NONMEM run output for sponsor's final model	PM Review Archive\2013\Dabrafenib_NDA202806_JCE\F Analyses\run2
.	Folder of NONMEM run output for sponsor's final model, excluding the effect of gender	PM Review Archive\2013\Dabrafenib_NDA202806_JCE\F Analyses\run3
.	Folder of PPK tool output for sponsor's NONMEM Runs	PM Review Archive\2013\Dabrafenib_NDA202806_JCE\F Analyses\PPKOutput
*.ssc	Exposure Response Analysis for Efficacy AND Safety	PM Review Archive\2013\Dabrafenib_NDA202806_JCE\F Analyses

4.2 Genomics Review

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS GROUP REVIEW

NDA/BLA Number	202806
Submission Date	7/30/12
Applicant Name	GSK
Generic Name	Dabrafenib
Proposed Indication	Metastatic melanoma with BRAF V600
Primary Reviewer	Christian Grimstein, Ph.D.
Secondary Reviewer	Rosane Charlab Orbach, Ph.D.
Acting Associate Director for Genomics	Michael A. Pacanowski, Pharm.D, M.P.H.

Executive Summary

Dabrafenib is a BRAF inhibitor proposed for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation as detected by an FDA-approved test. BRAF mutations are reported to be more common in certain clinical and pathological subsets of melanoma suggesting differences in disease etiology and behavior according with the mutation status. The purpose of the review is to retrospectively evaluate whether in Phase 2 studies BREAK-MB and BREAK-2, BRAF V600E and V600K mutations are associated with distinct clinicopathologic features and whether tumor responses in patients with metastatic melanoma differ by the specific BRAF V600 mutation. Our analysis showed an association between BRAF mutation status and age at screening and gender. Patients with V600K mutation were more likely to be men compared to patients with V600E mutation [82% vs. 60%, p=0.0048], and patients with BRAF V600K mutation were significantly older at screening [median (min, max): 63 (31, 87)] compared to patients with V600E mutation [median (min, max): 51 (19-79), p<0.0001]. Although pre- clinical data show similar IC50 values for the V600E and V600K mutations, limited clinical data from Phase 2 studies BREAK-MB and BREAK-2 suggest marginal dabrafenib activity in patients with the BRAF V600K mutation compared to patients harboring the V600E mutation. Furthermore, patients with BRAF V600K mutation were not included in the pivotal trial BREAK-3. These results collectively support a revised indication for the treatment of BRAF V600E metastatic melanoma providing that the clinical and statistical review determine a favorable benefit-risk.

1 Background

Melanoma is a heterogeneous disease characterized at molecular level by distinct genetic alterations [PMID: 16291983]. Among these, activating somatic mutations resulting in substitutions at the position 600 in the serine/threonine protein kinase BRAF have been identified in approximately 50% of melanoma patients, with about 75% of patients harboring the V600E, 19% harboring V600K and 6% harboring other less frequent V600 mutations such as V600R or V600D [PMID: 21343559, 21802280]. BRAF is a component of the MAP kinase

signaling pathway commonly deregulated and implicated in melanoma. Due to its oncogenic role, mutant BRAF has become a target for therapy of melanoma.

Dabrafenib is a BRAF inhibitor proposed for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation as detected by an FDA-approved test. Currently, vemurafenib is the only BRAF inhibitor approved for BRAF V600E mutated unresectable or metastatic melanoma as detected by an FDA-approved test.

BRAF mutations are reported to be more common in certain clinical and pathological subsets of melanoma, suggesting differences in disease etiology and prognosis according with the molecular landscape. Compared with BRAF wild type, BRAF V600-mutated melanoma has been primarily associated with younger age at diagnosis, tumors arising on skin without chronic sun-induced damage, truncal location and histopathologic subtype [PMID: 21997758, 21802280]. Most recently, the incidence and clinical correlates of the distinct melanoma BRAF V600-mutated genotypes have also been investigated. In a prospectively assembled cohort of Australian patients with advanced melanoma, the BRAF V600K mutation was found more commonly than the BRAF V600E mutation in metastatic tumors of patients who were older at diagnosis, and had evidence of cumulative sun-induced damage at the primary site. Patients harboring the V600K mutation had shorter distant metastasis free survival compared to those with V600E-mutated tumors [PMID: 22535154]. Similar results were reported by Jewell, et al. in primary melanoma, who also observed that a greater percentage of patients with V600K-mutated tumors were men [PMID: 23169438].

The sponsor restricted the Phase 3 registration trial (BREAK-3) to patients with the BRAF V600E mutation and only limited Phase 2 efficacy data is therefore available for patients with BRAF V600K mutation. As presented above, recent studies suggest that BRAF V600-mutated melanoma may be further classified in specific disease subtypes with distinct clinicopathologic features among BRAF mutant genotypes. Different BRAF mutations may have different functional consequences that could impact prognosis and/or sensitivity to BRAF inhibitors. The purpose of the review is to evaluate whether BRAF V600E and V600K mutations are associated with distinct clinicopathologic features and whether tumor responses in patients with metastatic melanoma differ by the specific BRAF V600 mutation.

2 Submission Contents Related to Genomics

The submission is supported by a Phase 3 [BRF113683] and two Phase 2 studies [BRF113710, BRF113929] as listed in table 1. BRAF mutation screening was performed with a Response Genetics Inc. IUO test using formalin fixed paraffin embedded tumor tissue from a metastatic site biopsy obtained prior to study entry. The Phase 2 studies were conducted in patients with BRAF V600E or V600K- mutated melanoma, while the Phase 3 study was restricted to patients with V600E- mutated tumors. Of note, two patients with a V600K mutation were randomized (in error) in Phase 3 and included in the Phase 3 ITT population. One of these patients discontinued the study prior to receiving the first dose. Study and population characteristics of the Phase 2 and 3 studies are depicted in Table 1.

Table 1: Phase 2 and Phase 3 studies with BRAF V600 mutation assessment

Study	Study design	Population	BRAF status	Sample size**	Assay used
BRF 113683 (BREAK-3)	Phase 3, open label dabrafenib vs DTIC	Previously untreated (for advanced/metastatic melanoma) BRAF V600E mutation positive advanced (StageIII) melanoma or metastatic (Stage IV) melanoma	BRAF V600E	248	Central testing in CLIA reference laboratory using Response Genetics Inc. (RGI) IUO assay
BRF 113710 (BREAK-2)	Phase 2, open label, single arm	Treatment naïve or previously treated, histological confirmed metastatic melanoma (Stage IV)	BRAF V600E BRAF V600K	76 16	
BRF113929 (BREAK-MB)	Phase 2, open label, two-cohort, single arm	Treatment naïve or previously treated, histological confirmed metastatic melanoma (Stage IV) Cohort A: no local therapy for brain metastasis; Cohort B: failed prior local therapy for brain metastasis	BRAF V600E [Cohort A] [Cohort B] BRAF V600K [Cohort A] [Cohort B]	139 [74] [65] 33 [15] [18]	

** In BREAK-3, two patients with a V600K mutation were randomized (in error) in Phase 3 and included in the Phase 3 ITT population for a total n=250.

3 Key Questions and Summary of Findings

3.1 Are clinicopathologic features different for patients with BRAF V600E and V600K metastatic melanoma?

Our analyses indicate that the BRAF mutation status is associated with gender (p=0.0044) and age at screening (p<0.0001). Patients with V600K mutation were more likely to be men compared to patients with V600E mutation [82% vs. 60%, p=0.0048]. In addition, patients with BRAF V600K mutation were significantly older at screening [median (min, max): 63 (31, 87)] compared to patients with V600E mutation [median (min, max): 51 (19-79), p<0.0001]. Our findings suggest that BRAF V600E and BRAF V600K mutations are associated with distinct clinicopathologic features and may define specific disease subtypes.

Reviewer's evaluation:

Methods:
Datasets were constructed by combining data from the Phase 2 studies, BREAK2 and BREAK-MB. Data from the Phase 3 study was not included in our analysis because this study was restricted to BRAF V600E mutated melanoma patients and the patient population was different from that of the Phase 2 studies (e.g., previously untreated vs. naïve or previously treated).

For all patients enrolled in Phase 2, age at screening (mean; <65 vs. ≥65), gender (male vs. female), ECOG status (1 vs. 0), disease type (visceral vs. non-visceral), prior therapy (prior chemotherapy, prior immunotherapy, prior biologic therapy, prior hormonal therapy, prior small molecule therapy), brain metastasis status (yes vs. no), LDH at screening (median; <235 IU/L vs. ≥235 IU/L) were tested for any association with BRAF mutation status using a stratified Cochran-Mantel-Haenszel test (with study as stratification factor) for categorical data and Mann-Whitney U test for continuous data. Age at screening and LDH levels at screening were tested as both, continuous as well as dichotomous variables.

The datasets were complete for the following categories: age at screening, gender, disease type, prior therapy, brain metastasis. Datasets were incomplete for ECOG status and LDH at screening with data available from 259/264 (98%) and 242/264 (92%), respectively. Of note, previous reports used "age at diagnosis" of primary or metastatic melanoma when association with BRAF mutation status was evaluated [PMID: 23169438, 22535154]. In the submission, it is unclear whether "age of diagnosis" data referred to diagnosis for primary or for metastatic disease. From the available datasets, "age at screening" was considered the best available estimate and therefore used in the analysis.

Results:

Preclinical:

Dabrafenib competitively inhibits ATP binding to BRAF and CRAF kinases. According to the sponsor, the IC50 for wildtype BRAF, wildtype CRAF, BRAF V600E, BRAF V600K and BRAF V600D are 3.2 nM, 5.0 nM, 0.65 nM, 0.5 nM and 1.84 nM, respectively.

Clinical:

Based on univariate analysis, BRAF V600 mutation status was associated with gender such that V600K mutated patients were more likely to be men, compared to patients with V600E mutations [82% vs. 60%, p=0.0048]. In addition, patients with BRAF V600K mutation were significantly older at screening [median (min, max): 63 (31, 87)] compared to patients with V600E mutation [median (min, max): 51 (19-79), p<0.0001]. BRAF mutation status was not associated with other assessed clinicopathologic features (Table 2).

Table 2: Frequencies of V600 mutation status by subcategory in Phase 2 studies

Clinico-patho-logic feature	Variable	BRF113929 (BREAK-MB)				BRF 113710 (BREAK-2)		Total (BREAK-MB+BREAK-2)		p-value
		Cohort A		Cohort B						
		V600E	V600K	V600E	V600K	V600E	V600K	**V600E**	**V600K**	
Age (years)	Median (min, max)	50 (19-76)	66 (46-75)	51 (20-75)	57.5 (31-87)	52 (22-79)	64.5 (49-83)	**51 (19-79)**	**63 (31-87)**	**<0.0001**
	<65	66 (89%)	6 (40%)	57 (88%)	12 (67%)	56 (74%)	8 (50%)	**179 (83%)**	**26 (53%)**	**<0.0001**
	≥65	8 (11%)	9 (60%)	8 (12%)	6 (33%)	20 (26%)	8 (50%)	**36 (17%)**	**23 (47%)**	
Gender	Male	53 (72%)	12 (80%)	41 (63%)	14 (78%)	35 (46%)	14 (88%)	**129 (60%)**	**40 (82%)**	**0.0048**
	female	21 (28%)	3 (20%)	24 (37%)	4 (22%)	41 (54%)	2 (12%)	**86 (40%)**	**9 (18%)**	
ECOG	0	44 (61%)	5 (33%)	42 (67%)	11 (61%)	38 (51%)	12 (75%)	**124 (59%)**	**28 (57%)**	0.79
	1	28 (39%)	10 (67%)	21 (33%)	7 (39%)	37 (49%)	4 (25%)	**86 (41%)**	**21 (43%)**	
Disease type	Visceral	73 (99%)	15 (100%)	62 (95%)	16 (95%)	57 (75%)	13 (81%)	**192 (89%)**	**44 (90%)**	0.99
	Non-visceral	1 (1%)	0 (0%)	3 (5%)	2 (5%)	19 (25%)	3 (19%)	**23 (11%)**	**5 (10%)**	
Prior ther-apy*	Yes	36 (49%)	7 (47%)	39 (60%)	13 (72%)	69 (91%)	14 (88%)	**144 (67%)**	**34 (69%)**	0.63
	No	38 (51%)	8 (53%)	26 (40%)	5 (28%)	7 (9%)	2 (12%)	**71 (33%)**	**15 (31%)**	
Brain metas-tasis	Yes	74 (100%)	15 (100%)	65 (100%)	18 (100%)	0 (0%)	0 (0%)	**139 (65%)**	**33 (67%)**	0.72
	No	0 (0%)	0 (0%)	0 (0%)	0 (0%)	76 (100%)	16 (100%)	**76 (35%)**	**16 (33%)**	
Base-line LDH [IU/L]	Median (IQR)	263 (182-452)	357 (204-457)	255 (162-401)	305 (180-535)	207 (164-400)	194 (169-215)	**237 (174-428)**	**228 (183-454)**	0.55
	<235	27 (40%)	5 (33%)	27 (46%)	7 (39%)	42 (62%)	12 (80%)	**96 (49%)**	**24 (50%)**	0.85
	≥235	40 (60%)	10 (67%)	32 (54%)	11 (61%)	26 (38%)	3 (20%)	**98 (51%)**	**24 (50%)**	

Percentage displayed in each cell represents proportion of patients with clinicopathologic feature within mutation subgroup

*prior therapy includes: prior chemotherapy, prior immunotherapy, prior biologic therapy, prior hormonal therapy, prior small molecule therapy

Cohort A: prior therapy for brain metastasis; Cohort B: patients without prior therapy for brain metastasis

IQR: interquartile range

n.s. non-significant

Both age at screening and gender remained associated with mutation status in a multivariate logistic regression analysis.

BRAF V600 mutation and response to dabrafenib

Studies BREAK-MB and BREAK-2: The Primary efficacy endpoints were overall intracranial response rate (OIRR) [study BRF113929 (BREAK-MB)] and overall response rate (ORR) [BRF 113710 (BREAK-2)] in patients with BRAF V600E mutation as assessed by investigators. Secondary endpoints included PFS, OS and duration of response (DOR) and response rates in patients with V600K mutations.

Table 3 presents a descriptive summary of OIRR, ORR and DOR (independent radiologist review) by mutation status in both BREAK-MB and BREAK-2 studies. Patients' positive for V600K mutation presented smaller OIRR (BREAK-MB), smaller ORR (BREAK-2) and shorter DOR (BREAK-2) when compared to BRAF V600E positive patients. Too few previously untreated patients without brain metastasis (i.e. patients in Phase 2 most closely resembling Phase 3 study population) and with a V600K mutation were enrolled in the Phase 2 trials to conduct a meaningful analysis.

Table 3: Outcomes by mutation status in dabrafenib Phase 2 trials as assessed by independent radiologist review.

Endpoint	Parameter	BRF113929 (BREAK-MB)				BRF 113710 (BREAK-2)	
		Cohort A		Cohort B			
		V600E (N=74)	V600K (N=15)	V600E (N=65)	V600K (N=18)	V600E (N=76)	V600K (N=16)
OIRR	CR [N (%)]	1 [1]	0	0	0	n.a.	n.a.
	PR [N (%)]	14 [19]	0	12 [18]	2 [11]	n.a.	n.a.
	CR+PR [N (%)] (95% CI)	15 [20] (11.8, 31.2)	0 (0.0, 21.8)	12 [18] (9.9, 30.0)	2 [11] (1.4, 34.7)	n.a.	n.a.
ORR	CR [N (%)]	0	0	0	0	2 (3)	0 (0)
	PR [N (%)]	21 [28]	0	15 [23]	2 [11]	29 [38]	4 [25]
	CR+PR [N (%)] (95% CI)	21 [28] (18.5, 40.1)	0 (0.0, 21.8)	15 [23] (13.5, 35.2)	2 [11] (1.4, 34.7)	31 [41] (29.7, 51.8)	4 [25] (3.8,46.2)
DOR	Median (weeks, 95% CI)	20.1 (18.6, NC) (N=21)	0	20.1 (12.3,NC) (N=15)	NC (N=2)	26.9 (22.1, NC) N=31	21.7 (14.9, NC) N=4

Reference: Study reports BRF113710; BRF113929 (submitted 7/30/2012)
OIRR: overall intracranial response rate; ORR: overall response rate NC: not calculable; n.a. not assessed
For endpoint assessment, independent radiologist assessment was used. The presented outcome measures rely on data reported by the sponsor; no re-analysis was performed by the reviewer.

4 Summary and Conclusions

BRAF mutations are reported to be more common in certain clinical and pathological subsets of melanoma. We assessed whether melanoma patients in Phase 2 studies BREAK-MB and BREAK-2 had different clinicopathologic features according to the BRAF V600 mutation (i.e.

V600E vs. V600K). Our analysis showed an association between BRAF mutation status and age at screening and gender. A greater proportion of patients with BRAF V600K mutation were male and older at screening compared to patients with the V600E mutation suggesting that mutant genotypes may define a subgroup of patients with distinct phenotypes. Although pre-clinical data show similar IC50 values for the V600E and V600K mutations, limited clinical data from Phase 2 studies BREAK-MB and BREAK-2 suggest marginal dabrafenib activity in patients with the BRAF V600K mutation compared to patients harboring the V600E mutation.

5 Recommendations

No labeling or post-approval actions are proposed at this time from the perspective of the Genomics Group. The proposed indication is for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation as detected by an FDA-approved test. The studies submitted with this application were conducted in patients with BRAF V600E or V600K-mutated melanoma, and therefore the specific BRAF V600 mutation genotype should be specified in the indication. Because (1) limited antitumor activity was observed in V600K patients in Phase 2 trials, (2) V600K patients were excluded from Phase 3, and (3) V600K patients may represent a distinct subset of melanoma patients with distinct clinicopathologic features, it is reasonable at this point to exclude V600K patients and have the indication revised for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E mutation as detected by an FDA-approved test, provided clinical and statistical reviews concur with demonstration of a favorable risk-benefit profile.

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/s/

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04/04/2013

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BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 202-806	**Reviewer**: Akm Khairuzzaman, Ph.D.	
Submission Date:	06/21/2012 (Part 1 of rolling submission date) 07/29/2012 (Completion of rolling submission date)		
Division:	Division of Oncology Products	**Team Leader:** Angelica Dorantes, PhD	
Sponsor:	GlaxoSmithKline, LLC One Franklin Plaza, 200 North 16th Street, Philadelphia, PA 19102		
Trade Name:	(b) (4) Capsules	**Date Assigned:**	08/01/2012
Established Name:	Dabrafenib	**Date of Review:**	12/27/2012
Indication:	Treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation	**Type of Submission:** Original NDA 505(b)1	
Formulation/strengths	Immediate Release Capsules, 50 mg & 75 mg		
Route of Administration	Oral		

EXECUTIVE SUMMARY:

Dabrafenib mesylate is very slightly soluble at pH 1 and practically insoluble in the pH range of 4 to 8 in aqueous media (b) (4) (used for the drug product manufacture). It has high bioavailability and therefore, this drug can be classified as BCS class II compound. The molecule has a log P value of 2.9 indicating its high lipophilicity and has three different pKa such as 6.6, 2.2 and -1.5. The particle size distribution of micronized dabrafenib mesylate is designated as a drug substance Critical Quality Attributes (CQA) based on its potential impact on bioavailability.

The drug product is a capsule dosage form formulated with excipients such as microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate. The drug product has been developed by utilizing Quality by Design strategy whereby the Quality Target Product Profile (QTTP) and Critical Quality Attributes (CQA) have been identified by the applicant. Dissolution is identified as one of the drug product CQA. The manufacturing process (b) (4) was developed, followed by encapsulation.

Extensive experiments were done to develop a useful dissolution method that can distinguish batches from a quality perspective. The setting of the dissolution limit was based on statistical analysis of the several clinical and scale up batches. Detail studies were conducted to evaluate the impact of variability (coming from formulation and

process) on dissolution. The Applicant has satisfactorily responded and provided appropriate data to address all the biopharmaceutics related questions that were raised by the reviewer during the course of review. Currently there are no pending biopharmaceutics related issues with this NDA.

RECOMMENDATION

NDA 202806 for (b) (4) (dabrafenib) Capsules is recommended for APPROVAL from the Biopharmaceutics perspective.

Akm Khairuzzaman, Ph.D. Date
Interdisciplinary Scientist, ONDQA

Angelica Dorantes, Ph.D. Date
Biopharmaceutics Team Leader, ONDQA

cc: NDA 202806/DARRTS, RLostritto

BIOPHARMACEUTICS ASSESSMENT

SUBMISSION:

This NDA is being submitted under the Section 505(b)(1) of the Food, Drug and Cosmetic Act. The NDA was submitted as a rolling submission using the electronic common technical (eCTD) format. The drug product is an immediate release capsule dosage form that contains Dabrafenib mesylate which is a selective RAF kinase inhibitor of the mutated forms BRAF V600E, BRAF V600K, and BRAF V600D as well as human wild type BRAF and CRAF enzymes.

The drug product is an immediate release capsule dosage form formulated with excipients such as microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate. The drug product has been developed by utilizing Quality by Design strategy, whereby the Quality Target Product Profile (QTTP) and Critical Quality Attributes (CQA) have been identified by the Applicant. Dissolution is identified as one of the drug product CQA.

PHYSICAL-CHEMICAL PROPERTIES OF THE DRUG

- *Solubility*: Dabrafenib mesylate is very slightly soluble at pH 1 and practically insoluble in the pH range of 4 to 8 in aqueous media.

Solvent	Solution pH	Solubility (µg/mL) at 37°C
SGF[1]	1.2	43
FesSIF[2]	4.9	6.8
FasSIF[3]	6.3	6.2

1. SGF = simulated gastric fluid
2. FeSSIF = fed state simulated intestinal fluid
3. FaSSIF = fasted state simulated intestinal fluid

- *Solid State:* Dabrafenib exist (b) (4) (used for the drug product manufacture).
- *pKa*~6.6, 2.2, -1.5, *Log P* ~ 2.9,
- *Melting Point*: 250 °C, (b) (4) Micronized DS (b) (4)
- *Absolute in vivo bioavailability BA* ~ 94.5%, highly permeable (from in vitro study)
- *BCS Class*: Possibly a BCS class II compound.
- Dabrafenib has long half-lives with low peak to trough ratios
- *Food effect*: 51% reduction in C_{max} and 30% reduction in AUC, 4 hr delay in T_{max}
- *Biowaver*: There is no biowaver request in this application and no IVIVC was developed/submitted.
- The (b) (4) manufacturing process (b) (4) was developed, followed by encapsulation.

1. The reviewer's analyses on the formulation development :

Evaluation: Acceptable.

The formulation development of Dabrafenib used a QbD-like approach. Dissolution was defined as a CQA. The drug product is a capsule dosage form (50 mg and 75 mg) (b) (4) (b) (4) A manufacturing process followed by encapsulation was selected to manufacture the drug product. Followings are the formulation composition used at different phase of clinical trials:

Table 1. Phase 1 & 2 Formulation:

Component	Quantity mg/capsule					
Strength	1	5	25	50	75	100
Formulation Code	(b) (4)					
Dabrafenib Mesylate, Micronized[2]	(b) (4)			59.25	88.88	(b) (4)
Microcrystalline Cellulose						(b) (4)
Magnesium Stearate						
Colloidal Silicon Dioxide						
Total Unit Dose						
Hard Gelatin Capsule						

Table 2. Phase III/Final Formulation:

Component	Quantity [mg/capsule]	
	50 mg	75 mg
Dabrafenib Mesylate, Micronized[1]	59.25	88.88
Microcrystalline Cellulose	(b) (4)	
Magnesium Stearate		
Colloidal Silicon Dioxide		
Total Unit Dose		
Hypromellose Capsules[3]		

Effect of formulation on dissolution and bioavailability:

The effect of API particle size was found to be very significant on the relative bioavailability of the formulation. Interestingly, none micronized particles showed higher dissolution compared to that of the micronized particles as presented below in Figure 1.

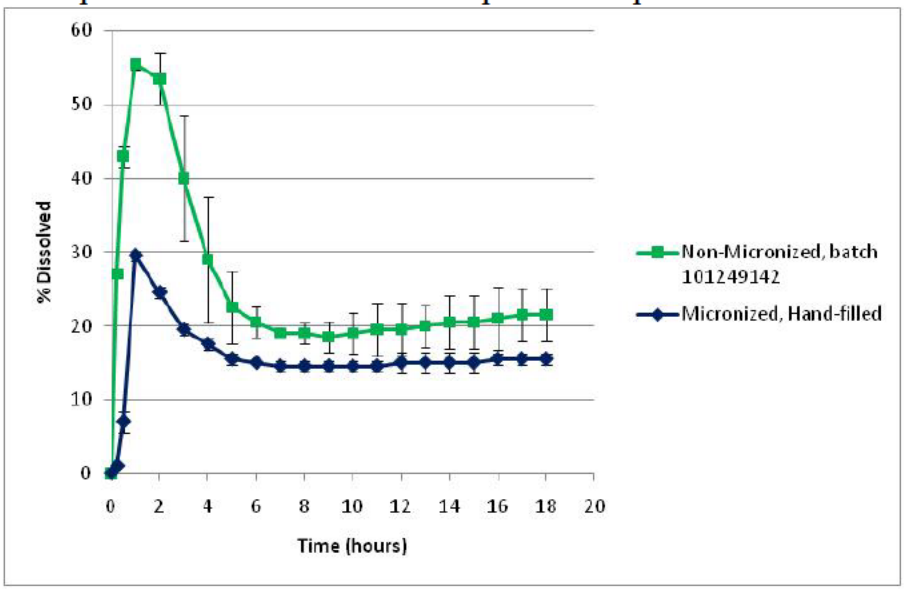

Fig. 1. Effect of API particle size on dissolution

Despite of these findings, the Applicant developed their product using micronized DS to avoid uniformity problem. A comparative bioavailability study was conducted between the non micronized and micronized formulation. Surprisingly, non micronized particles showed higher bioavailability compared to that of the micronized particles as follows:

Table 3. Effect of API particle size on PK Parameters

PK Parameter	Micronized-Regimen A[1]	Non-Micronized Regimen B[1]	Ratio (90% CI)[1]
Cmax (ng/mL)	1068	1522	1.42 (1.06,1.91)
AUC(0-t) (ng*hr/mL)	6548	8080	1.23 (0.95,1.61)
AUC(0-∞) (ng*hr/mL)	6664[2]	9608[3]	1.44 (1.13,1.83)

Effect of capsule shell type on relative bioavailability: The HPMC Capsule shell formulation showed higher BA than the gelatin formulation (both used micronized DS) as follows:

Table 4. Effect of Capsule Shell Type on PK Parameters

PK Parameters	Gelatin Capsule Shell	HPMC Capsule Shell	Ratio (90% CI)
Cmax (ng/mL)	1068	2160	2.02 (1.42,2.87)
AUC(0-t) (ng*hr/mL)	6548	11843	1.81 (1.36,2.41)
AUC(0-∞) (ng*hr/mL)	6767	12168	1.80 (1.32,2.46)

The following question was sent out to the Applicant on October 12th, 2012:

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) [redacted] *can impact the dissolution of the drug product. Therefore, provide additional dissolution profile data* (b) (4) [redacted]

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Reviewer's Final Evaluation: ***Acceptable***.
Encapsulation parameter setting with the proposed range does not have any impact on the drug product dissolution.

3. Reviewer's evaluation on dissolution method development:

Evaluation: Acceptable.\

The Applicant's goal for the dissolution method development was based on an Analytical Target Profile and Design Intent as follows:

- Detection (b) (4) is achieved.
- The probability is maximized for the detection of unforeseen changes to the drug product. (b) (4)
- A gradual dissolution profile is obtained (b) (4)
- The analytical procedure can be validated against generally accepted criteria.
- Both 50 mg and 75 mg strengths can be analyzed using a common method.

The entire dissolution method development history is summarized in table 9:

Table. 9. Method Details for the Determination of Dissolution of Dabrafenib Capsules

Parameter	Method 1	Method 2	Method 3 (Stability and Registration)
Capsule Shell Type	(b) (4)		Gelatin and Hypromellose
Medium			0.1N HCl + 0.2% (w/v) CTAB
Apparatus			Paddles
Sinkers			Yes
Rotation Speed			65 rpm for all strengths (50 mg and 75 mg)
Detection Wavelength (nm)			335
Background correction wavelength (nm)			420

Method 1 was used for phase 1 clinical products. Later, it was found to be not discriminating and the method 2 was developed. (b) (4)

(b) (4)

Therefore, Method 3, which is the proposed registration method, was developed with paddles and sinkers (b) (4)

During the course of method development, the Applicant conducted the following studies

Effect of pH on dissolution: ***Acceptable.***

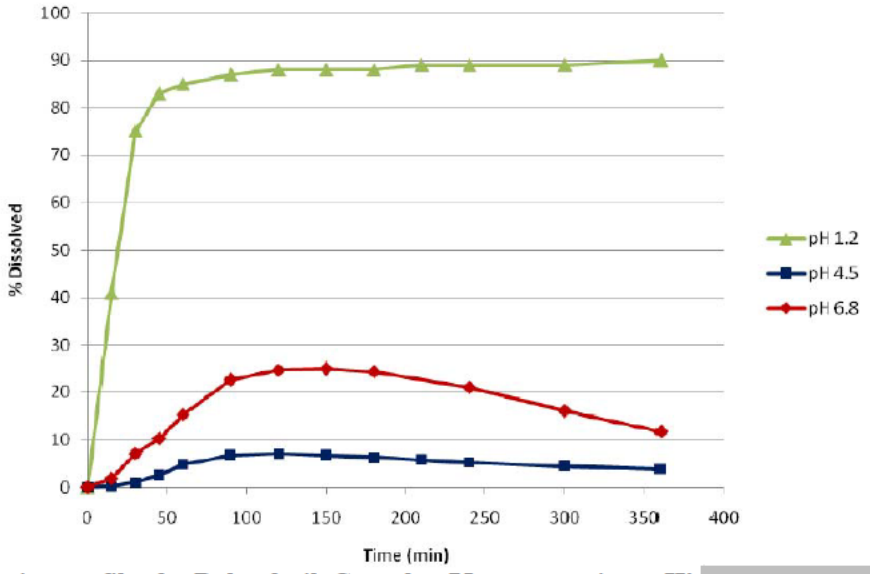

Fig. 8. Dissolution profiles for Dabrafenib Capsules, 75 mg, at various pH's (b) (4)

Effect of surfactant: ***Acceptable.***

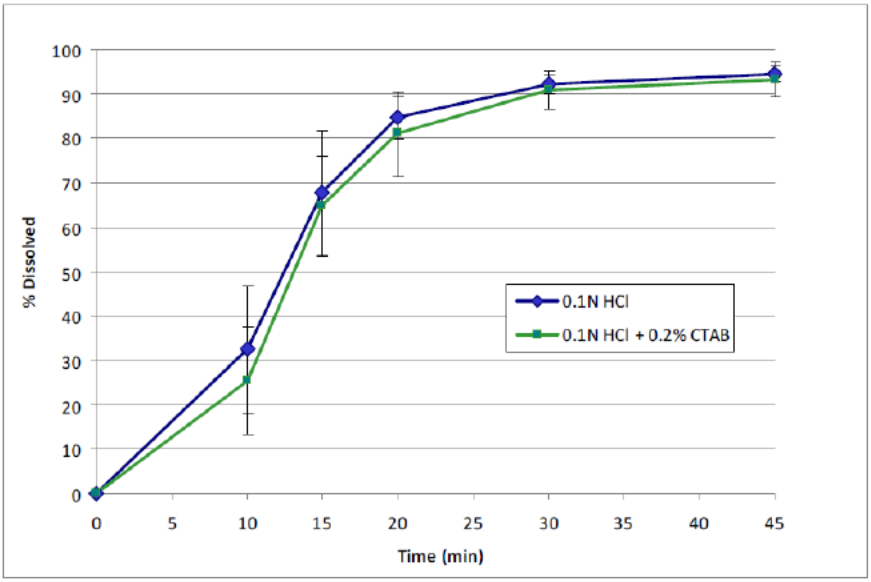

Fig. 9. Comparison of Dissolution Profiles for Dabrafenib Capsules, 75 mg (Batch 101274762), in 0.1N HCl with and without 0.2% CTAB (65 RPM in 900 mL, n=12)

Table. 10. Multivariate Confidence Region Comparison of Dissolution Profiles for Dabrafenib Capsules, 75 mg (Batch 101274762), in 0.1N HCl with and without 0.2% CTAB (65 RPM in 900 mL, n=12)

Global Distance	90% Confidence Interval for Global Distance	Global Similarity Limit	Similar?
1.07	(0.0004, 2.57)	3.67	Yes

Reviewer's Evaluation: Acceptable.

(b) (4)

Therefore use of 0.2% CTAB in 0.1N HCl is justified in order to producing a reliable dissolution method with acceptable solution stability.

Effect of paddle speed: Acceptable.

A fractional factorial design of experiments (DOEs) was done to evaluate the impact of paddle speed. (b) (4) Therefore, this Reviewer is in agreement with the proposed paddle speed of 65 RPM.

(b) (4)

(b) (4)

4. **Reviewer's evaluation on the propose dissolution method and acceptance criteria :**

Evaluation: Acceptable.

The data supporting the development of the dissolution method was already discussed under the discussion point # 3. The dissolution method is as follows;

USP Apparatus/ RPM	Medium	Volume	Assay	Acceptance Criterion
II - Paddle at 65 rpm	0.1N HCl with 0.2% w/v of CTAB	900 mL	UV at 335 nm	Q = (b) (4) in 30 min

The discussion on the proposed dissolution limit for the acceptance criterion is discussed in the next section.

5. **Reviewer's evaluation on the dissolution data and statistical analysis supporting the proposed dissolution criterion :**

Evaluation: Acceptable.

The selection of the dissolution limit was based on the statistical analysis of mean dissolution release data for 23 production-scale batches of capsules, 10 of which were used in the Phase 3 clinical trial, a criterion of Q= (b) (4) at 30 minutes has been proposed for the regulatory specification of the drug product. The proposed limit is based on a one-sided lower 95% tolerance interval to capture 99% of the population of mean dissolution

results. The individual dissolution data at the 30 minutes timepoint from the 10 pivotal clinical trial batches are presented in Figure 14 below.

Fig. 14. Individual Dissolution Values for 10-Pivotal Clinical Batches, 50 mg and 75 mg

The following table summarizes the batch information and its respective dissolution data in 30 minutes from the batches that were used in the statistical analysis.

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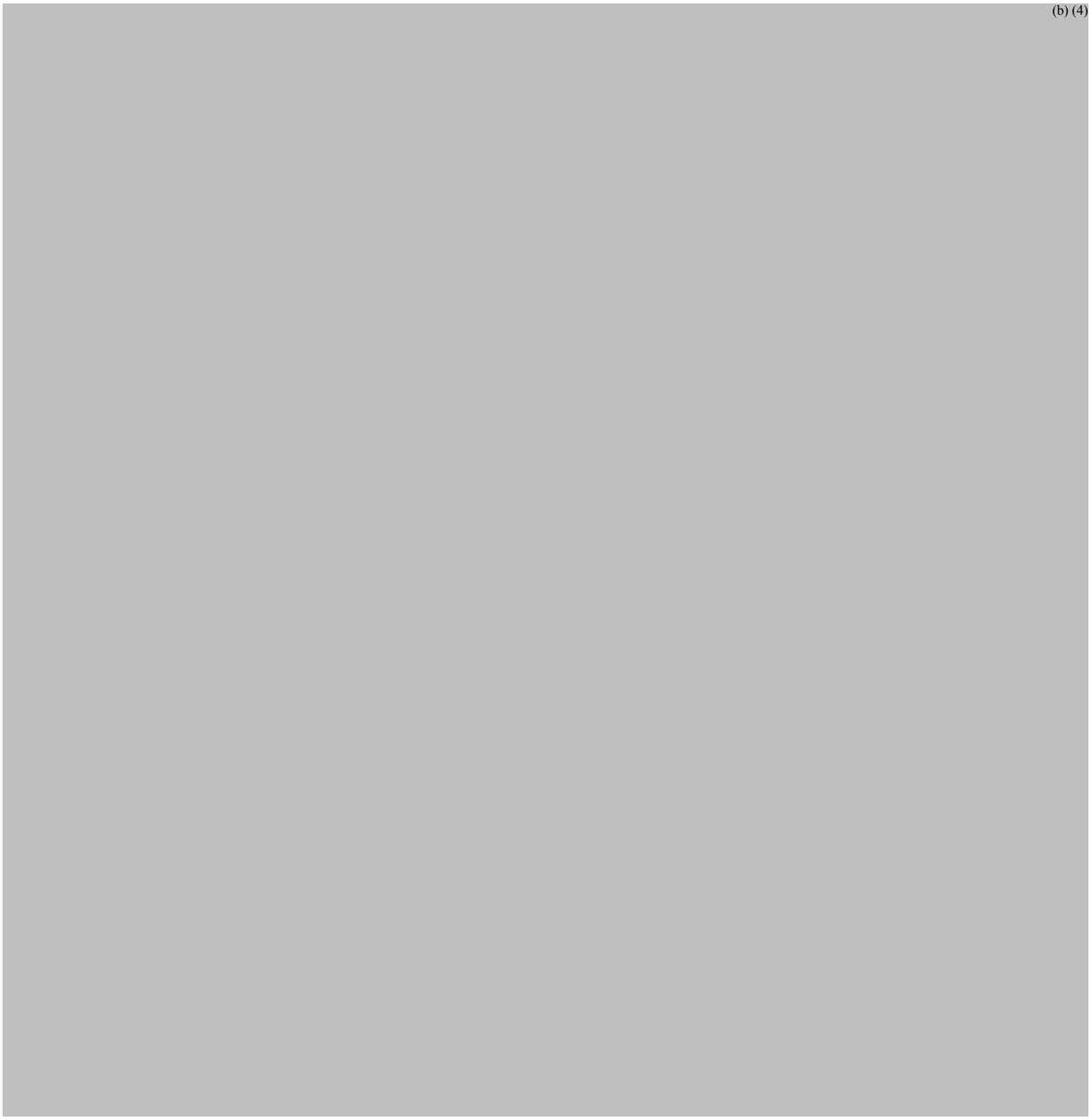

RECOMMENDATION: From Biopharmaceutics perspective, NDA 202-806 for (b) (4) (dabafrenib) is recommended for approval. There are no pending issues from biopharmaceutics point of view.

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/s/

AKM KHAIRUZZAMAN
02/08/2013
Recommended for Approval from Biopharmaceutics Point of Vew

ANGELICA DORANTES
02/08/2013

CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR NDA # 202806

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**202806**	**Brand Name**	**(b) (4) (under review)**
OCP Division (I, II, III, IV, V)	**V**	**Generic Name**	**dabrafenib**
Medical Division	**Oncology**	**Drug Class**	**Small molecule; Kinase inhibitor**
OCP Reviewer	**Jian Wang, Ph.D.**	**Indication(s)**	**Melanoma with BRAF V600 mutation**
OCP Team Leader	**Hong Zhao , Ph.D.**	**Dosage Form**	**50, 75 mg capsules**
Pharmacometrics Reviewer	**Justin Earp, Ph.D.**	**Dosing Regimen**	**150 mg orally twice daily**
Pharmacometrics Team Leader	**Nitin Mehrotra, Ph.D.**		
Pharmacogenomics Reviewer	**Christian Grimstein, Ph.D.**		
Pharmacometrics Team Leader	**Rosane Charlab-Orbach, Ph.D.**		
Date of Submission	**7/30/2012**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**3/30/2012**	**Sponsor**	**GSK**
Medical Division Due Date	**4/30/2012**	**Priority Classification**	**Standard**
PDUFA Due Date	**5/30/2013**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**4**		
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		**113463**
Isozyme characterization:	**X**	**2**		**recombinant human CYP isoforms**
Blood/plasma ratio:	**X**	**1**		**blood-plasma partitioning**
Plasma protein binding:	**X**	**1**		
Pharmacokinetics -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	**X**	**5**		**112860, 113468, 113771, 113463,113479**
multiple dose:	**X**	**4**		**113710, 113929, 113683, 112680**

Dose proportionality -				
fasting / non-fasting single dose:	**X**	**1**		
fasting / non-fasting multiple dose:	**X**	**1**		
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	**2**		**113220(phenytoin) 113771(ketoconazole, gemifibrozil, ongoing)**
In-vivo effects of primary drug:	**X**	**3**		**112680 (midazolam) 113929 (dexmethasone) 113771(warfarin, ongoing)**
In-vitro:	**X**	**8**		**CYP inhibition and induction, PXR binding, BCRP, MDR1, OATP1B1, OATP1B3, OAT1, OAT3**
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD - QT Study:	**X**	**1**		**E-R analysis**
Phase 2:	**X**	**2**		
Phase 3:	**X**	**1**		
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**2**		
Phase 3 clinical trial:	**X**	**1**		
Population Analyses -				
Data rich:	**X**	**4**		
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability	**X**	**1**		**113479**
Relative bioavailability -	**X**	**2**		**113468, 113463**
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**2**		**113468, 112680**
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	**X**			
Total Number of Studies		**49**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-	X			

	be-marketed product(s) and those used in the pivotal clinical trials?				
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?				
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in			X	

	this submission?				

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

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

N/A

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

Potential PMRs:

1. *Renal and hepatic impairment trials*
2. *DDI trials*

Jian Wang, Ph.D. 9-8-2012

Clinical Pharmacology Reviewer **Date**

Hong Zhao, Ph.D. 9-8-2012

Clinical Pharmacology Team Leader **Date**

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

/s/

JIAN WANG
10/02/2012

HONG ZHAO
10/02/2012
I concur.

BIOPHARMACEUTICS INITIAL ASSESSMENT and FILING REVIEW Office of New Drugs Quality Assessment			
Application No.:	NDA 202-806	**Reviewer**: Akm Khairuzzaman, Ph.D.	
Submission Date:	06/21/2012 (Part 1 of rolling submission date) 07/29/2012 (Completion of rolling submission date)		
Division:	Division of Oncology Products	**Team Leader:** Angelica Dorantes, PhD	
Sponsor:	GlaxoSmithKline, LLC One Franklin Plaza, 200 North 16th Street, Philadelphia, PA 19102		
Trade Name:	(b) (4)	**Date Assigned:**	08/01/2012
Established Name:	Dabrafenib	**Date of Review:**	08/27/2012
Indication:	Treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation	**Type of Submission:** Original NDA 505(b)1	
Formulation/strengths	Capsule, 50 mg & 75 mg		
Route of Administration	Oral		

SUBMISSION:
This NDA is submitted under the Section 505(b)(1) of the Food, Drug and Cosmetic Act. The NDA was submitted as a rolling submission using the electronic common technical (eCTD) format. The drug product is an immediate release capsule dosage form that contains Dabrafenib mesylate which is a selective RAF kinase inhibitor of the mutated forms BRAF V600E, BRAF V600K and BRAF V600D as well as human wild type BRAF and CRAF enzymes.
Dabrafenib mesylate is very slightly soluble at pH 1 and practically insoluble in the pH range of 4 to 8 in aqueous media (b) (4) (used for the drug product manufacture). It has high bioavailability and therefore, this drug can be classified as BCS class II compound. The molecule has a log P value of 2.9 indicating its high lipophilicity and has three different pKa such as 6.6, 2.2 and -1.5. The particle size distribution of micronized dabrafenib mesylate is designated as a drug substance CQA based on its potential impact on bioavailability. The (b) (4) manufacturing process (b) (4) was developed, followed by encapsulation.
The drug product is a capsule dosage form formulated with excipients such as microcrystalline cellulose, colloidal silicon dioxide, and magnesium stearate. The drug product has been developed by utilizing Quality by Design strategy whereby the Quality Target Product Profile (QTTP) and Critical Quality Attributes (CQA) have been identified by the Applicant. Dissolution is identified as one of the drug product CQA.

BIOPHARMACEUTIC INFORMATION: In support of approval, this NDA includes the following Biopharmaceutics data for review and evaluation:

- Critical Quality Attributes: Dissolution

- Proposed dissolution method and acceptance criteria, with justification
- Dissolution method development report
- Comparative dissolution data including all clinical batches
- Drug product dissolution stability data.

COMMENTS & RECOMMENDATION: The 50 mg and 75 mg strength capsules used in the clinical studies and the primary stability batches were manufactured at commercial scale at the commercial manufacturing facility at GSK (b) (4) (b) (4) No stability and site equivalence data (in vitro dissolution comparison) were found in the application. Therefore, this was initially considered as a major deficiency from the Biopharmaceutics point of view. However, On August 30th, 2012 at 1:00 pm, the review team has initiated a T-con with the applicant and has expressed the concern regarding the (b) (4) site. In order to resolve this potential filing issue, applicant has agreed to remove the (b) (4) site (see letter below) from the applicant and proceed with this NDA. This approach is reasonable from biopharmaceutics point of view.

From a biopharmaceutics perspective, NDA 202-806 for (b) (4) (dabafrenib) is considered fileable. There are sufficient Biopharmaceutics data to permit a substantive review.

Akm Khairuzzaman, Ph.D.
Biopharmaceutics Reviewer, ONDQA

Angelica Dorantes, Ph.D.
Biopharmaceutics Team Leader, ONDQA

ATTACHMENT 1

August 30, 2012

Patricia Keegan, M.D., Division Director
Division of Oncology Products 2
Center for Drug Evaluation and Research
Office of Hematology and Oncology Products
Food and Drug Administration
Division of Oncology Products 2
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 202806; Rafinlar (dabrafenib) Capsules
Amendment to Pending Application: CMC - Withdrawal of Ware, UK manufacturing site

Dear Ms. Keegan,:

Based on the teleconference with the Agency on August 30, 2012, GSK agrees to withdraw the (b) (4) manufacturing site from the pending NDA application 202,806.

(b) (4)

Sincerely,

Kathleen Church

Kathleen Church
Assistant Director
New Submissions, North America

Trade secret and/or confidential commercial information contained in this submission is exempt from public disclosure to the full extent provided under law.

cc:
Jewell Martin
Norma Griffin

A. ONDQA-BIOPHARMACEUTICS **Initial** overview of the NDA application for filing				
	Parameter			**Comment**
1.	Is the QTPP (Quality Target Product Profile) defined for drug release? (3.2.P.2)	**Yes** ☒	**No** ☐	The design intent has been defined
2.	Has the risk assessment been performed to evaluate the criticality of the in vitro release? (3.2.P.2/3.2.P.5)	**Yes** ☒	**No** ☐	
3.	Is there any manufacturing parameter evaluated using in vitro release as an end point?	**Yes** ☒	**No** ☐	
4.	Is there any design space proposed using in vitro release as an end point?	**Yes** ☐	**No** ☒	
5.	Is the control strategy related to in vitro dissolution/drug release? (3.2.P.2/3.2.P.5)	**Yes** ☒	**No** ☐	Particle size specification as a part of API, DP batch release testing, (b) (4) limit of the capsule shell as a part of excipient acceptance criteria
6.	Solubility (3.2.S.1)	**High** ☒	**Low** ☒	very slightly soluble at pH 1 and practically insoluble in the pH range of 4 to 8 in aqueous media
7.	Permeability (2.7.1)	**High** ☒	**Low** ☐	Absolute bioavailability ~ 94.5%
8.	BCS Class	**I** ☐ **II** ☒	**III** ☐ **IV** ☐	This is reviewer's opinion based on solubility and in vivo bioavailability data
9.	Is the study report included for the development of the in vitro release method? (3.2.P.2/3.2.P.5)	**Yes** ☒	**No** ☐	The dissolution method development report is provided in P.5.3.
10.	In the study report, are the individual data, the mean, the standard deviation and the plots provided?	**Yes** ☒	**No** ☐	Individual dissolution data with standard deviations are not provided in the method development. However, all profiles are provided with standard deviations in the graphs.
11.	Has the discriminating ability been shown for the in vitro release methodology using formulation variants? (3.2.P.2/3.2.P.5)	**Yes** ☒	**No** ☐	
12.	Is the justification provided for the acceptance criteria of the in vitro release? (3.2.P.2/3.2.P.5)	**Yes** ☒	**No** ☐	Applicant provided dissolution values for 10-Pivotal Clinical Batches and other 25 batches data to justify their dissolution limit.
13.	Are the proposed acceptance criteria adequate? (3.2.P.5)	**Yes** ☒	**No** ☐	Acceptance criteria appear to be reasonable. However, it requires further review in order to make a final decision
14.	Is the to-be-marketed formulation the same as that used in pivotal clinical trials?	**Yes** ☒	**No** ☒	Commercial formulation will be manufactured at a different site. In vitro site equivalence is required.
15.	Are all the to-be-marked strengths used in the pivotal clinical trials?	**Yes** ☐	**No** ☒	For 15 mg strength there is a biowaver request in the application
16.	Have any biowaivers been requested? (1.12/2.7.1)	**Yes** ☐	**No** ☒	
17.	Is there any IVIVC information submitted? (5.3.1)	**Yes** ☐	**No** ☒	
18.	If the IVIVC information presented, are the study report and data provided?	**Yes** ☐	**No** ☐	Not applicable

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
19.	**IS THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	**Yes** ☒	**No** ☐	➢ The NDA is filable from the Biopharmaceutics Perspective ➢ The acceptability of the proposed dissolution method and acceptance criteria will be a review issue.
20.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	**Yes** ☐	**No** ☐	Not applicable.
21.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.	**Yes** ☐	**No** ☐	Not applicable.
22.	Are there any potential review issues identified?	**Yes** ☐	**No** ☐	None at this stage

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/s/

AKM KHAIRUZZAMAN
08/31/2012
This NDA is fileable from biopharmaceutics point of view

ANGELICA DORANTES
08/31/2012