CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204114Orig1s000

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 6, 2013

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

Subject: NDA 204114: 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 8, 2013, the following were the signatories:

Ruby Leong
Jingyu Yu
Stacy Shord
Nitin Mehrotra
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NDA Clinical Pharmacology Review

NDA	NDA 204114/0 \\Cdsesub1\evsprod\NDA204114\0002
Type/Category	NME (orphan and fast track)
Brand Name	Mekinist
Generic Name	Trametinib (GSK1120212)
Receipt Date	August 3, 2012
PDUFA Date	June 3, 2013
Proposed Indication	Treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutations as detected by an FDA-approved test
Dosage Form	0.5, 1, 2 mg tablets
Route of Administration	Oral
Dosing Regimen and Strength	2 mg once daily
Applicant	GlaxoSmithKline
OCP Division	Division of Clinical Pharmacology V
OND Division	Division of Oncology Products 2
Clinical Pharmacology Reviewer	Ruby Leong, Pharm.D.
Clinical Pharmacology Team Leader	Hong Zhao, Ph.D.
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1 EXECUTIVE SUMMARY

Trametinib (GSK1120212) is an inhibitor of mitogen-activated extracellular signal regulated kinase 1 and 2 (MEK1 and MEK2) activation and kinase activity. BRAF V600 mutations result in constitutive activation of the BRAF pathway including [redacted] (b) (4) proteins MEK1 and MEK2.

The proposed indication is for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutations as detected by an FDA-approved test. The bioMerieux THxID BRAF assay is reviewed in parallel with this NDA by CDRH (PMA #P120014). The proposed dosing regimen is 2 mg daily by oral administration one hour before or two hours after a meal. Given that a single dose of trametinib taken with a high-fat meal resulted in a 24% decrease in systemic exposure and the clinical efficacy of trametinib was established under fasted conditions, the review team recommends avoiding administration of trametinib with a high-fat meal to preserve clinical efficacy while providing a less restricted dosing condition for better compliance.

A registration trial was conducted in patients with BRAF V600 mutation-positive metastatic melanoma who were randomized 2:1 to receive trametinib (n=214) or chemotherapy consisting of either dacarbazine 1000 mg/m^2 or paclitaxel 175 mg/m^2 intravenously every 3 weeks (n=108) until disease progression or unacceptable toxicity. Treatment with trametinib resulted in a statistically significant and clinically meaningful improvement in progression-free survival (PFS) compared to treatment with chemotherapy. The most common adverse reactions (≥ 20%) associated with trametinib were rash, diarrhea, fatigue, peripheral edema, nausea, and dermatitis acneiform. Important safety concerns that have been identified for MEK inhibitors include cardiac (decrease of left ventricular ejection fraction [LVEF], hypertension), and ocular (blurry vision, dry eyes, retinal vein occlusion, central serous retinopathy) adverse events.

The Clinical Pharmacology Section of the NDA is supported by dose escalation, food effect, mass balance, and absolute bioavailability studies conducted in cancer patients as well as *in vitro* studies to assess drug interaction potential of trametinib with cytochrome P450 (CYP450) and transporters. Population pharmacokinetic (PopPK) and exposure-response (E-R) analyses using PK data across clinical studies did not identify significant covariates influencing trametinib PK or evident exposure-response relationships for effectiveness and safety.

1.1 RECOMMENDATIONS

This NDA is acceptable from a clinical pharmacology perspective provided that the Applicant and the FDA come to an agreement regarding the labeling language and the identified clinical studies to be conducted as post marketing requirements.

1.2 PHASE 4 REQUIREMENTS AND COMMITMENTS

1.2.1 Post Marketing Requirements (PMR)

The Applicant is required to conduct the following studies under the post marketing requirements (PMRs). These studies will be included in the Approval letter with milestones agreed upon after negotiation with the Applicant.

Key Drug Development Question	Rationale	PMR
Does trametinib prolong QT/QTc intervals?	No adequate data to rule out the QT prolongation potential of trametinib.	Complete a clinical trial to evaluate the potential for trametinib to prolong the QT/QTc interval in an adequate number of patients administered repeat doses of trametinib in accordance with the principles of the FDA Guidance for Industry entitled "*E14 Clinical Evaluation of QT/QTc Interval Prolongation*." Submit the final report that includes central tendency, categorical and concentration-QT analyses, along with a thorough review of cardiac safety data. Final Protocol Submission: Submitted Trial Completion: August 2014 Final Report Submission: April 2015
Should the dose of trametinib be reduced in patients with moderate and severe hepatic impairment?	Fraction of dose excreted is >80% in feces indicating that hepatic elimination is the major elimination pathway.	Conduct a pharmacokinetic trial to determine the appropriate dose of trametinib in patients with hepatic impairment in accordance with the FDA Guidance for Industry entitled "*Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*." Final Protocol Submission: September 2013 Trial Completion: June 2015 Final Report Submission: December 2015

1.2.2 Additional Comment to Be Conveyed under IND 102175

Consider conducting an *in vitro* study to determine if trametinib is a substrate of OATP in accordance with the draft FDA Guidance for Industry "*Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling*."

Signatures:

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DCPV: DDD – B Booth

A Required Office of Clinical Pharmacology Office Level Briefing was held on February 8, 2013.

1.3 SUMMARY OF IMPORTANT CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

ADME: The mean absolute bioavailability of a single 2 mg oral dose of trametinib is 72%, with median time to achieve peak concentrations (T_{max}) of 1.5 hours. The increase in exposure is greater than dose proportional after a single dose of 0.125 to 10 mg, and dose-proportional following repeat doses of 0.125 to 4 mg. Following oral administration of 2 mg trametinib daily (QD), geometric mean C_{max}, C_{trough} (pre-dose concentration), and $AUC_{(0-\tau)}$ at day 15 are 22.2 ng/mL, 12.1 ng/mL, and 370 ng·hr/mL, respectively. Inter-patient variability at steady state is 22% in AUC and 28% in C_{max}. Trametinib is highly protein bound (97.4%).

Trametinib undergoes non-CYP450 mediated metabolism predominantly via deacetylation to form M5 or in combination with hydroxylation to form M7. Following repeat doses of trametinib, the parent drug is the major component (≥ 75%) in plasma, with M5 and M7 each constituting approximately 10% of drug-related material. Following oral administration of [^{14}C]-trametinib, > 80% of excreted radioactivity was recovered in the feces while < 20% of excreted radioactivity was recovered in the urine with < 0.1% of the excreted dose as parent drug in urine. The estimated elimination half-life based on the population pharmacokinetic (popPK) analysis is 3.9 to 4.8 days. The accumulation ratio on day 15 relative to day 1 is approximately 6.

Food Effect: Administration of a single 2 mg dose of trametinib with a high-fat, high-calorie meal resulted in a 70% decrease in C_{max} and a 24% decrease in AUC_{0-168h}, compared to fasted conditions. The Applicant recommends that trametinib be administered one hour before or two hours after a meal, similar to the fasted conditions in clinical trials. Considering the approximately lower peak to trough ratio at steady state (2) as compared to that after a single dose (4 to 5), a 70% decrease in C_{max} observed after a single dose would be less pronounced after repeat dosing, and a 24% decrease in AUC is not considered clinically important as efficacy was also achieved in patients whose dose was reduced to 1.5 mg (a 25% dose reduction due to intolerability) in the registration trial. However, given that a single dose of trametinib taken with a high-fat meal resulted in a 24% decrease in systemic exposure and the clinical efficacy of trametinib was established under fasted conditions, the review team recommends avoiding administration of trametinib with a high-fat meal to preserve clinical efficacy while providing a less restricted dosing condition for better compliance.

Organ Impairment: Formal clinical studies have not been conducted to evaluate the effect of organ impairment on the pharmacokinetics (PK) of trametinib. A popPK analysis showed that mild and moderate renal impairment and mild hepatic impairment did not influence the apparent clearance of trametinib, hence no dose adjustment is recommended for patients with mild or moderate renal impairment and for patients with mild hepatic impairment. No data is available in patients with severe renal impairment and in patients with moderate or severe hepatic impairment. Based on the results of a mass balance study and the popPK analysis suggesting that hepatic elimination is the major route while renal excretion is a minor route of elimination for trametinib, the Applicant is requested to conduct a clinical trial to determine the appropriate trametinib dose in patients with hepatic impairment under a post marketing requirement (PMR).

Drug Interactions: Trametinib is not a substrate of CYP450 or efflux transporters P-gp or BCRP *in vitro*. However, it is not known if trametinib is a substrate for OATP. An IND comment will be sent to the applicant to consider conducting an *in vitro* study to determine if trametinib is a substrate of OATP.

In vitro studies with human hepatic microsomes showed that trametinib (at concentrations of 0.01 to 10 µM) does not inhibit CYP enzymes including CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, and transporters including OATP1B1, OATP1B3, P-gp, and BCRP at a clinically relevant systemic concentration of 0.04 µM (calculated R_1 values < 1.1). Trametinib inhibits CYP2C8 with an R_1 value of 1.2, which is slightly greater than the cutoff value of 1.1.

In vitro studies with primary human hepatocytes indicated that trametinib has the potential to induce CYP3A4, but not CYP2B6 or CYP2C8. Based on cross-study comparisons, oral administration of trametinib 2 mg QD with everolimus (sensitive CYP3A4 substrate) 5 mg QD had no clinically important effect on the exposure (AUC and C_{max}) of everolimus.

Population PK and Exposure-Response Analyses: The popPK analysis did not identify clinically important effects of body weight, age, gender, mild and moderate renal impairment, or mild hepatic impairment as covariates on clearance or volume of distribution of trametinib. Using PK, efficacy, and safety data from the registration trial, no evident exposure-response (E-R) relationships were found for the efficacy endpoint of PFS or for adverse events (AEs) including cardiac-related events, diarrhea, visual disorders, hypertension, skin-related events, hepatic disorders, and pneumonitis.

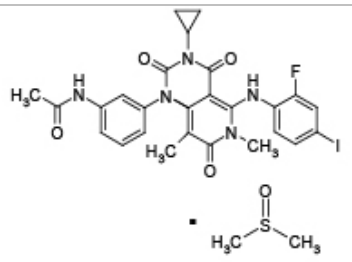
2 QUESTION-BASED REVIEW

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?

Due to low solubility of the trametinib parent form, a dimethyl sulfoxide (DMSO) solvate form, trametinib DMSO (GSK1120212B) is used [redacted] (b) (4) Trametinib DMSO (**Figure 1**), herein referred to as trametinib, has a molecular weight of 693.5 g/mol, Log P value of 4.99, and basic pKa of 0.25. The proposed drug product is available as 0.5, 1, and 2 mg tablets.

Figure 1. Chemical structure of trametinib DMSO



Trametinib is practically insoluble in Simulated Gastric Fluid (SGF, pH=1.2) and in aqueous media of the pH range 2 to 8. Since trametinib solubility appears independent of pH (**Table 1**) and it is only soluble in either fasted state Simulated Intestinal Fluid (FaSSIF, pH=6.3) or fed state Simulated Intestinal Fluid (FeSSIF, pH=4.9), a study to assess the effect of gastrointestinal pH-elevating agents on the PK of trametinib is not warranted.

Table 1. Solubility of trametinib

Solvent	Solubility[1] (µg/mL)			
	0.5 hour	2 hours	4 hours	24 hours
pH2	ND[2]	0.1	0.3	0.4
pH4	ND	0.1	0.3	0.3
pH6	ND	0.1	0.3	0.3
pH8	ND	0.1	0.2	0.2
SGF[3]	ND	0.4	0.6	0.4
FaSSIF[4,6]	10.8	2.3	1.5	0.8
FeSSIF[5,6]	49.1	16.8	8.9	3.9

[1] Determined at 37°C on material typical of commercial drug substance

[2] ND – not detected, detection limit (DL)=0.025 µg/mL

[3] Simulated Gastric Fluid, pH=1.2

[4] Fasted State Simulated Intestinal Fluid, pH=6.3

[5] Fed State Simulated Intestinal Fluid, pH=4.9

[6] The fall in solubility over time is ascribed to precipitation of the less soluble non solvated parent

Source: 3.2.S.1.3. General Properties, p 3.

Trametinib showed high permeability across MDCK-II-MDR1 cells. The mean absolute bioavailability of a single 2 mg oral dose of trametinib is 72%. The Applicant claims that trametinib is a BCS Class 2 compound with high permeability and low solubility.

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

Trametinib is an inhibitor of mitogen-activated extracellular signal regulated kinase 1 and 2 (MEK1 and MEK2). BRAF V600 mutations result in constitutive activation of the BRAF pathway including (b) (4) proteins MEK1 and MEK2. Inhibition of BRAF catalyzed MEK activation and kinase activity of phosphorylated MEK leads to decreased cellular proliferation in tumors with BRAF V600 mutations.

The proposed indication is for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutations as detected by an FDA-approved test.

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

The Applicant's proposed dosing regimen is 2 mg once daily (QD) by oral administration, taken either one hour before or two hours after a meal. The Clinical Pharmacology review team recommends avoiding administration of trametinib with a high-fat meal. Refer to **Section 2.5.3** regarding this recommendation.

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 2 lists the relevant completed clinical pharmacology and clinical studies included in the application.

Table 2. Summary of clinical pharmacology and clinical studies

Study Number	Study Design	Study Population	Assessment	Dosing regimen
MEK111054	*Part 1*: Phase 1, FIH, open label, dose escalation *Part 2*: Cohort expansion *Part 3*: PD characterization	*Part 1*: Solid tumors or lymphomas (n=55) *Part 2*: Melanoma, pancreatic, colorectal, non-small cell lung cancer with BRAF mutation (n=112) *Part 3*: Patients who can provide pre- and post-dose tumor biopsies (n=39)	MTD, PK, PD, clinical activity	*Part 1*: 0.125, 0.25, 0.5, 1.0, 2.0 mg for 21 days QD followed by a 7-day rest; LD on day 1 or days 1 and 2 followed by QD dosing - 6/2 mg, 10/10/3 mg, 6/6/2 mg, 8/8/2.5 mg; 2.5, 3.0, 4.0 mg QD *Part 2*: 2.0 mg or 2.5 mg QD *Part 3*: QD on days 1-15 followed by QD dosing - 0.5/2.0, 1.0/2.0, 0.5/2.5, 1.0/2.5, 2.0/2.5 mg; 2.0 or 2.5 mg QD
MEK113708	Phase 1, open label, single dose	Solid tumors (n=2)	ADME	2 mg [^{14}C]-trametinib oral solution (5 mL) containing 79 µCi radioactivity
MEK113709	Phase 1, open label, randomized, crossover with 7-day washout	Solid tumors (n=24)	Food effect	Single 2 mg dose in the fasted state or administered with a high-fat, high-calorie meal
MEK115064	Phase 1, open label, single dose	Solid tumors (n=4)	Absolute bioavailability	2 mg coadministered with IV microdose (5 µg) of [^{14}C]-trametinib
MEK112111	Phase 1B, combination with gemcitabine	Solid tumors (n=31)	RP2D, PK, safety, clinical activity	Trametinib 1, 2, 2.5 mg QD Gemcitabine 1000 mg/m^2 IV on days 1, 8, and 15 every 28 days
MEK113583	Phase 2, open label *Cohort A*: With or without prior BRAF inhibitor *Cohort B*: At least one prior chemotherapy or immunotherapy (no	BRAF V600E, V600K, or V600D mutation-positive metastatic cutaneous melanoma *Cohort A* (n=40) *Cohort B* (n=57)	Efficacy, safety, popPK	2 mg QD

Study Number	Study Design	Study Population	Assessment	Dosing regimen
	BRAF inhibitor)			
MEK114267	Phase 3, open label, randomized (2:1), active-controlled	Advanced or metastatic BRAF V600E or V600K mutation- positive melanoma	Efficacy, safety, popPK	2 mg QD trametinib or chemotherapy: dacarbazine 1000 mg/m^2 Q3W or paclitaxel 175 mg/m^2 Q3W
ADME: Absorption, distribution, metabolism, excretion; FIH: First-in-human; LD: Loading dose; PD: Pharmacodynamics; PK: Pharmacokinetics; PopPK: Population pharmacokinetics; QD: Once daily; Q3W: Every three weeks				

Trametinib plasma concentration data from Study MEK111054, MEK113583, and MEK114267 were used to develop a PopPK model [Report No. 120486] to assess the potential influence of covariates on inter-patient variability in trametinib PK parameters. Trametinib plasma concentration data from Study MEK113583 and MEK114267 were used to explore exposure-response relationships for selected efficacy and safety endpoints [Report No. 130902].

2.2.2 What is the basis for selecting the response endpoints or biomarkers and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy outcome measure of the registration trial MEK114267 was progression-free survival (PFS), as assessed by blinded independent review committee (BIRC).

Exploratory PD biomarkers indicative of MAP-kinase pathway inhibition (pERK), tumor cell proliferation (Ki67), and apoptosis induction (p27) were assessed by immunohistochemistry (IHC) staining of tumor tissue collected at baseline and day 15 of cycle 1 in Study MEK111054. See **Section 2.2.4.1** for assessment of relationships between dose and exploratory PD biomarkers.

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?

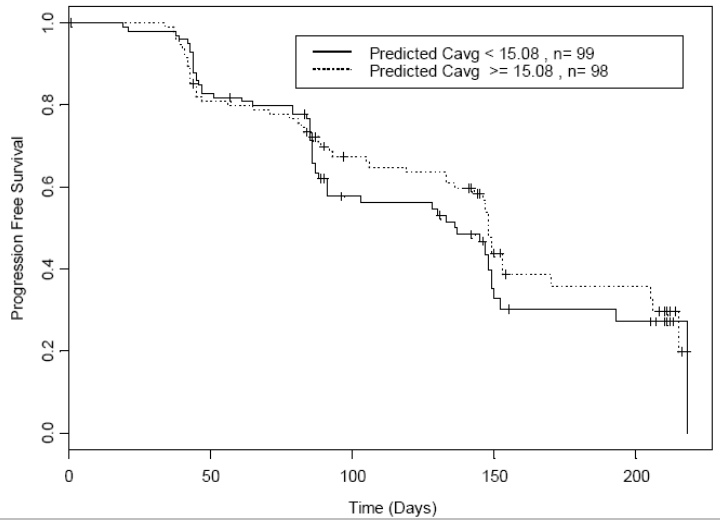
Yes. Trametinib was the major component in human plasma after oral administration and it was appropriately identified and measured to assess PK parameters (refer to **Section 2.6**). Although the M5 metabolite inhibited BRAF catalyzed MEK1 activation by binding to unphosphorylated MEK1 (U-MEK1) and cellular ERK phosphorylation at IC_{50} values similar to that of trametinib, M5 accounted for < 11% of plasma radioactivity and in blood, trametinib was the major component (> 75%), with M5 constituting < 7% of drug-related material.

2.2.4 Exposure-response

2.2.4.1 *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?*

The Pharmacometrics review concluded that based on data from Study MEK114267, there is no evident exposure-response (E-R) relationship for the efficacy endpoint of PFS as determined by a multivariate Cox-proportional hazards analysis (**Figure 2**). In addition, there is no E-R relationship for response rate (complete and partial response) (data not shown).

Figure 2. PFS by predicted average trametinib concentration (C_{avg}) for the registration trial (MEK114267)



Source: Report No. 130902, Figure 1, Page 30

Given that only one dose level of 2 mg QD was evaluated in the Phase 2 and 3 studies and the range of exposure was narrow ($C_{min,obs}$, $C_{min,pred}$, and C_{avg} ranging from 6-34 ng/mL, 7-23 ng/mL, and 10-26 ng/mL, respectively), a full exploration of E-R relationships is not possible.

Dose-response for exploratory biomarkers

Baseline and post-dose (day 15) paired tumor biopsies were obtained for IHC analysis in 22 patients who received trametinib at doses of 0.5, 1.0, or 2.0 mg QD in Study MEK111054. Higher doses resulted in greater inhibition of pERK and Ki67 and increase in p27, with the magnitude of change appearing more pronounced in patients with BRAF V600 mutation-positive melanoma versus patients with all tumor types and mutation status, although the sample size is small.

Table 3. Median percent change from baseline in H scores of exploratory biomarkers by dose

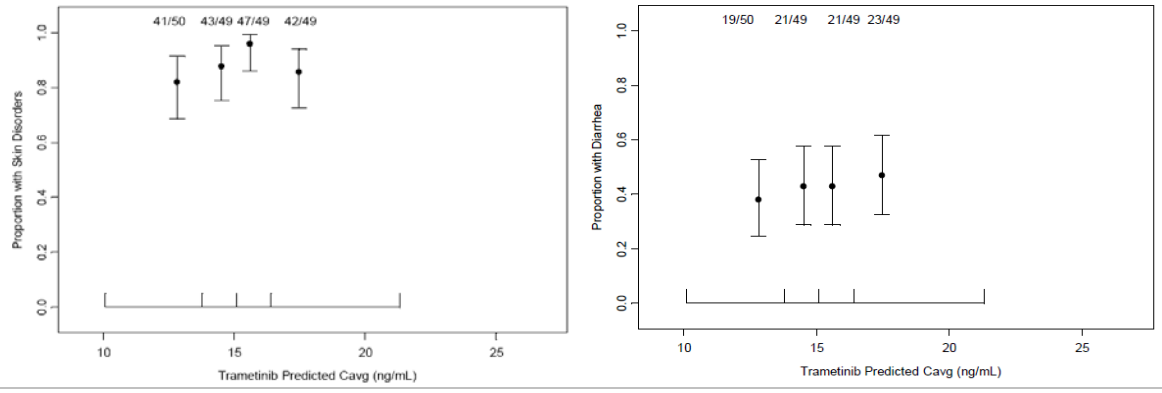
	All tumor types and mutation status[b]				**BRAF V600 mutation positive melanoma**		
	pERK	**Ki67**	**p27**		**pERK**	**Ki67**	**p27**
0.5 (n=8)	2.6	-3.9	3.6	0.5 (n=0)	N/A[a]	N/A[a]	N/A[a]
1.0 (n=4)	3.8	-2.1	35.2	1.0 (n=2)	7.5	12.5	46.1
2.0 (n=10)	-30.0[c]	-54.4	83.0	2.0 (n=4)	-61.5[d]	-83.0	171

[a] No patients with BRAF V600 mutation-positive melanoma in the 0.5 mg dose group
[b] Source: Study MEK111054 final study report, Table 12.1, Pages 1514-5
[c] n=9; [d] n=3

2.2.4.2 *What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?*

Analyses conducted by the Applicant showed that there were no evident E-R relationships for AEs including cardiac-related events, diarrhea, visual disorders, hypertension, skin-related events (**Figure 3**), hepatic disorders, and pneumonitis. Patients with a higher C_{avg} appear to have a higher incidence of diarrhea (**Figure 3**).

Figure 3. Proportion of patients with skin-related adverse events (left) and diarrhea (right) versus predicted average trametinib concentration (C_{avg}) for the registration trial (MEK114267)



Source: Report No. 130902, Figure 6, Pages 42-43

Three cases of chorioretinopathy were reported in patients receiving loading doses of trametinib (6/6/2 mg [n=6] and 10/10/3 mg [n=4]) or trametinib 4 mg QD [n=3] in Study MEK111054, suggesting that these ocular events may be related to initial higher exposure to trametinib after loading doses.

2.2.4.3 *Does this drug prolong the QT or QTc interval?*

The Applicant included an analysis of QT/QTc intervals in 50 patients with solid tumors from Study MEK111054. The final study report for a dedicated cardiovascular safety study (MEK114655) will be submitted post marketing.

The predicted median change in QTcP at mean steady state C_{max} (22 ng/mL) following 2 mg QD dosing was 2.2 ms (90% CI: 0.2, 4.0). At the highest C_{max} observed following 2 mg QD and the 10/10/3 mg loading dose regimen, the median change in QTcP was 3.2 ms (0.3, 6.0) and 8.0 ms (0.7, 14.9), respectively. Using a non-linear mixed effects model, the Applicant determined that the slope of the relationship between QT interval corrected for heart rate with a population factor (QTcP) and trametinib concentrations was not statistically significant with 95% CI including the null value (slope of 0.0987 [-0.0001, 0.197] ms per ng/mL).

2.2.4.4 *Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and is there any unresolved dosing or administration issue?*

The rationale for the Applicant's proposed dosing regimen of 2 mg QD was based on the following:

- Response rate (partial response and complete response) in BRAF V600 mutation-positive melanoma patients of 44% (7/16) at 2 mg QD compared to 36% (5/14) at 2.5 mg QD.
- Less AEs ≥ Grade 3, rash or skin-related toxicities ≥ Grade 2, rate of ocular events, and incidence of AEs leading to dose reductions at 2 mg QD compared to 2.5 or 3 mg QD.
- Greater inhibition of pERK and Ki67 and increase in p27 biomarkers at 2 mg versus doses of 0.5 or 1.0 mg. Mean trametinib concentrations following 2 mg QD dosing exceed the pre-clinical target concentration of 10.4 ng/mL over the 24-hour dosing interval.

Given that only one dose level was studied in the Phase 2 and 3 trials and evident E-R relationships for efficacy and safety were not found with the 2 mg QD dose regimen, a conclusion on the appropriateness of the proposed dose regimen based on a relationship between dose-concentration-response cannot be drawn.

The Applicant proposes in the labeling that trametinib should be administered one hour before or two hours after a meal, consistent with fasting conditions in all the clinical trials. Given that a single dose of trametinib taken with a high-fat meal resulted in a 24% decrease in systemic exposure and the clinical efficacy of trametinib was established under fasted conditions, the review team recommends avoiding administration of trametinib with a high-fat meal to preserve clinical efficacy while providing a less restricted dosing condition for better compliance. Refer to **Section 2.5.3** for the results of the food effect study and **Section 3** for recommended labeling modifications.

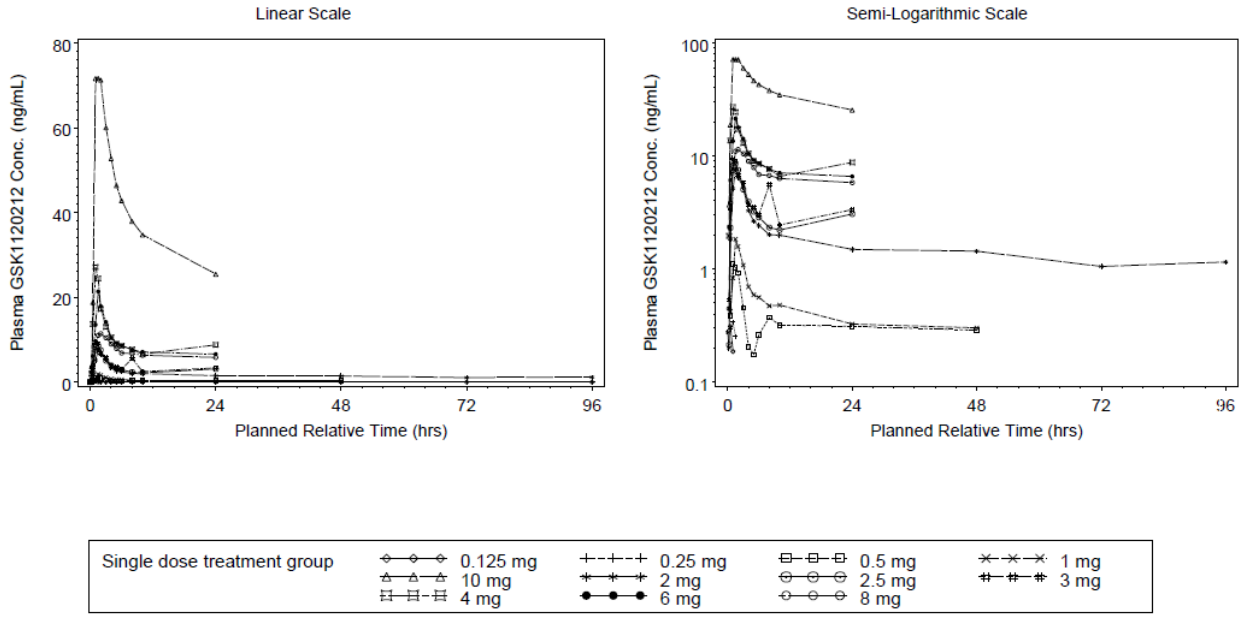
2.2.5 What are the PK characteristics of the drug?

2.2.5.1 *What are the single dose and multiple dose PK parameters?*

The increase in exposure (AUC) is greater than dose proportional after a single dose of 0.125 to 10 mg and dose-proportional following repeat doses of 0.125 to 4 mg. Trametinib has approximately 6-fold accumulation with 2 mg repeat QD dosing. The estimated elimination half-life based on the population PK model is 3.9 to 4.8 days.

Single dose PK parameters: In the FIH Study MEK111054, PK samples were collected up to 24 or 96 hours after the first dose of 0.125 to 10 mg trametinib and mean concentration-time profiles are shown in **Figure 4**. Single dose PK parameters of trametinib were determined using noncompartmental analyses and summarized in **Table 4**.

Figure 4. Mean concentration-time profiles after a single dose of trametinib (day 1)



Source: Study MEK111054 final study report, Figure 2, Page 118

Table 4. PK parameters following a single dose of trametinib (day 1)

Dose (mg)	N	AUC (0-24) (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)
0.125	1[a]	NA	0.622	0.50
0.25	1[a]	NA	0.339	1.03
0.5	2[b]	NA, 9.69	0.85, 1.21	1.5, 1.5
1	2	13.4, 12.2	1.71, 1.96	1.5, 1.5
2	3	54.4 (31%) (44.2-77.4)	6.68 (25%) (5.40-8.81)	1.5 (1.5-2.0)
2.5	9	66.4 (26%)[c] (47.3-96.7)	9.32 (29%) (6.70-16.2)	1.5 (1.0-2.0)
3	12	64.9 (51%)[d] (27.6-122)	9.30 (81%) (2.82-22.9)	1.25 (0.5-3.0)
4	3	218 (25%) (167-273)	25.8 (42%) (16.2-34.2)	1.0 (1.0-1.0)
6[e]	10	178 (51%) (96.7-320)	20.1 (65%) (6.91-37.2)	1.5 (1.1-8.1)
8[e]	7	139 (63%) (62.4-308)	11.9 (84%) (4.28-32.0)	3.0 (1.0-24.0)
10[e]	4	880 (12%) (772-981)	78.2 (14%) (65.1-87.8)	1.5 (1.0-2.0)

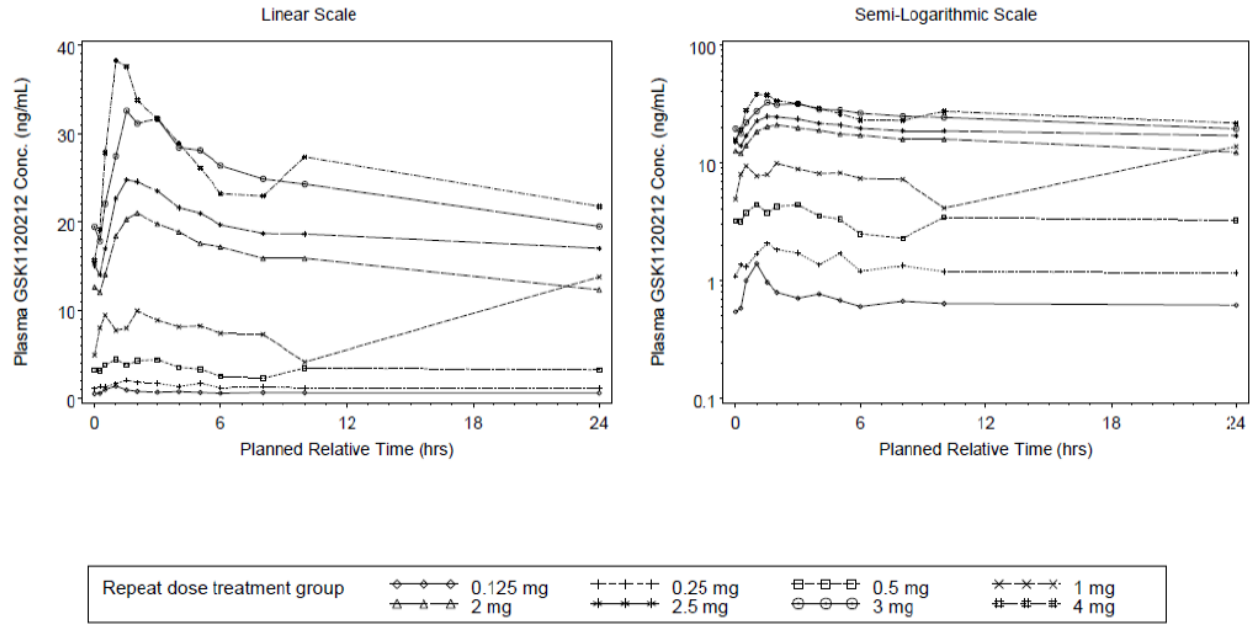
Data Source: Table 11.10 and Listing 11.3
Abbreviations: NA = Not available, BQL=Below quantifiable limit, CVb%= between subject coefficient of variation
Note: Pharmacokinetic parameters listed for individuals if subject number <=2; listed as geometric mean, (CVb%) and range if subject number > 2; Tmax reported as median (range); T1/2 and AUC(0-∞)not displayed as a terminal phase could not be identified

a. Subjects in the low dose cohorts had limited samples (≤3 quantifiable samples) and AUC(0-24) is not reported; One subject (1201; dose=0.125mg) had BQL for all samples and subject data was not included in PK analysis.
b. 1304 omitted from AUC(0-24) calculation due to lack of data in absorption and terminal phase; listed as NA.
c. For 2.5 mg dose, n=7 for AUC(0-24).
d. For 3 mg dose, n=11 for AUC(0-24).
e. Administered as loading dose on Day 1.

Source: Study MEK111054 final study report, Table 66, Page 117

Multiple dose PK parameters: In the FIH Study MEK111054, PK samples were collected up to 24 hours post-dose on day 15 and mean concentration-time profiles after 0.125 to 4 mg QD dosing of trametinib are shown in (**Figure 5**). Multiple dose PK parameters of trametinib were determined using noncompartmental analysis and summarized in **Table 5**.

Figure 5. Mean concentration-time profiles after QD doses of trametinib (day 15)



Source: Study MEK111054 final study report, Figure 3, Page 121

Table 5. PK parameters following repeat doses of trametinib (day 15)

Dose (mg)	N	AUC(0-24) (ng.h/mL)	Cmax (ng/mL)	Tmax (hr)	C24 (ng/mL)	AR	T1/2, eff (hr)
0.125	2	17.8, 14.6	1.21, 1.58	1.0, 1.5	0.66, 0.58	NA, NA	NA, NA
0.25	1	31.4	2.08	1.5	1.16	NA	NA
0.50	2	60.2, 98.9	3.91, 5.38	2.08, 1.0	2.21, 4.29	NA, 10.2	NA, 161
1	2	245, 95.1	15.8, 7.96	0.75, 1.5	8.44, 19.1	18.3, 7.80	296, 121
2[a, b]	13	370 (22%) (256-500)	22.2 (28%) (14.0-32.9)	1.75 (1.0-3.0)	12.1 (19%) (8.26-16.9)	5.97 (33%) (4.03-11.5)	90.2 (36%) (58.4-183)
2.5[a,c]	16	410 (41%) (215-865)	24.1 (49%) (12.4-63.2)	2.0 (1.0-10.2)	15.1 (52%) (6.86-40.5)	4.39 (83%) (1.02-13.1)	57.6 (137%) (4.01-210)
3[a,d]	16	540 (38%) (261-968)	33.4 (41%) (15.6-60.9)	2.05 (0.5-10.0)	17.9 (44%) (7.77-35.5)	5.93 (85%) (1.50-18.0)	86.1 (106%) (15.1-291)
4	3[e]	946, 546[e]	62.8[e], 43.8	1.0, 1.5	17.0 (103%) (8.01-42.8)	3.46[e], 2.40	48.8, 30.9

Data Source: Table 11.11 and Listing 11.3

Abbreviations: AR = Accumulation Ratio; NA = Not applicable; CVb%=between subject coefficient of variation; T1/2, eff =Effective Half-Life and calculated as follows: T1/2, eff= -0.693*tau/ln(1-(1/AR)

Note: Pharmacokinetic parameters listed for individuals if subject number <=2; listed as geometric mean (CVb%) and range if subject number > 2; Tmax is reported as median (range).

a. Contains subjects at both loading and continuous dosing regimens.
b. For 2 mg dose, n=11 for AUC(0-24), T1/2, eff, and AR; n=12 for Cmax and Tmax.
c. For 2.5 mg dose, n=14 for AR and T1/2, eff.
d. For 3 mg dose, n=13 for AR and T1/2, eff; n=14 for AUC(0-24) and Tmax.
e. Subject 1210 omitted from analysis (exception of C24) due to drug being withheld and incomplete dosing information so PK parameters only calculated on 2 subjects.

Source: Study MEK111054 final study report, Table 67, Page 120

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

Trametinib has not been studied in healthy volunteers.

2.2.5.3 *What are the characteristics of drug absorption?*

In the absolute bioavailability study, [^{14}C]-trametinib was administered as an intravenous (IV) push 1.5 hours post-oral dose to coincide with the t_{max} of trametinib following oral administration. PK samples were collected up to 240 hours post-oral dose and PK parameters for unlabeled trametinib and [^{14}C]-trametinib are shown in **Table 6**. The mean absolute bioavailability of trametinib is 72.3% (90% CI: 50%, 105%), determined by the ratio of dose-normalized $AUC_{0\text{-last}}$ observed after a 2 mg oral dose of unlabeled trametinib and a 5 µg IV microdose of [^{14}C]-trametinib. The geometric mean $AUC_{0\text{-last}}$ and $AUC_{0\text{-}\infty}$ were 289- and 337-fold lower, respectively, after an IV microdose relative to the 2 mg oral dose (for a 400-fold difference in dose).

Table 6. PK parameters following a 2 mg oral dose of unlabeled trametinib and a 5 µg IV microdose of [^{14}C]-trametinib

Parameter Units	GSK1120212 (Oral)	[^{14}C]GSK1120212 (IV)	Total Radioactivity[3] (IV)
Tmax[2] (hr)	1.50 (1.00, 1.58)	0.08 (0.08, 0.08)	0.08 (0.08,0.08)
Cmax[1] (ng/mL)	8.03 [1.82, 35.4] (2.56, 24.31)	0.105 [0.038, 0.289] (0.044, 0.190)	0.118 [0.053, 0.262] (0.058, 0.177)
AUC(0-t)[1] (ng*hr/mL)	248 [78.1, 790] (99.8, 580)	0.858 [0.368, 2.00] (0.546, 1.76)	1.68 [0.734, 3.83] (1.18, 3.60)
AUC(0-∞) (ng*hr/mL)	525 [300, 917]) (333, 783)[1]	1.56 [0.965, 2.51] (1.26, 2.39)[1]	4.92[4], 5.91[4]
t1/2 (hr)	264 [106, 655] (130, 481)[1]	229 [125, 419] (144, 348)[1]	643[4], 176[4]
CL or CL/F[1] (L/hr)	3.81 [2.18, 6.66] (2.56, 6.01)	3.21 [1.99, 5.18] (2.09, 3.97)	NA
Vd[1] (L)	ND	1060 [365, 3073] (435, 1985)[1]	ND

Data Source: Table 11.4, Table 11.5, Table 11.6
Abbreviations: IV, intravenous; max, maximum; min, minimum; NA, not applicable; ND, not determined
1. Results are presented as geometric mean [95% CI] (min, max) for n >2.
2. Tmax results are presented as median (min, max)
3. Total radioactivity concentration units are ng equivalents GSK1120212/mL
4. Elimination half-life and AUC(0-∞) for Total Radioactivity estimated in 2 of 4 subjects; individual subject values are listed.

Source: Study MEK115064 final study report, Table 6, Page 28

Administration of a single 2 mg dose of trametinib with a high-fat, high-calorie meal resulted in decreased rate and extent of absorption, indicated by a 70% and 24% decrease in C_{max} and $AUC_{0\text{-last}}$, respectively, as compared to fasted conditions. Refer to **Section 2.5.3**.

2.2.5.4 *What are the characteristics of drug distribution?*

Following a 5 µg IV dose of trametinib, the volume of distribution is determined to be 1060 L. Given that CL and $t_{1/2}$ after a 5 µg IV microdose relative to the 2 mg oral dose were comparable (**Table 6**), this volume of distribution determined by a subtherapeutic IV dose of 5 µg is considered reliable. The apparent central (V_c/F) and peripheral volume of distribution (V_p/F) as determined by the population PK analysis is 214 L and 568 L, respectively.

Trametinib is 97.4% and 96.2% bound to human plasma proteins (type of plasma proteins, albumin or alpha glycoprotein, is unspecified) at concentrations of 500 ng/mL and 5,000 ng/mL, respectively [Study UH2007/00095].

The mean blood to plasma ratio in human blood *in vitro* is concentration-dependent, ranging from 3.4, 3.2, to 1.1 at concentrations of 1, 10, and 50 ng/mL, respectively [Study 11DMM044]. Results from the mass balance study (MEK113708) showed that there is preferential association of radioactivity with red blood cells, reaching a plateau three hours post-dose with a blood to

plasma concentration ratio of approximately 3.

2.2.5.5 *Does the mass balance study suggest renal or hepatic as the major route of elimination?*

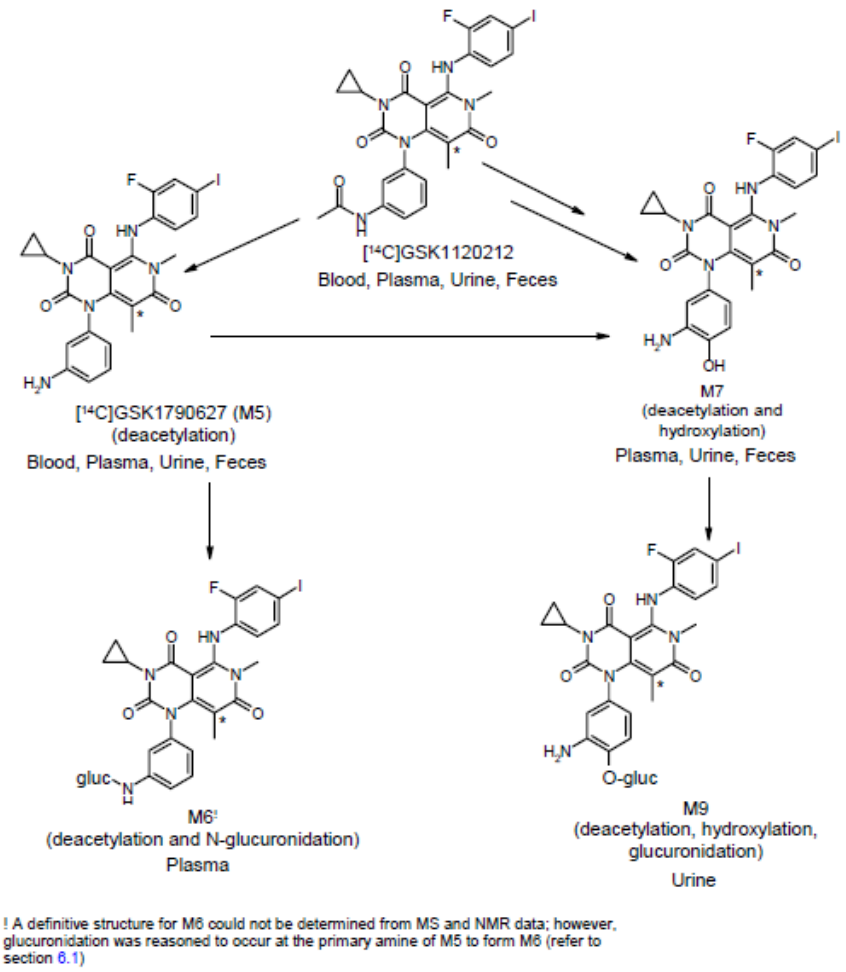
The mass balance study (MEK113708) in two patients with solid tumors who received a single dose of 2 mg [^{14}C]-trametinib as an oral solution and whose blood, urine, and feces samples were collected up to 240 hours (10 days) post-dose, suggests that hepatic elimination appears to be the major route of elimination.

2.2.5.6 *What are the characteristics of drug metabolism?*

Results from an *in vitro* study [07DMM114] using human cDNA expressed isozymes (CYP1A2, 2C8, 2C9, 2C19, 2D6, and 3A4) and human liver microsomes showed formation of metabolites in the absence of NADPH, indicating that trametinib primarily undergoes non-CYP450 mediated metabolism. Incubations with microsomal protein and recombinant CYPs resulted in metabolism < 7% of [^{14}C]-trametinib. Metabolites formed from NADPH-dependent oxidative metabolism accounted for approximately 1% and 3% of [^{14}C]-trametinib radioactivity in human liver microsomes and recombinant CYP450 enzymes, respectively, indicating that CYP450-mediated oxidative metabolism is a minor pathway. CYP3A4 was the only isoenzyme of those tested that appears to be involved in the formation of metabolites (M7, M12, M13, M16, M17, M22), as shown by the absence of metabolites in incubations with azamulin (CYP3A4 inhibitor) and presence of metabolites in incubations with recombinant CYP3A4.

Trametinib is metabolized via deacetylation to form M5; deacetylation in combination with hydroxylation to form M7; glucuronidation of M5 to form M6, and glucuronidation of M7 to form M9 (**Figure 6**). The specific enzyme responsible for deacetylation has not been identified; however the Applicant claims that deacetylation is likely mediated by hydrolytic esterases.

Figure 6. The metabolism of trametinib after a single radiolabeled dose in two patients



Source: Study 11DMM005 final study report, Figure 7, Page 35

After a single oral 2 mg dose of [^{14}C]-trametinib, plasma samples were collected at 2, 6, 24, and 48 hours post-dose for metabolite profiling in two patients (Study MEK113708). The percentages of plasma radioactivity for unchanged [^{14}C]-trametinib, M5, M6, and M7 in both patients are shown in **Table 7**. In blood, trametinib was the major component (>75%), with M5 constituting <7% of drug-related material [Report No. 11DMM005].

Table 7. Major components in plasma after a single 2 mg oral dose of [^{14}C]-trametinib[†]

	Patient 1001	Patient 1004
Parent	25.7-42.5%	63.5-71.8%
M5	<LLQ-9.4%	6.5-10.9%
M6	19.0-23.7%	<LLQ-9.63%
M7	<LLQ-14.2%	<LLQ-13.0%

[†] Data are presented as a range of the lowest to highest % plasma radioactivity at 2, 6, 24, and 48 hours post-dose
LLQ: Lower limit of quantitation

Source: Report 11DMM005, Table 2, Pages 21-22

After administration of trametinib 10 mg on days 1 and 2, followed by 3 mg on days 3 to 15, plasma and urine samples were pooled over 24 hours for analysis of metabolites in two patients (Study MEK111054). Trametinib was the major component (≥75%), with M5 and M7 each constituting approximately 10% of drug-related material in plasma [Report No. 09DMM056].

The M5 metabolite inhibited BRAF catalyzed MEK1 activation by binding to unphosphorylated MEK1 (U-MEK1) and cellular ERK phosphorylation at IC_{50} values similar to that of trametinib (**Table 8**). However, M5 accounted for <11% of plasma radioactivity and in blood, trametinib was the major component (>75%), with M5 constituting <7% of drug-related material.

Table 8. Enzymatic and cellular activities of trametinib and M5

	Enzyme IC_{50} (nM)		SK-MEL-28	
compound number	p-MEK1	U-MEK1	pERK IC_{50} (nM)	Proliferation IC_{50} (nM)
GSK1120212	14.10 ± 0.35	0.72 ± 0.01	1.6 ±0.6	0.9 ±0.3
GSK1790627	34.55 ± 6.15	1.01 ± 0.05	2.0 ±0.1	1.7 ±0.1

GSK1120212: Trametinib
GSK1790627: M5

Source: Report 2012N139081, Table 1, Page 13

2.2.5.7 *What are the characteristics of drug excretion?*

Results from the mass balance study (MEK113708) showed that 48.2% and 37.1% of [^{14}C]-GSK1120212 was recovered from excreta over 240 hours in two patients (1001 and 1004, respectively). Following oral administration of [^{14}C]-trametinib, >80% of excreted radioactivity was recovered in the feces while <20% of excreted radioactivity was recovered in the urine (**Table 9**). Approximately <0.1% of the excreted dose was recovered as parent in the urine (**Table 10**).

Table 9. Percentage of [^{14}C]-GSK1120212 recovered from excreta (urine and feces)

	Patient 1001	Patient 1004
Total [^{14}C]-GSK1120212 recovered from excreta	48.2%	37.1%
Feces		
% of excreted dose	81.3%	94.3%
% of oral dose	39.2%	35.0%
Urine		
% of excreted dose	18.6%	5.6%
% of oral dose	9.0%	2.1%
Source: Study MEK113708 final study report		

Table 10. Major radiolabeled components of excreted dose found in urine and feces[†‡]

	Urine	Feces
Parent	0.02%, *	27.4%, 45.0%
M5	1.78%, *	16.3%, <LLQ
M7	4.48%, *	22.4%, <LLQ
M9	0.08%, *	ND

[†] Results are shown for Patient 1001, Patient 1004
[‡] Results are approximate as information on parent and metabolite identification in urine were missing at time intervals of 6-12h, 12-24h, 72-96h, 96-120h, 144-168h, 192-216h; and time intervals of 0-24h, 24-48h, 96-120h, 144-168h, 192-216h in feces
* Not characterized due to low levels of radioactivity
LLQ: Lower limit of quantitation; ND: Not detected

Source: Report 11DMM005, Table 4 and 5, Pages 25-28

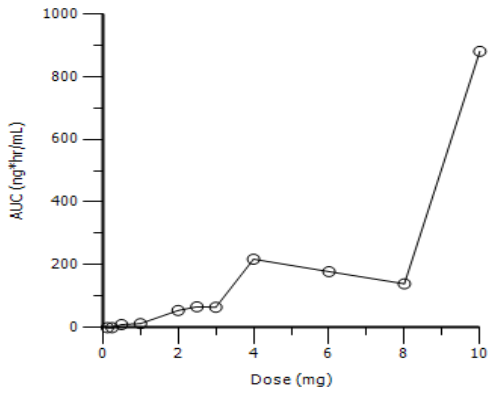
Additional metabolites, M12, M13, M15, and M17, were found in urine samples collected over 24 hours following administration of trametinib 10 mg on days 1 and 2, and 3 mg on days 3 to 15.

Elimination
CL/F of trametinib determined by noncompartmental analyses is 5.4 L/hr, similar to the apparent clearance of 4.9 L/hr in women and 6.2 L/hr in men estimated using a population PK analysis. The plasma IV CL is 3.21 L/hr, which represents approximately 1% of liver blood flow (assuming human liver blood flow of 81 L/hr and a blood to plasma ratio of 3.0). The moderate to high absolute bioavailability and low CL suggest low hepatic extraction of trametinib. The estimated elimination half-life based on the population PK model is 3.9 to 4.8 days.

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

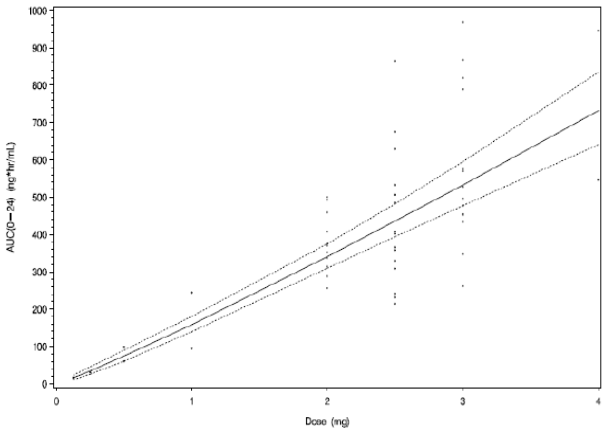
After single doses of 0.125 to 10 mg, $AUC_{0\text{-}24h}$ of trametinib is generally linear up to 3 mg (**Figure 7**), and greater than dose proportional at higher doses as indicated by a mean slope (90% CI) of 1.30 (1.08, 1.52) using a power model. C_{max} increases dose-proportionally with a mean slope (90% CI) of 1.08 (0.90, 1.25). Both $AUC_{0\text{-}24h}$ and C_{max} are dose proportional after repeat QD doses of 0.125 to 4 mg as indicated by a mean slope (90% CI) of 1.10 (1.00, 1.21) and 1.03 (0.91, 1.15), respectively, using a power model (**Figure 8**).

Figure 7. Dose-exposure relationship following single doses of 0.125 to 10 mg trametinib



Source: Study MEK111054 final study report, Table 11.10, Pages 1468-71

Figure 8. Dose proportionality of trametinib after repeat QD doses



Source: Study MEK111054 final study report, Figure 4, Page 122

2.2.5.9 *How do the PK parameters change with time following chronic dosing?*

The mean accumulation ratio (day15/day1) with repeat doses of 2 mg trametinib is approximately 6.0. Refer to **Table 4** and **Table 5** for single and multiple dose PK parameters.

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

Trametinib has not been studied in healthy volunteers. Inter-patient variability on day 15 is 22% in AUC and 28% in C_{max}. Based on the population PK analysis, the inter-patient variability in apparent clearance (CL/F) and apparent central volume of distribution (V_c/F) was 24% and 77%, respectively.

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

datasets were Caucasian (97%), and did not receive CYP3A4 inhibitors (97%) or inducers (99%).

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

No formal studies have been conducted to assess the effect of age, race, weight, height, or organ dysfunction on exposure and response to trametinib. The Applicant's population PK (popPK) analysis, verified by our pharmacometrics review, did not identify clinically important effects of body weight, age, gender, mild and moderate renal impairment, and mild hepatic impairment as covariates on clearance or volume of distribution of trametinib.

Relationship between Gender and Exposure

The popPK analysis showed that CL/F of trametinib in men was 26% higher than that in women (6.2 vs. 4.9 L/hr), which is not considered to be a clinically important difference requiring dose modification. The difference in body weight between men and women may contribute in part to this observed gender difference.

Relationship between Race and Exposure

Assessment of the effect of race using a popPK analysis is not possible, as the majority of the patients (97%) in the clinical trials are Caucasian.

Relationship between Weight and Exposure

Patients with minimum or maximum body weight were estimated to have AUC, C_{max}, and trough concentration (C_{trough}) within 15%, 30%, and 10%, respectively, of the typical values of a median body weight of 79 kg. This difference is not considered to be clinically important, suggesting that the fixed (flat) dosing approach is acceptable.

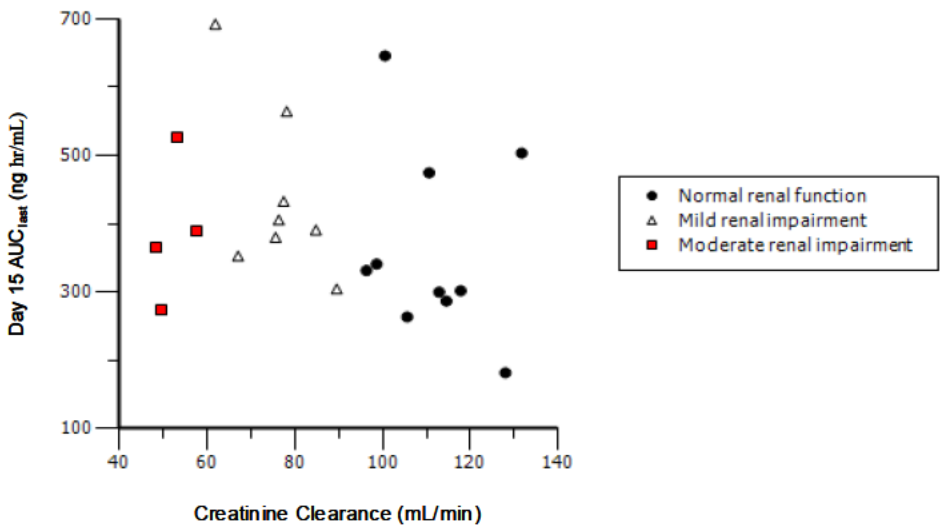
Relationship between Age and Exposure

The popPK analysis showed that age (<65 years [n=351, 71%], 65-75 years [n=114, 23%], and ≥75 years [n=28, 6%]) has no notable influence on trametinib PK.

Relationship between Renal Impairment and Exposure

The Applicant did not conduct a formal study to assess the effect of renal impairment on the PK of trametinib. Results from the mass balance study (MEK113708) showed that <20% of the excreted dose was recovered in the urine, indicating that renal excretion is a minor route of elimination. No differences in trametinib exposure (AUC) were observed in patients with mild to moderate renal impairment relative to patients with normal renal function (**Figure 9**).

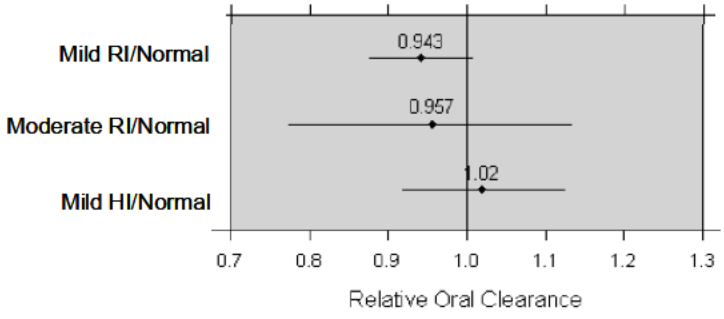
Figure 9. Exposure of trametinib by renal function



Data includes patients from Study MEK111054 who received 2 mg trametinib. Normal renal function (CLcr ≥ 90 mL/min); mild renal impairment (CLcr 60-89 mL/min); moderate renal impairment (CLcr 30-59 mL/min).

Based on a popPK analysis which included patients with mild (n=223, GFR 60 to <90 mL/min/1.73 m^2) or moderate (n=35, GFR 30 to <60 mL/min/1.73 m^2) renal impairment, there was no clinically important effect of mild and moderate renal impairment on the apparent clearance of trametinib (**Figure 10**). The PK of trametinib has not been characterized in patients with severe renal impairment.

Figure 10. Apparent clearance of trametinib in patients with organ impairment versus normal renal or hepatic function



HI: Hepatic impairment
RI: Renal impairment

Relationship between Hepatic Impairment and Exposure

The Applicant did not conduct a formal study to assess the effect of hepatic impairment on the PK of trametinib. Based on a popPK analysis which included patients with mild hepatic impairment (n=64, total bilirubin ≤ULN and AST >ULN or total bilirubin >1.0-1.5 x ULN and any AST), there was no clinically important effect of mild hepatic impairment on the apparent clearance of trametinib (**Figure 10**). The PK of trametinib has not been studied in patients with moderate or severe hepatic impairment.

Genetics

Differences in clinicopathological features have been observed in patients with BRAF V600 mutated melanoma according to the V600 mutation (e.g., V600E vs. V600K), which may have implications for patient selection for treatment with trametinib, other MEK inhibitors, or BRAF inhibitors. The purpose of this review is to retrospectively evaluate whether BRAF V600 mutations correlate with demographic or disease-specific factors and whether tumor response in patients with metastatic melanoma enrolled in Studies MEK114267 and MEK113583 differs by the specific V600 mutation. Few patients with BRAF V600K melanoma (N=52, 7.5%) were enrolled in these two trials. Our assessment showed that a greater proportion of patients with BRAF V600K melanoma were male (V600E, 54% vs. V600K, 79%, P=0.0007) and older at initial diagnosis (median age: V600E, 48 years vs. V600K, 57 years, p<0.0001) compared to patients with the more common V600E mutation; similar differences have been observed in published retrospective analyses. These features were not prognostic in these trials and thus, not likely to confound assessments of activity. Trametinib exhibited antitumor activity in nonclinical BRAF V600 mutated melanoma models and in clinical trials of patients with BRAF V600E and V600K mutation-positive melanoma without prior treatment with a BRAF inhibitor. These results support an indication for treatment of BRAF V600E and V600K metastatic melanoma providing that the clinical and statistical reviews determine a favorable benefit-risk. Additional studies might be warranted to determine the association of less common BRAF V600 mutations with clinicopathological features of melanoma and sensitivity to MEK and BRAF inhibitors. Refer to the attached Genomics review in **Section 4.2**.

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, what dosage regimen adjustments, if any, are recommended for each of these groups?

No dosage regimen adjustments are recommended as no clinically important PK differences have been identified in specific patient populations. The Applicant is requested to conduct a clinical trial to determine the appropriate trametinib dose in patients with hepatic impairment under a PMR.

2.3.2.1 *Elderly*

Age was not identified as a significant covariate influencing trametinib PK based on a popPK analysis which included patients <65 (n=351, 71%), 65-75 (n=114, 23%), and ≥75 (n=28, 6%) years of age.

2.3.2.2 *Pediatric*

Trametinib has been granted an orphan drug status for the proposed indication. The Applicant requests a waiver for pediatric studies stating that studies are impossible or highly impractical, as the number of pediatric patients with the proposed indication is extremely small. Potential trametinib pediatric development plans were discussed at the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee (ODAC) meeting held on December 4, 2012.

2.3.2.3 *Gender*

Gender was not identified as a significant covariate influencing trametinib PK based on a popPK analysis which included 203 (41%) women and 290 (59%) men. The popPK analysis showed that CL/F of trametinib in men was 26% higher than that observed in women (6.2 vs. 4.9 L/hr), which is not considered to be a clinically important difference requiring any gender-related dose adjustment. The difference in body weight between men and women may contribute in part to this observed gender difference.

2.3.2.4 *Race/Ethnicity*

The effect of race on trametinib PK was not evaluated given that the majority of patients in the clinical trials are Caucasian (97%).

2.3.2.5 *Renal Impairment*

Renal impairment was not identified as a significant covariate influencing trametinib PK based on a popPK analysis which included patients with normal renal function (GFR ≥90 mL/min/1.73m^2, n=231, 47%), mild renal impairment (GFR 60 to <90 mL/min/1.73m^2, n=223, 45%), and moderate renal impairment (GFR 30 to <60 mL/min/1.73m^2, n=35, 7%). Given that renal excretion is not the major elimination pathway, a PMR for a study in patients with severe renal impairment is not warranted. Refer to **Section 2.3.1**.

2.3.2.6 *Hepatic Impairment*

Hepatic impairment was not identified as a significant covariate influencing trametinib PK based on a popPK analysis which included patients with normal hepatic function (total bilirubin and AST ≤ULN, n=429, 87%) and mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin >1.0-1.5 x ULN and any AST, n=64, 13%). Based on the results of the mass balance study suggesting that hepatic elimination is the major route of elimination, the Applicant is requested to conduct a clinical trial to determine the appropriate trametinib dose in patients with hepatic impairment under a PMR. Refer to **Section 2.3.1**.

2.3.2.7 *What pregnancy and lactation use information is there in the application?*

The proposed labeling states that trametinib can cause fetal harm when administered to pregnant women, and lists trametinib under pregnancy category D.

It is not known whether trametinib is excreted in human milk. The proposed labeling states that a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

2.3.3 Does genetic variation impact exposure and/or response?

Refer to **Section 2.3.1** and the attached Genomics review in **Section 4.2**.

2.3.4 Immunogenicity

Not applicable. Trametinib is a small molecule drug.

2.4 EXTRINSIC FACTORS

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

The effects of extrinsic factors such as herbal products, diet, smoking and alcohol use on the dose-exposure and/or dose-response for trametinib were not assessed given the small likelihood that these factors would have a clinically important effect on trametinib PK due to minimal involvement of CYP enzymes in its metabolic pathway.

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.

2.4.2.2 *Is the drug a substrate of CYP enzymes?*

No, trametinib undergoes primarily non-CYP450 mediated metabolism.

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

Inhibition

As shown by the R_1 values calculated with clinically relevant exposure (maximal steady-state concentration of 22 ng/mL or 0.04 μM) (**Table 11**), trametinib did not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 based on an *in vitro* study using pooled human liver microsomes [Study 07DMM083]. These R_1 values of < 1.1 (with the exception of that calculated for CYP2C8) suggest that *in vivo* drug interaction studies are not necessary. An *in vivo* study to evaluate the drug interaction potential of trametinib with co-administered drugs that are CYP2C8 substrates are not warranted given that the R_1 value for CYP2C8 is slightly > 1.1, and substrates of CYP2C8 are limited and not relevant for the indicated patient population.

Table 11. IC_{50} and calculated R_1 values for trametinib inhibition of CYP activities in human liver microsomes

P450 Isozyme	Substrate	Trametinib IC_{50} (µM)	R_1 value ($1+I/K_i$)
CYP1A2	Phenacetin	> 10	1.008
CYP2A6	Coumarin	> 10	1.008
CYP2B6	Bupropion	> 10	1.008
CYP2C8	Rosiglitazone	0.34	1.235
CYP2C9	Diclofenac	4.1	1.020
CYP2C19	S-mephenytoin	5.0	1.016
CYP2D6	Bufuralol	>10	1.008
CYP3A4	Atorvastatin, nifedipine	> 10	1.008
Calculation of R values based on maximal steady-state concentration of 22 ng/mL or 0.04 µM [I] K_i assumed to be $IC_{50}/2$ for competitive inhibition			

Trametinib is not a time dependent inhibitor of CYP1A2, 2C9, 2C219, 2D6, or 3A4, as there was no apparent increase in percent inhibition or decrease in IC_{50} values with pre-incubation in the presence of NADPH.

Induction

As shown by the R_3 values using the basic model (**Table 12**), trametinib has the potential to induce CYP3A4, but not 2B6 and 2C8 based on an *in vitro* study with human hepatocytes from three donors [Study 07DMM105].

Table 12. EC_{50}, E_{max}, and calculated R_3 values for trametinib induction of CYP activities in human hepatocytes

P450 Isozyme	Substrate	EC_{50} (µM)	E_{max} (%)	Mean R_3 value ($1/(1+d \times E_{max} \times [I]/(EC_{50}+[I]))$)[a]
CYP1A2	Omeprazole	NA[b]	NA[b]	-
CYP2B6	Phenytoin	ND[c]	75	-
CYP3A4	Rifampicin	2.7	37.3	0.54[d]
[a] Calculation of R values based on maximal steady-state concentration of 22 ng/mL or 0.04 µM [I] [b] NA: Not available. No notable increase in CYP1A2 mRNA [c] ND: Not determined because the dose-response did not reach a plateau [d] Mean of individual donor R_3 values of 0.42, 0.68 and 0.53				

Investigation with a mechanistic model showed that the predicted fold change in midazolam (sensitive CYP3A substrate) AUC was 0.5 (< 0.8) with consideration of both hepatic and gut

components, which further indicates that trametinib has the potential to induce CYP3A4 (**Table 13**).

Table 13. AUC ratio of midazolam (sensitive CYP3A probe substrate)

Trametinib concentration	Extrapolated fold Change in AUC		
	Midazolam		
	Hepatic Component	Gut Component	Combined Gut & Hepatic Component
Estimated Unbound Hepatic Inlet Concentration	0.97	0.50	0.48

Source: Response to information request (SN 29)

Although *in vitro* results showed that trametinib has the potential to induce CYP3A4, cross-study comparisons suggest that oral administration of 2 mg trametinib QD with everolimus (sensitive CYP3A4 substrate) 5 mg QD had no clinically important effect on the exposure (AUC and C_{max}) of everolimus *in vivo* (**Table 14**). Therefore, a PMR for a drug interaction study to evaluate the effect of trametinib as an inducer of a CYP3A4 probe substrate is not warranted.

Table 14. Steady-state PK parameters of everolimus following monotherapy and in combination with trametinib

	AUC_{0-6h} (%CV) [Range]	**C_{max} (%CV) [Range]**	**C_{trough} (%CV) [Range]**
Study MEK112110[a] (trametinib 2 mg QD plus everolimus 5 mg QD) (n=5; cohort 6)	113 (26.0) [75.9-148]	38.5 (31.0) [27.9-57.3]	5.38 (51.9) [2.8-8.0]
Everolimus 5 mg QD monotherapy[b] (n=4)	97.1 (33.3) [56.6-129]	30.2 (31.1) [18.0-38.7]	5.28[c] (41.6) [3.1-7.3]
[a] PK samples collected on day 15 at pre-dose (0), 1, 2, 4, and 6 hours post-dose [b] Data from Study C2101 submitted in NDA 22334. PK samples collected at week 4 at pre-dose (0), 1, 2, 4, 6, 8, and 24 hours post-dose [c] n=3			

2.4.2.4 *Is the drug an inhibitor and/or an inducer of transporters?*

Trametinib is not considered an *in vivo* inhibitor of P-glycoprotein (P-gp), Breast Cancer Resistance Protein (BCRP), OATP1B1, or OATP1B3 [Study 07DMM111] as the calculated R values are <0.1 (**Table 15**). Furthermore, trametinib R values calculated from predicted gastrointestinal concentrations were <10 for inhibition of P-gp and slightly greater than 10 for BCRP, suggesting that *in vivo* drug interaction studies are not warranted.

Table 15. IC_{50} and calculated R values for trametinib inhibition of transporters

Transporter	Substrate	Trametinib IC_{50} (μM)	R value ($[I]_1/IC_{50}$) in Blood	R value ($[I]_2/IC_{50}$) in Gut
P-gp	Digoxin	5.5	0.007	2.09
BCRP	Cimetidine	1.1	0.036	10.45
OATP1B1	Estradiol 17β-D-glucuronide	1.3	0.031	-
OATP1B3	Estradiol 17β-D-glucuronide	0.94	0.043	-
Calculation of R values based on plasma maximal steady-state concentration of 22 ng/mL or 0.04 μM $[I]_1$ $[I]_2 = I_{gut}$: Calculated as the theoretical maximal gastrointestinal drug concentration after oral administration of the clinical dose in a volume of 250 mL (11.5 μM)				

2.4.2.5 *Are there other metabolic/transporter pathways that may be important?*

Trametinib is not a substrate for efflux transporters P-gp or BCRP *in vitro* as the net flux ratio is 1.9 and 1.3 (both <2) in MDCKII-MDR1 cells, respectively [Study 06MCD1102 and 08DMR003]. It is unknown if trametinib is a substrate for uptake organic anion transporter polypeptides (OATP). The Applicant is requested to consider conducting an *in vitro* study to determine if trametinib is a substrate of OATP.

2.4.2.6 *Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?*

No, trametinib is used as monotherapy for this marketing application.

2.4.2.7 *What other co-medications are likely to be administered to the target population?*

Concomitant medications used by ≥ 20% of patients treated with trametinib in the registration trial include doxycycline (47%), paracetamol (28%), and hydrocortisone (22%). Doxycycline and hydrocortisone were utilized for rash management. No clinically important drug interactions with these concomitant medications are anticipated given that the major metabolic pathways for trametinib do not involve CYP450.

2.4.2.8 *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?*

No data is available as no *in vivo* drug interaction studies have been conducted or are warranted based on the negative results obtained in the *in vitro* studies.

2.4.2.9 *Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?*

No data are available.

2.4.2.10 *Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?*

The Applicant is requested to address the question of whether trametinib is a substrate of OATP. Refer to **Section 2.4.2.5**.

2.4.3 What issues related to dose, dosing regimens, or administration are unresolved and represent significant omissions?

None.

2.5 GENERAL BIOPHARMACEUTICS

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

The Applicant classifies trametinib as BCS Class 2 based on data showing that trametinib has high permeability in MDCKII-MDR1 cells [Study 10DMM026] and poor aqueous solubility (**Table 1**). The *in vitro* permeability of trametinib ranged from 162 to 595 nm/sec at pH 7.4, and 186 to 611 nm/sec at pH 5.5 (**Table 16**). The trametinib permeability at both pH levels exceeded that of labetalol, the permeability reference marker ($F_{abs} \geq 90\%$), at all time points and concentrations; however, the mean absolute bioavailability of 72% after a single 2 mg oral dose of trametinib is <90%.

Table 16. Permeability at pH 7.4 and 5.5 in MDCKII-MDR1 cells

GSK1120212 Concentration (µg/mL)	Time Period (min)	$P_{7.4}$ (nm/sec) (Mean ± SD)	Mass Balance A to B $P_{7.4}$ (Mean ± SD)	$P_{5.5}$ (nm/sec) (Mean ± SD)	Mass Balance A to B $P_{5.5}$ (Mean ± SD)
0.08	20 - 45	285 ± 56	90 ± 7	236 ± 58	93 ± 3
	45 - 90	501 ± 59	80 ± 4	453 ± 59	83 ± 2
	90 - 120	217 ± 65	89 ± 1	271 ± 103	96 ± 12
0.8	20 - 45	208 ± 30	93 ± 8	186 ± 54	96 ± 1.6
	45 - 90	280 ± 67	91 ± 5	305 ± 23	92 ± 3.7
	90 - 120	402 ± 150	85 ± 6	537 ± 178	92 ± 4
4	20 - 45	242 ± 37	108 ± 18	360 ± 210	95 ± 13
	45 - 90	447 ± 173	95 ± 11	582 ± 189	94 ± 8
	90 - 120	162 ± 110	102 ± 20	NR	96 ± 7
8	20 - 45	227 ± 31	92 ± 6	247 ± 26	97 ± 7
	45 - 90	595 ± 171	90 ± 2	611 ± 37	96 ± 8
	90 - 120	NR	86 ± 3	NR	96 ± 14

Data are the mean ± standard deviation from three monolayers for each time point.
NR: Data not reported. The permeation function of MDCK-MDR1 was compromised at high concentration and 120 min incubation time.

Source: Study 10DMM026, Table 2, Page 16

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

There were two minor differences between the 0.5, 1.0, and 2.0 mg tablets used in the clinical trials and the commercial tablet dosage form. The (b) (4) was replaced with (b) (4) Yellow for the 0.5 mg tablet strength in order to (b) (4), and the (b) (4). These modifications are not expected to change bioavailability of the to-be-marketed formulation.

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?

The effect of food on trametinib PK was evaluated in a single dose, two period crossover study with a 7-day washout period. Given the long half-life of 4-5 days for trametinib, the washout period was not adequate and a correction factor was applied to account for residual

concentrations in Period 1. Administration of a single 2 mg dose of trametinib with a high-fat, high-calorie meal resulted in a 70% decrease in corrected C_{max} and a 24% decrease in corrected $AUC_{0\text{-}168h}$, compared to fasted conditions (n=22) (Study MEK113709) (**Table 17**). A high-fat, high-calorie meal delayed t_{max} by a median of 3.9 hours.

Table 17. PK parameters of a single dose of trametinib after a high-fat meal compared to fasted conditions

PK Parameter	Geometric Least Squares Mean		Ratio (90% CI)
	2.0 mg/High-fat, High-calorie meal	2.0 mg/Fasted	
corrAUC(0-∞) (ng*hr/mL)	365.90	407.73	0.897 (0.800, 1.007)
corrAUC(0-last) (ng*hr/mL)	195.81	257.83	0.759 (0.697, 0.828)
corrCmax (ng/mL)	2.739	9.111	0.301 (0.243, 0.371)

Source: Study 113709 final study report, Table 13, Page 35

The Applicant proposes trametinib be administered one hour before or two hours after a meal, similar to the fasted conditions in clinical trials. Considering the approximately lower peak to trough ratio at steady state (2) as compared to that after a single dose (4 to 5), a 70% decrease in C_{max} observed after a single dose would be less pronounced after repeat dosing, and a 24% decrease in AUC is not considered clinically important as efficacy was also achieved in patients whose dose was reduced to 1.5 mg (a 25% dose reduction due to intolerability) in the registration trial. Therefore, unnecessary restriction of trametinib administration in the fasted state may be burdensome to patients, resulting in a compliance issue. Although it is uncertain whether the amount of food, caloric content, or fat content contributed to decreased exposure of trametinib, a high-fat meal is typically expected to have a more marked effect on bioavailability than a low-fat meal. Given that a single dose of trametinib taken with a high-fat meal (worst-case scenario) resulted in a 24% decrease in systemic exposure and the clinical efficacy of trametinib was established under fasted conditions, the review team recommends avoiding administration of trametinib with a high-fat meal to preserve clinical efficacy while providing a less restricted dosing condition for better compliance.

2.5.4 When would a fed BE study be appropriate and was one conducted?

Not applicable.

2.5.5 How do dissolution conditions and specifications ensure in vivo performance and quality of the product?

Refer to Biopharmaceutics review.

2.5.6 If different strength formulations are not bioequivalent based on standard criteria, what clinical safety and efficacy data support the approval of various strengths of the to-be-marketed product?

Not applicable as no bioequivalence studies are necessary and all available tablet strengths (0.5, 1, and 2 mg) will be marketed. Refer to CMC review.

2.5.7 If the NDA is for a modified release formulation of an approved immediate product without supportive safety and efficacy studies, what dosing regimen changes are necessary, if any, in the presence or absence of PK-PD relationship?

Not applicable.

2.5.8 If unapproved products or altered approved products were used as active controls, how is BE to the 'to-be-marketed' product? What is the basis for using either in vitro or in vivo data to evaluate BE?

Not applicable.

2.5.9 What other significant, unresolved issues in relation to in vitro dissolution of in vivo BA and BE need to be addressed?

None.

2.6 ANALYTICAL SECTION

2.6.1 How are the active moieties identified and measured in the plasma and the other matrices?

Trametinib was identified in human plasma and measured using validated HPLC-MS/MS methods.

2.6.2 Which metabolites have been selected for analysis and why?

Concentrations of M5 were not measured as M5 was not considered to be a major circulating metabolite at steady state.

2.6.3 For all moieties measured is free, bound or total measured?

Given that trametinib is 97.4% bound to human plasma proteins, total plasma concentrations were measured.

2.6.4 What bioanalytical methods are used to assess concentrations?

Trametinib concentrations in human plasma were measured by HPLC mass spectrometry (MS)/MS [Validated Report No. CD2008/00957, 2010N108094].

Plasma samples of [^{14}C]-trametinib collected in the absolute BA study (MEK115064) were measured by liquid scintillation counting and accelerator mass spectrometry (AMS) to detect radiolabeled carbon [Validated Report No. 2011N126160].

2.6.4.1 *What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?*

Trametinib

The standard curve was generated using 8 calibration samples in the concentration range of 0.25 (LLOQ) to 250 ng/mL and weighted ($1/x^2$) linear regression. This standard curve range was adequate for the purposes of determining plasma concentrations of trametinib in the clinical studies.

[^{14}C]-trametinib

The standard curve was generated using 7 calibration samples in the concentration range of 1.1 to 104 pg/mL (0.10 to 10 disintegrations per minute (dpm)/mL) using non-weighted linear regression. This standard curve range was adequate for the purposes of determining plasma concentrations of [^{14}C]-trametinib in the absolute BA study (MEK115064).

2.6.4.2 *What are the lower and upper limits of quantification?*

See **Section 2.6.4.1**.

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

The RE% of the accuracy and the CV% of the precision of the QC samples were ≤ 15% (**Table 18**), and are acceptable based on the current FDA Guidance for Industry *Bioanalytical Method Validation*.

Table 18. Summary of inter-assay accuracy and precision of calibration standards and quality controls used in clinical studies

Report No.	Study	Calibration standards		Quality controls	
		Mean accuracy (%RE)	Mean precision (%CV)	Mean accuracy (%RE)	Mean precision (%CV)
2012N135243	114267	-4.2 to 3.8%	2.0 to 5.2%	0.3 to 5.4%	2.5 to 3.3%
2011N121812	111054	-2.3 to 1.3%	2.5 to 4.9%	-3.3 to 4.8%	6.4 to 11%
2011N121174	113583	-1.8 to 2.1%	1.1 to 3.8%	-1.2 to 0.3%	2.8 to 3.5%
2011N128882	113708	-3.8 to 2.2%	0.5 to 4.0%	-0.1 to 5.3%	1.5 to 5.8%
2012N136471	113709	-2.8 to 3.7%	1.5 to 5.6%	-2.0 to -0.5%	5.0 to 6.2%

The selectivity of the method was established by the analysis of samples of control human plasma from 6 individual volunteers, and inclusion of blank and double blank samples prepared from pooled control human plasma in validation assays.

2.6.4.4 *What is the sample stability under the conditions used in the study? (long-term, freeze-thaw, sample-handling, sample transport, autosampler)*

Trametinib was stable in human plasma following:

- Three freeze-thaw cycles from -80°C to room temperature at concentrations of 0.75 and 200 ng/mL

- Three freeze-thaw cycles from -20°C to room temperature at concentrations of 1.0 and 200 ng/mL
- ≥ 24 hours at room temperature
- ≥ 96 hours at room temperature (processed samples)
- ≥ 602 days at -20°C
- ≥ 260 days at -80°C

Trametinib was unstable in human blood at 37°C for 4 hours, but stable on wet ice for 4 hours. Stock solutions (2 mg/mL) may be stored for at least 62 days at 4°C.

2.6.4.5 *What is the QC sample plan?*

Four QC samples at concentrations of 0.75, 1.0, 10, and 200 ng/mL were prepared in duplicate in each run.

3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included. The Agency's suggested changes to the proposed labeling are shown in underline blue text and removal of content shown by ~~red strikethroughs~~.

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dose
The recommended daily dose of MEKINIST is 2 mg (b) (4) -Do not take MEKINIST with a high-fat meal. Continue dosing until disease progression or the development of unacceptable toxicity. Do not take (b) (4) a missed dose (b) (4) within 12 hours (b) (4) of the next dose.

7 DRUG INTERACTIONS
(b) (4)

As trametinib is not a substrate or a strong inhibitor or inducer of human cytochrome P450 *in vitro*, no formal clinical studies have been conducted to evaluate CYP450-mediated drug interactions with trametinib *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.7 Hepatic Impairment

No formal clinical study has been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of trametinib. No dose adjustment is recommended in patients with mild hepatic impairment based on a population pharmacokinetic analysis (b) (4) [redacted] *[see Clinical Pharmacology (12.3)]*. The appropriate dose of trametinib has not been established in patients with moderate or severe hepatic impairment.

(b) (4) [redacted]

8.8 Renal Impairment

No formal clinical study has been conducted to evaluate the effect of renal impairment on the pharmacokinetics of trametinib. No dose adjustment is recommended in patients with mild or moderate renal impairment based on a population pharmacokinetic analysi (b) (4) [redacted] *[see Clinical Pharmacology (12.3)]*. The pharmacokinetics of trametinib has not been studied in patients with severe renal impairment. (b) (4) [redacted]

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

(b) (4) [redacted]

[redacted] ~~a~~Administration of 1 mg and 2 mg trametinib to patients with BRAF V600 mutation-positive melanoma resulted in dose-dependent changes in tumor biomarkers including inhibition of phosphorylated ERK, inhibition of Ki67 (a marker of cell proliferation), and increases in p27 (a marker of apoptosis). (b) (4) [redacted]

12.3 Pharmacokinetics

The pharmacokinetics (PK) of trametinib ~~were~~ was characterized following single~~-~~ and repeat~~-~~oral administration (b) (4) [redacted]

[redacted] in patients with solid tumors and BRAF V600 mutation-positive metastatic melanoma.

Absorption:

[redacted] After oral administration, the median time to achieve peak plasma concentrations (T_{max}) is [redacted] 1.5 hours post-dose. The mean absolute bioavailability of a single 2 mg oral dose of trametinib tablet is 72% [redacted] The increase in exposure (C_{max} and AUC) was greater than dose proportional after a single dose of 0.125 to 10 mg and dose-proportional [redacted] after repeat ~~dosing~~ doses of 0.125 to 4 mg. [redacted] Inter-subject variability in AUC and C_{max} at steady state was 22% and 28%, respectively [redacted]

Administration of a single dose of trametinib with a high-fat, high-calorie meal decreased AUC by 24%, C_{max} by 70%, and delayed T_{max} by approximately 4 hours [redacted] compared to fasted conditions *[see Dosage and Administration (2.1)]*.

Distribution:

[redacted] Trametinib [redacted] is 97.4% bound to human plasma proteins. The apparent volume of distribution is 214 L. [redacted]

Metabolism:

[redacted] Trametinib is metabolized predominantly via deacetylation alone or with mono-oxygenation or in combination with glucuronidation biotransformation pathways *in vitro*. [redacted] Deacetylation is likely mediated by hydrolytic enzymes, such as carboxyl-esterases or amidases.

Following a single dose of [^{14}C]-trametinib, [redacted] approximately 50% of circulating radioactivity is represented as the parent compound. However, based on metabolite profiling after repeat dosing of trametinib, ≥75% of drug-related material in plasma is the parent compound.

Elimination:

The estimated elimination half-life based on the population PK model is 3.9 to 4.8 days. The apparent clearance is 4.9 L/hr. [redacted]

[redacted] Following oral administration of [^{14}C]-trametinib, [redacted] >80% of excreted radioactivity was recovered in the feces while [redacted] <20 [redacted]% of excreted radioactivity was recovered in the urine with [redacted] ≤0.1% of the excreted dose [redacted] as parent [redacted]

Specific [redacted] Populations:

Based on a population PK analysis, age, gender, and body weight do not have a clinically important effect on the exposure of trametinib. There are insufficient data to evaluate potential differences in the exposure of trametinib by race or ethnicity.

Hepatic Impairment: Based on a population PK analysis in 64 patients with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN or total bilirubin >1.0-1.5 x ULN and any AST), mild hepatic impairment has no clinically important effect on the systemic exposure of trametinib. The [redacted] PK of trametinib has not been studied in patients with moderate or severe hepatic impairment [redacted] *[see Use in Specific Populations (8.[redacted])]*.

Renal Impairment: As renal excretion of trametinib is low (<20%), ~~R~~renal impairment is unlikely to have a clinically [redacted] important effect on the exposure of trametinib [redacted] Based on a population PK analysis in 223 patients with mild renal impairment (GFR 60 to <90 mL/min/1.73 m^2) and 35 patients with moderate renal impairment (GFR 30 to <60 mL/min/1.73 m^2), mild and moderate renal impairment have no clinically important effect on the systemic exposure of trametinib. The PK of trametinib has not been studied in patients with severe renal impairment [redacted] *see Use in Specific Populations (8.[redacted])]*.

[redacted]

Pediatrics: No studies have been conducted to [redacted] evaluate the ~~pharmacokinetics~~PK of trametinib in pediatric patients.

Drug Interactions:

No formal drug interaction studies have been conducted with trametinib.

Trametinib is not a substrate of CYP enzymes or efflux transporters P-gp or BCRP *in vitro*.

[redacted]

Based on studies with human hepatic microsomes, trametinib is not an inhibitor of CYP450 including CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, and

transporters including OATP1B1, OATP1B3, P-gp, and BCRP at a clinically relevant systemic exposure of 0.04 µM. Trametinib is an inhibitor of CYP2C8 *in vitro*.

Studies with primary human hepatocytes showed that trametinib is an inducer of CYP3A4 *in vitro*. Based on cross-study comparisons, oral administration of trametinib 2 mg once daily with everolimus (sensitive CYP3A4 substrate) 5 mg once daily had no clinically important effect on the AUC and C_{max} of everolimus.

(b) (4)

4 APPENDICES

4.1 PHARMACOMETRICS 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.

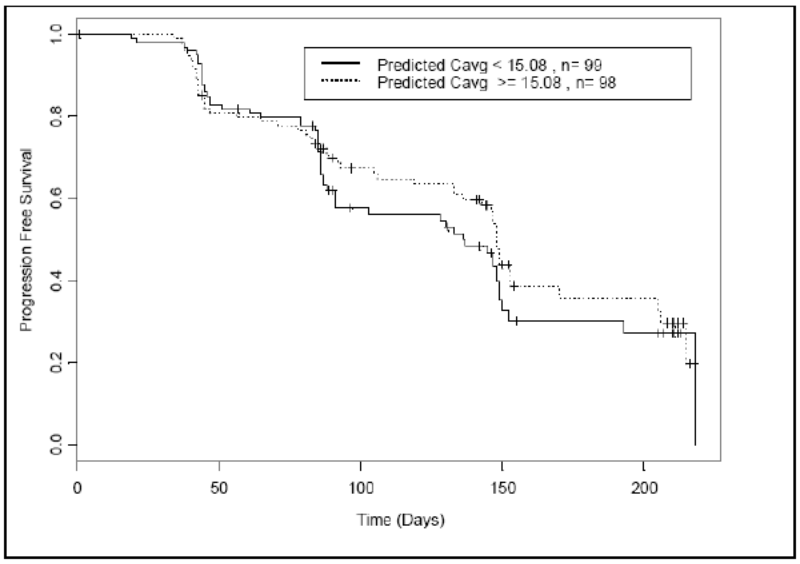
1.1.1 Does the exposure-response (E-R) relationship for efficacy support the proposed dose of 2 mg q.d.?

The data is not sufficient to draw conclusions regarding whether the proposed dose of 2 mg q.d. is appropriate based on E-R relationship for efficacy. Nearly all subjects (>97%) were included in the E-R analysis. However, only 2 mg q.d. dose was used in Phase 2 and Phase 3 studies, the range of exposure was narrow with C_{avg} ranging from 0 to 26 ng/mL due to the low between-subject variability (CV%=26%). This limits the full exploration of E-R relationship to predict the efficacy profile at a higher or lower dose than 2 mg q.d.

There is no evident relationship between exposure and progression free survival (PFS). Lactate dehydrogenase (LDH) was the most significant predictor of response in the Cox model. Patients with LDH>ULN have shorter survival (HR(High LDH vs Normal)=2.1). After including LDH in the Cox model, exposure is not a significant predictor for PFS.

As shown in **Figure 1**, subjects with exposure above median value appear to have longer PFS than those below median exposure. Despite the numerical difference in PFS between low and high exposure group, trametinib exposure is not a statistically significant covariate for PFS for both Phase 2 and Phase 3 studies after LDH is included in the Cox model. Conclusion regarding E-R relationship remains the same when response rate (complete or partial response) is used as efficacy variable. In summary, there is no evidence of E-R relationship for efficacy.

Figure 1: Progression-Free Survival (PFS) by Predicted Average Trametinib Concentration (C_{avg}) for Phase 3 Study (MEK114267)



Source: Sponsor's Report: Exposure-Response Analysis of the Effect of Trametinib, a MEK inhibitor, on Efficacy and Safety Endpoints, Page 30

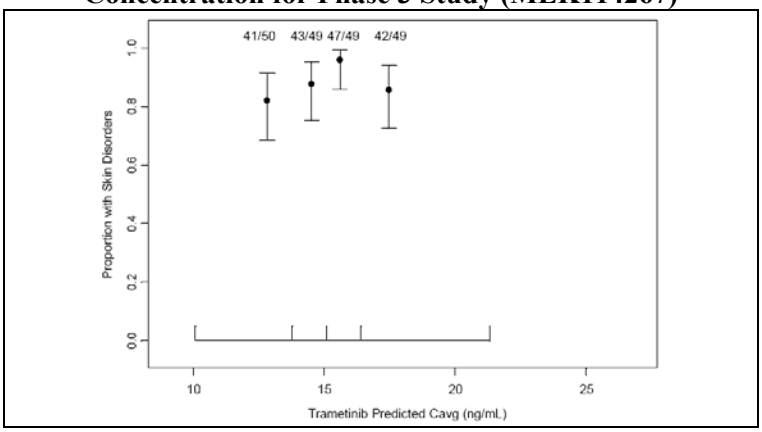
1.1.2 Does the exposure-response relationship for safety support the proposed dose of 2 mg q.d.?

The data is not sufficient to draw conclusions regarding whether the proposed dose of 2 mg q.d. is appropriate based on E-R relationship for safety due to the narrow exposure range caused by low PK variability and one dose regimen used in Phase 2 and Phase 3 trials. This limits the full exploration of E-R relationship to predict the safety profile at a higher or lower dose than 2 mg q.d.

The E-R relationship for AEs was explored by the sponsor for the following adverse events, including: skin-related events, hepatic disorders, cardiac-related events, diarrhea, visual disorders, hypertension and pneumonitis. The most commonly reported AEs were skin-related events and diarrhea. Based on data from Phase 2 and Phase 3 studies, there was no clear E-R relationship for skin disorders (**Figure 2**) and any other AEs examined.

Thus, (b) (4) .

Figure 2: Proportion of Subjects with Skin Disorders versus Predicted Average Trametinib Concentration for Phase 3 Study (MEK114267)



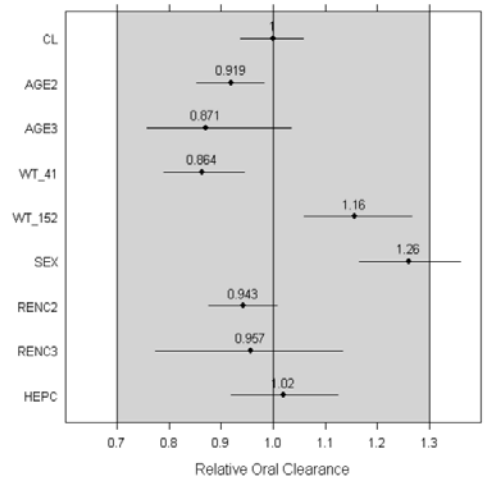
Sources: Sponsor's Report: Exposure-Response Analysis of the Effect of Trametinib, a MEK inhibitor, on Efficacy and Safety Endpoints, Page 43

1.1.3 Is dose adjustment warranted for intrinsic or extrinsic factors based on population PK analysis?

No. **Figure 3** suggests that body weight, age, gender, normal (n=231)/mild (n=223) /moderate (n=35) renal impairment, and normal (n=429)/mild (n=64) hepatic impairment are not clinically important covariate on oral clearance of trametinib. It does not support a dose adjustment for these intrinsic factors.

A total of 493 cancer subjects treated with trametinib were included in the population PK dataset. The majority of subjects was White/Caucasian (96.8%), and did not receive CYP3A4 inhibitors (97.2%) or inducers (99.4%). Thus the effects of race, CYP3A4 inhibitors or inducers on oral clearance of trametinib were not clear based on population PK model.

Figure 3: Relationship Between Key Covariates and Oral Clearance of Trametinib based on Population PK model



AGE2= Age 65-75 years; AGE3= Age ≥75 years; CL= Oral clearance; RENC2= 60≤ Glomerular filtration rate (GFR) < 90; RENC3= GFR <60; HEPC= Mild hepatic impairment; WT= Body weight

Note: Mild hepatic impairment was defined by bilirubin≤ Upper Limit of Normal, AST> Upper Limit of Normal, or bilirubin> 1X-1.5X Upper Limit of Normal, AST: any value.

Sources: Sponsor's Population PK Report, *Page 40*

1.2 RECOMMENDATIONS

Please see clinical pharmacology QBR for recommendations.

1.3 LABEL STATEMENTS

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

2 PERTINENT REGULATORY BACKGROUND

This New Drug Application (NDA) is submitted for marketing approval of trametinib for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation as detected by an FDA approved test. Trametinib has not received marketing approval for any indication in any market at this time. Orphan designation for treatment of BRAF V600 mutation positive Stage IIb through IV melanoma was received on December 20, 2010.

Phase III trial was a randomized two-arm, open-label, international, multicenter study to evaluate the efficacy and safety of single agent trametinib compared with chemotherapy. For patients regardless of BRAF V600E or V600K mutation or history of brain metastases (ITT Population), a statistically significant improvement in PFS was observed in the trametinib arm compared with the chemotherapy arm (investigator assessed: HR=0.45; p<0.001 and independent review: HR=0.42; p<0.0001). In subjects with V600E mutation-positive melanoma with no prior brain metastases (Primary Efficacy Population), there was a statistically significant and clinically meaningful improvement for the primary endpoint of investigator-assessed PFS, with median PFS of 4.8 months in the trametinib arm and 1.4 months in the chemotherapy arm (HR=0.44; p<0.0001, Table 2).

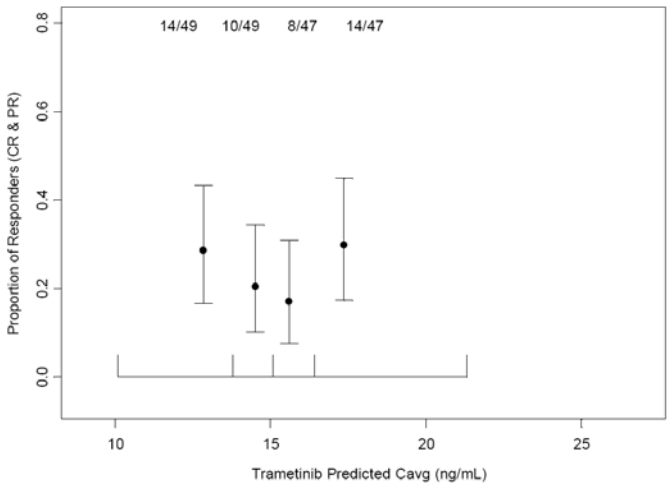
3 RESULTS OF SPONSOR'S ANALYSIS

3.1 E-R ANALYSIS

The summary of E-R analysis for efficacy (i.e., PFS) and safety was provided in Section 1.

E-R analysis was also conducted for efficacy using response rate as efficacy variable. Covariates including ECOG performance status, mutation type, trial, disease stage, LDH, number of lesions at baseline, presence of brain metastases, sex, and age, were tested. Disease stage (M1c vs other) was found to be only significant variable with a lower response rate in subjects with M1c. Exposure was not statistically significant variable after disease stage (M stage) was included in the model. There is no evident E-R relationship for response rate as shown in **Figure 4**.

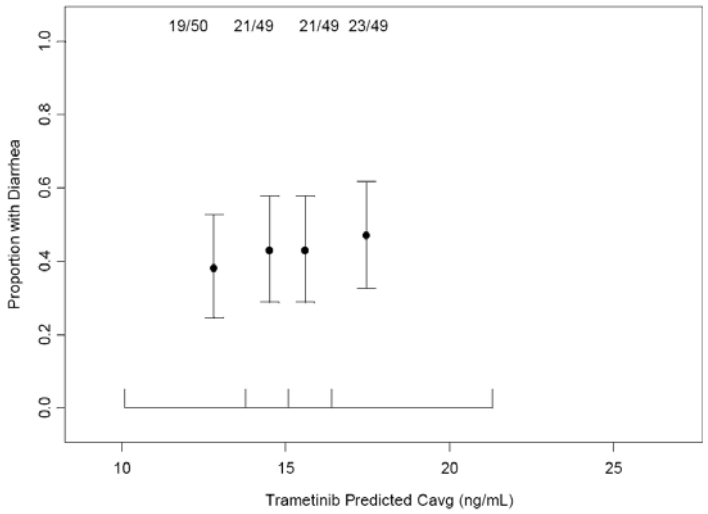
Figure 4: Proportion of Responders versus Predicted Trametinib Average Concentration (Cavg) for Phase 3 Study (MEK114267)



Sources: Sponsor's Report: Exposure-Response Analysis of the Effect of Trametinib, a MEK inhibitor, on Efficacy and Safety Endpoints, Page 32

The most commonly reported AEs were skin-related events and diarrhea. There was no clear exposure-response relationship with skin-related events (**Figure 2**), diarrhea (**Figure 5**) and any other AEs examined, including cardiac-related events, visual disorders, hypertension, hepatic disorders, pneumonitis.

Figure 5: Proportion of Subjects with Diarrhea versus Predicted Average Trametinib Concentration for Phase 3 Study (MEK114267)



Reviewer's Comments: We agree that there is no evident E-R relationship for efficacy and safety based on data from Phase 2 and Phase 3 trial. However, the data is not sufficient to draw conclusions regarding whether or not the proposed dose of 2 mg q.d. is appropriate based on E-R relationship for efficacy and safety due to the narrow exposure range caused by low PK variability and one dose regimen used in Phase 2 and Phase 3 trial. This limits the full exploration of E-R relationship to assess the benefit risk profile at a higher or lower dose than 2 mg q.d.

3.2 POPULATION PK ANALYSIS

The primary goal of population PK analysis was to characterize the population PK of trametinib, assess sources of variability in PK parameters based on data collected in three clinical studies and identify clinical relevant covariates that influence exposure to trametinib. The population PK model is a 2-compartment model with first order elimination with fast and slow first-order absorption rate constant.

Continuous covariates were included using a power model, an example is shown in equation below for the effect of body weight on CL/F:

$$TVCL = THETA(1) * (Weight/79)^{THETA(2)}$$

Categorical covariates were included as shown in equation below for the effect of Sex on CL/F (SEX=0 for female and SEX=1 for male)

$$TVCL = THETA(1) * THETA(3)^{SEX}$$

In the final model, the clearance is described as below:

$$TVCL = 4.91 * (weight / 79)^{0.211} * (1.26)^{Sex}$$

The results suggested a low variability of CL/F (24%), but high variability on distribution and absorption parameters (77% on Vc/F, 215% on Q/F, and 96% on Ka1) (Table 1). Body weight, age, gender, normal/mild /moderate renal impairment, and mild/normal hepatic impairment has no meaningful effect on exposure of trametinib (**Figure 3** and **Table 1**).

Table 1: Population PK Parameters of Trametinib – Full and Final Models

Population PK Parameters	Full Model (NONMEM)	Full Model (BOOTSTRAP)	Final Model (NONMEM)	Final Model (BOOTSTRAP)
	Typical Values (RSE%) BSV% (RSE%)	Typical Values (95% CI)	Typical Values (RSE%) BSV% (RSE%)	Typical Values (95% CI)
CL/F (L/h)	5.20 (3.4) 23.2% (7.3)	5.18 (4.85, 5.48)	4.91 (3.0) 23.9% (6.9)	4.90 (4.64, 5.18)
Vc/F (L)	212 (13.9) 71.5% (9.1)	208 (141, 255)	214 (13.7) 76.9% (13.2)	208 (143, 264)
Q/F (L/h)	60.0 Fixed 213.1% (7.6)	60 Fixed	60.0 Fixed 215.4% (15.8)	60 Fixed
Vp/F (L)	544 (7.4) 15.0% Fixed	506 (428, 636)	568 (9.1) 15.0% Fixed	551 (466, 672)
Ka1 (h^{-1})	0.135 (14.0) 102.5% (21.0)	0.177 (0.101, 0.271)	0.142 (26.8) 96.1% (22.3)	0.169 (0.101, 0.282)
Ka2 (h^{-1})	2.14 (9.5) 15.0% Fixed	2.27 (1.16, 3.77)	2.05 (28.4) 15.0% Fixed	2.07 (1.03, 3.42)
MTIME (h)	0.398 (2.4) 15.0% Fixed	0.411 (0.386, 0.457)	0.400 (4.1) 15.0% Fixed	0.410 (0.382, 0.456)
Error Model				
Additive Error (ng/mL)	1.37 (5.4)	1.10 (1.08, 1.13)	1.37 (1.2)	1.10 (1.08, 1.13)

Covariate Effect	Typical Values (RSE%)	Typical Values (95% CI)	Typical Values (RSE%)	Typical Values (95% CI)
Weight on CL/F	0.224 (31.3)	0.223 (0.0864, 0.360)	0.211 (37.9)	0.216 (0.0402, 0.360)
Age on CL/F (65 – 75 yrs)	0.923 (3.5)	0.919 (0.853, 0.982)	--	--
Age on CL/F (≥ 75 yrs)	0.883 (9.3)	0.871 (0.758, 1.03)	--	--
Sex on CL/F (male)	1.27 (3.5)	1.26 (1.17, 1.36)	1.26 (3.4)	1.25 (1.17, 1.33)
Mild renal impairment on CL/F (60 ≤ GFR < 90 mL/min/1.73m^2)	0.941 (3.3)	0.943 (0.875, 1.01)	--	--
Moderate renal impairment on CL/F (GFR <60 mL/min/1.73m^2)	0.956 (8.5)	0.955 (0.772, 1.13)	--	--
Mild hepatic impairment on CL/F	1.01 (4.7)	1.02 (0.918, 1.13)	--	--
Weight on Vc/F	0.540 (56.7)	0.730 (-0.137, 1.59)	--	--
Age on Vc/F (65 – 75 yrs)	0.839 (15.0)	0.866 (0.630, 1.14)	--	--
Age on Vc/F (≥ 75 yrs)	0.976 (39.3)	1.01 (0.391, 1.91)	--	--
Sex on Vc/F (male)	1.36 (17.0)	1.36 (0.986, 1.90)	--	--
Weight on Q/F	4.87 (23.8)	4.10 (1.23, 8.09)	5.90 (31.4)	5.43 (2.67, 9.43)
Sex on Q/F (male)	0.438 (39.7)	0.528 (0.141, 1.43)	--	--

BSV= Between-subject variability; CI= Confidence interval; CL/F= Oral clearance; GFR= Glomerular filtration rate; Ka1= First-order absorption rate; Ka2= First-order absorption rate after MTIME; MTIME= Time when absorption rate changes; Q/F= Distributional clearance; RSE= Relative standard error; Vc/F= Central volume of distribution; Vp/F= Peripheral volume of distribution

Sources: Sponsor's Population PK Report, *Page 42*

Table 2: Effect of Body Weight and Gender – Final Models

Sex	Body Weight (kg)		Cmax (ng/mL)	AUC (ng.h/mL)	Cτ (ng/mL)
Male	Median	79	17.9	322	11.7
	Minimum	52	18.8	344	10.7
	Maximum	152	12.8	281	10.6
Female	Median	79	21.2	402	15.0
	Minimum	41.2	22.1	**430**	14.0
	Maximum	131	16.3	363	14.0

AUC = Area under the curve; Cmax = Maximum concentration; Cτ = Trough concentration

Note: Individual PK exposure values were derived from rich concentration-time profile simulated using the 2 mg trametinib once daily dosing regimen and the posthoc values derived with the final population PK model.

Figure 6: Goodness-of-Fit – Final Model – Log Scale. Black points: Observed concentration Phase I; Grey points: Observed concentration Phase II; Blue points: Observed concentration Phase III; Red points: CWRES>4; Orange points: CWRES>3; IDENT = Identity line; LOESS = Locally weighted scatter plot smoothing

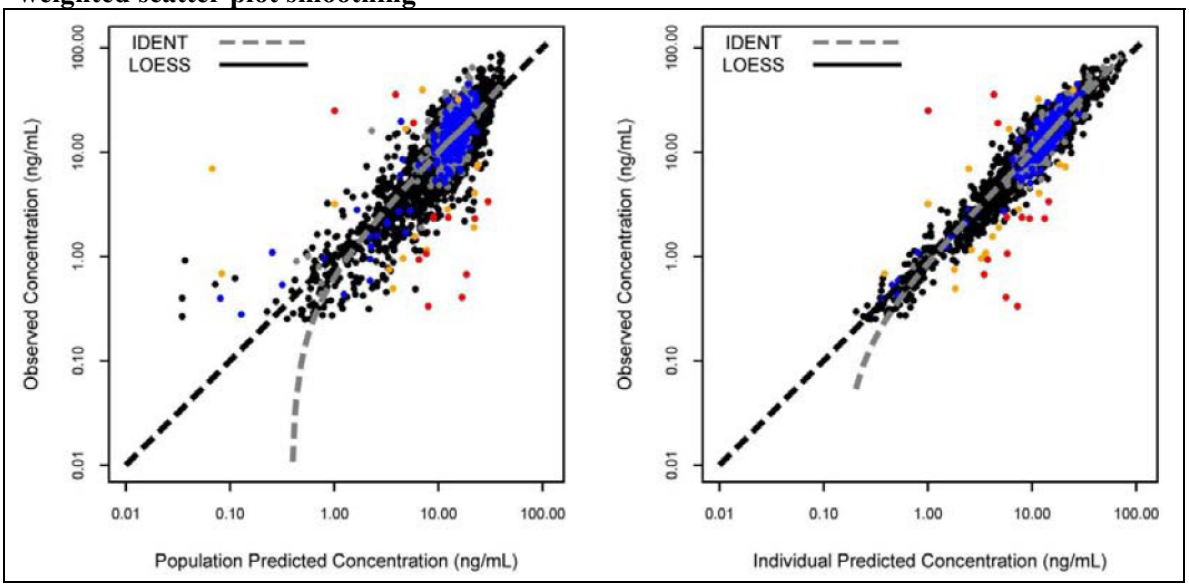
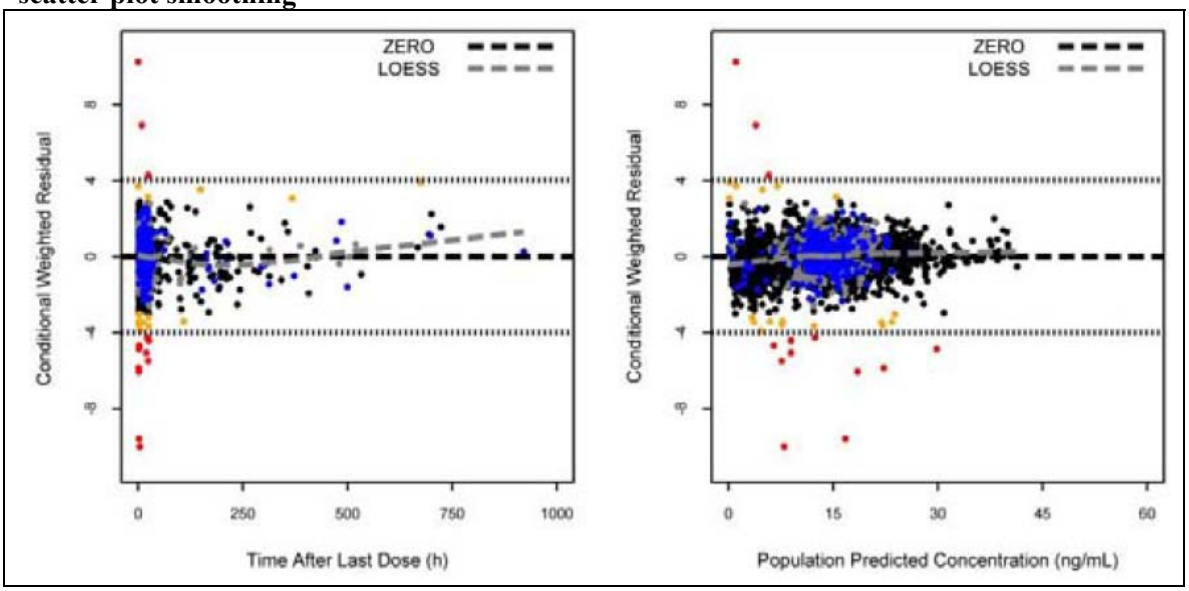


Figure 7: Goodness-of-Fit – Final Model - Residuals. Black points: Observed concentration Phase I; Grey points: Observed concentration Phase II; Blue points: Observed concentration Phase III; Red points: CWRES>4; Orange points: CWRES>3; ZERO = Identity line; LOESS = Locally weighted scatter plot smoothing



Sources: Sponsor's Population PK Report, *Page 27, 29*

***Reviewer's Comments**:*

1. *The population PK model adequately described the PK profiles of trametinib in cancer patients (Figure 6 and Figure).*
2. *The results suggested a low between-subject variability of CL/F (24%). Body weight and gender were identified as significant covariate in population PK model. However, the magnitude of their*

effect on exposure to trametinib is not clinically relevant (

3. *Table).*
4. *Overall, body weight, age, gender, normal (n=231)/mild (n=223) /moderate (n=35) renal impairment, and normal (n=429)/mild (n=64) hepatic impairment are not meaningful covariate on exposure of trametinib. No dose adjustment is required for these intrinsic factors.*
5. *It was not clear from population PK analysis regarding the effects of race, CYP3A4 inhibitors or inducers on oral clearance of trametinib due to the limited number of non-Caucasian patients and patients taking CYP inhibitor or inducer in clinical trials.*

4.2 GENOMICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS GROUP REVIEW

NDA Number	204114
Submission Date	August 3, 2012
Applicant Name	GlaxoSmithKline
Generic Name	Trametinib (Mekinist, GSK1120212B)
Proposed Indication	Treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutations as detected by an FDA-approved test
Primary Reviewer	Stacy S. Shord, Pharm.D.
Secondary Reviewer	Rosane Charlab Orbach, Ph.D.
Acting Associate Director for Genomics	Michael A. Pacanowski, Pharm.D., MPH

EXECUTIVE SUMMARY

Differences in clinicopathological features have been observed in patients with BRAF V600 mutated melanoma according to the V600 mutation (e.g., V600E vs. V600K), which may have implications for patient selection for treatment with trametinib, other MEK inhibitors, or BRAF inhibitors. The purpose of this review is to retrospectively evaluate whether BRAF V600 mutations correlate with demographic or disease-specific factors and whether tumor response in patients with metastatic melanoma enrolled in Studies MEK114267 and MEK113583 differs by the specific V600 mutation. Few patients with BRAF V600K melanoma (N=52, 7.5%) were enrolled in these two trials. Our assessment showed that a greater proportion of patients with BRAF V600K melanoma were male (V600E, 54% vs. V600K, 79%, P=0.0007) and older at initial diagnosis (median age: V600E, 48 years vs. V600K, 57 years, p<0.0001) compared to patients with the more common V600E mutation; similar differences have been observed in published retrospective analyses. These features were not prognostic in these trials and thus, not likely to confound assessments of activity. Trametinib exhibited antitumor activity in nonclinical BRAF V600 mutated melanoma models and in clinical trials of patients with BRAF V600E and V600K mutation-positive melanoma without prior treatment with a BRAF inhibitor. These results support an indication for treatment of BRAF V600E and V600K metastatic melanoma providing that the clinical and statistical reviews determine a favorable benefit-risk. Additional

studies might be warranted to determine the association of less common BRAF V600 mutations with clinicopathological features of melanoma and sensitivity to MEK and BRAF inhibitors.

1 BACKGROUND

Trametinib is an (b) (4) inhibitor of the mitogen-activated extracellular signal regulated kinases 1 and 2 (MEK1 and MEK2). The proposed indication is for the treatment of unresectable or metastatic melanoma with BRAF V600 mutations as detected by an FDA-approved test. Currently, the BRAF inhibitor vemurafenib is the only targeted drug approved specifically for the treatment of BRAF V600E mutated unresectable or metastatic melanoma as detected by an FDA-approved companion diagnostic test.

MEK and BRAF are components of the mitogen-activated protein kinase (MAPK) pathway (Appendix Figure 1), which is considered central to melanoma biology [PMID: 21343552]. Traditionally, melanoma has been classified according to clinical and pathologic features. Over the past few years, melanoma has been further categorized at the molecular level based on mutations in several oncogenes, including BRAF, NRAS and MEK. Activating BRAF mutations have been identified in about 50% of patients with metastatic melanoma [PMID: 22180178] and these mutations constitutively activate MEK signaling, thereby promoting tumor proliferation and metastases [PMID: 22013435]. The most common BRAF mutations in melanoma are missense mutations, which introduce an amino acid substitution at valine 600 and are collectively known as V600 mutations. The two most common V600 mutations are V600E (approximately 72% of BRAF mutations) and V600K (approximately 22%) [PMID: 22180178]. Other V600 mutations (e.g. V600R, V600D) have been reported in less than 5% of BRAF mutated melanoma [PMID: 20630094].

BRAF V600 mutated melanoma has been associated with several clinicopathological features that distinguish this molecular subset from BRAF wild-type melanoma. Recently, differences in clinicopathological features between BRAF V600E and V600K mutated tumors have also been reported suggesting that BRAF V600 mutated melanoma can be further categorized into biologically and clinically distinct V600 genotypes with distinct phenotypes [PMID: 22535154; 22039425]. The various V600 BRAF mutations might have different functional consequences that could affect prognosis or drug response. As such, the purpose of this review is to evaluate whether BRAF V600E and V600K mutations are associated with demographic or disease-specific factors and whether tumor responses in patients with metastatic melanoma differ by the specific V600 mutation.

2 SUBMISSION CONTENTS RELATED TO GENOMICS

NONCLINICAL STUDIES

Two studies were completed to evaluate the ability of trametinib to inhibit tumor growth in BRAF V600 mutated cells (i.e. V600E/K) [Study Report 2011N116395] and in BRAF V600E cells with acquired resistance to dabrafenib [Study Report 2011N113694].

One study was completed to evaluate the effect of trametinib on tumor growth in nude mice harboring human BRAF V600E melanoma xenografts [Study Report UH2008/0051/02].

CLINICAL STUDIES

Patients with BRAF V600E and V600K metastatic melanoma were enrolled into one of three trials. A description of the clinical trials is provided in (**Table 1)**. Study MEK111054 was excluded from our review as this trial was a dose-finding trial with no assessment of clinical activity.

Table 1. Clinical Trials with Patients with BRAF V600 Mutation Positive Melanoma

Study	**MEK111054 Dose Escalation**	**MEK113583 Safety**	**MEK114267 Efficacy**
Study Population	**30** patients with BRAF-V600 mutated advanced melanoma not previously treated with a BRAF inhibitor	**97** patients with BRAF-V600 mutated metastatic melanoma previously treated with or without BRAF inhibitor	**322** patients with BRAF V600E or K advanced or metastatic melanoma randomized 2:1 to trametinib or chemotherapy stratified for LDH levels and prior treatment for metastatic disease
BRAF testing	• Local laboratory • Archived or fresh tumor tissue • Primary or metastatic site not specified	• Local laboratory[1] • Archived or fresh tumor tissue • Primary or metastatic site not specified	• Central laboratory • Archived or fresh tumor tissue • Metastatic site
Primary Analyses of Antitumor Activity	-	Overall response rate	Intention-to-Treat (ITT): Investigator progression free survival (PFS) in patients with BRAF V600E or K melanoma[2]
Treatment	Trametinib	Trametinib	Trametinib vs. Chemotherapy

[1] Archived or fresh tumor sample was collected to confirm mutation status.
[2] As conducted by the clinical and statistical review teams

3 KEY QUESTIONS AND SUMMARY OF FINDINGS

3.1 Are clinicopathological features and tumor response to trametinib different for patients with BRAF V600E and V600K metastatic melanoma?

Yes. Our analyses suggest that a greater proportion of patients with BRAF V600K melanoma were male (V600E, 54% vs. V600K, 79%, P=0.0007) and older at initial diagnosis (median age: V600E, 48 years vs. V600K, 57 years, p<0.0001) compared to patients with BRAF V600E melanoma. Differences in age and gender between V600E and V600K mutations have also been noted in recent published literature. However, these factors were not associated with tumor response in the Studies MEK113853 and MEK114267 and unlikely to confound the clinical trial results.

LITERATURE REVIEW

Differences between BRAF V600 Mutated and Wild-type Melanoma

Compared to patients with BRAF wild-type melanoma, patients with BRAF V600 mutated melanoma were younger at diagnosis of distant metastases and of primary melanoma. The primary tumors demonstrated fewer markers of chronic sun damage, had truncal location and differed on the histopathologic subtype [PMID: 21343559; 22039425].

Differences between BRAF V600 Mutant Genotypes

Patients with non-V600E mutant tumors (e.g. V600K) were older at diagnosis of distant

metastases, had a higher degree of cumulative sun damage and a shorter distant metastasis-free survival time compared to those with the most common V600E mutation [PMID: 22535154]. In addition, a greater proportion of patients with V600K melanoma were male [PMID: 23169438] and had more frequent brain and lung metastases [PMID: 22039425]. These patients were also found to be at an increased risk of relapse compared to those with BRAF wild-type, BRAF V600E or NRAS mutated melanoma [PMID: 22535154; 23169438; 22039425].

METHODS

The clinicopathological features of patients enrolled into Studies MEK113583 and MEK114267 were retrospectively correlated with BRAF V600E and V600K mutation status using appropriate nonparametric and parametric tests for each study and across studies. Factors included in these analyses were age at study entry (continuous and dichoctimized), age at initial diagnosis (derived from the difference between the date of birth and the date of the first treatment), gender, baseline performance status, M stage, presence of visceral disease, number of metastatic sites, and LDH levels measured at the screening visit (continuous and dichoctimized). The age was dichotomized at 65 years, since patients aged older than 65 years have a worse prognosis [PMID: 22800552]. LDH levels were dichotomized based on the upper limit of normal use to stratify patients in Study MEK114267. The Breslow-Day test was used to evaluate homogeneity of odds ratios. The datasets submitted on September 24, 2012, were used for analysis.

Additional clinicopathological features such as tumor location and histopathologic subtype, and features associated with specific BRAF V600 mutations (e.g., age at diagnosis of metastatic disease, primary melanoma site, cumulative sun-induced damage, disease free interval) [PMID: 11078491, 22800552; 22535154; 23169438] were not available for our analyses.

Additional analyses retrospectively correlated mutation status and clinicopathological features that we found to be different between V600E and V600K mutations with tumor response for each study. Please refer to the clinical and statistical reviews for analyses of PFS in Study MEK114267.

RESULTS

Nonclinical Studies

Trametinib as a single agent inhibited the tumor growth of BRAF V600E (4 out of 5 cell lines) and V600K (4 out of 4 cell lines) cells. The IC_{50} values ranged from 1.4 to 6.7 nM in V600E cell lines vs. 0.3 to 0.7 nM in V600K cell lines. In BRAF V600E and V600K cells with acquired resistance to dabrafenib, the IC_{50} values were markedly higher for trametinib alone in the resistant cells as compared to the parent cells; the resistant cell lines harbored additional mutations in the MAPK signaling pathway, such as NRAS or MEK mutations.

Trametinib inhibited tumor growth in nude mice harboring human BRAF V600E melanoma xenografts following oral administration daily for 14 days by at least 50% (p-value < 0.05).

Clinical Studies

Archived or fresh tumor tissue was analyzed for BRAF V600 mutations using local or central [with an allele-specific polymerase chain reaction (PCR) assay] testing. For details regarding the applicant's companion diagnostic submitted in parallel with this NDA, refer to the CDRH review of the assay.

Most tumors were positive for either V600E or V600K mutations (**Table 2**). In Study MEK113583, 6 patients with tumors positive for other mutations were excluded from our analyses; these patients had discordant results from the central and local testing.

Table 2. The BRAF Mutations Identified for Patients Enrolled into Studies MEK113583 and MEK114267

	MEK113583		**MEK114267**	
BRAF Mutation	**Cohort A** (n=40)	**Cohort B** (n=57)	**Trametinib** (n=214)	**Chemotherapy** (n=108)
V600E	33 (82.5%)	46 (80.6%)	184 (85.9%)	97 (89.8%)
V600E/V600K	1 (2.5%)	1 (1.8%)	-	-
V600E/K601E	1 (2.5%)	-	-	-
V600K	4 (10.0%)	8 (14.0%)	30 (14.1%)	10 (9.2%)
V600K/V600R	-	1 (1.8%)	-	-
K601E	-	1 (1.8%)	-	-
Not Specified	1 (2.5%)	-	-	1 (1.0%)

Clinicopathological Features

Table 3 lists the clinicopathological features for patients enrolled into Studies MEK113583 and MEK114267 (individual and combined datasets). All patients with a BRAF V600E or V600K mutated melanoma were included in these analyses regardless of treatment assignment. Results using the combined dataset indicate that patients with V600K mutations were more likely to be male and older at the start of the study and at initial diagnosis compared to patients with a V600E mutation. These differences were not observed when the smaller study (MEK113583) was analyzed individually, but were observed in the larger efficacy study (MEK114267). Both age and gender remained associated with mutation status in a multivariate analysis.

No differences related to the presence of visceral disease or to the number of metastatic sites were observed in Study MEK114267; these data were not available for Study MEK113583. No differences in other evaluable demographic or disease-specific factors were identified.

Table 3. Demographics and Disease Specific Characteristics at Baseline for Patients with a BRAF V600E or V600K Mutation							
	MEK113583		**MEK114267**		**MEK113583 + MEK114267**		
	V600E n=79	**V600K** n=12	**V600E** n=281	**V600K** n=40	**V600E** N=360	**V600K** N=52	P Value[1]
Age at Initial Diagnosis (years)							
Median (Min-Max)	49 (24-75) n=56	50 (38-69) n=10	48 (2-80) n=280	57 (32-77) n=40	48 (2-80) n=336	57 (32-77) n=50	<.0001
Age at Study (years)							
Median (Min-Max)	54 (23-79)	62 (40-73)	53 (21-85)	62 (33-78)	54 (21-85)	64 (33-78)	<.0001
Time Elapse from Initial Diagnosis to Study (years)							
Median (Min-Max)	2.5 (0.2-22.5)	3.1 (0.5-15.2)	2.5 (0.1-36.2)	2.6 (0.4-9.6)	2.5 (0.1-36.2)	2.8 (0.4-15.2)	NS
Age Category at Study (n, %)							
< 65 years	60 (76)	7 (58)	227 (81)	24 (60)	287 (80)	31 (60)	0.0012
≥ 65 years	19 (24)	5 (42)	54 (19)	16 (40)	73 (20)	21 (40)	
Sex, n (%)							
Male	53 (67)	9 (75)	141 (51)	32 (80)	194 (54)	41 (79)	0.0007
Female	26 (33)	3 (25)	140 (49)	8 (20)	166 (46)	11 (21)	
ECOG Performance Status, n (%)							
ECOG 0	51 (64)	8 (67)	178 (63)	27 (68)	229 (64)	35 (67)	NS
ECOG 1	27 (35)	4 (33)	103 (37)	13 (32)	130 (36)	17 (33)	
M stage at screening, n (%)							
M0	1 (1)	0	11 (4)	2 (5)	12 (3)	2 (4)	NS
M1a	9 (11)	2 (17)	38 (14)	3 (8)	47 (13)	5 (10)	
M1b	10 (13)	1 (8)	50 (18)	7 (18)	60 (17)	8 (15)	
M1c	59 (75)	9 (75)	181 (65)	28 (70)	240 (67)	37 (71)	
Histology at Initial Diagnosis, n (%)							
In Situ	3 (4)	1 (1)	-	-	3 (1)	1 (2)	NE
Superficial Spreading	8 (10)	2 (16)	78 (27)	8 (20)	86 (24)	10 (19)	
Nodular	6 (8)	-	62 (22)	12 (30)	68 (19)	12 (23)	
Acral Lentiginous	3 (4)	-	1 (1)	-	4 (1)	-	
Lentigo Maligna	-	2 (16)	-	-	-	2 (4)	
Unknown	59 (74)	7 (58)	140 (50)	20 (50)	199 (55)	27 (52)	
Baseline LDH, IU/L							
Median (Min-Max)	437 (91- 3907)	473 (104-1057)	199 (100-3263)	219 (137-057)	212 (91-3907)	236 (104-1057)	NS
Baseline LDH Category, n (%)							
≤ 234	20 (28)	4 (33)	165 (64)	21 (54)	185 (56)	25 (49)	NS
> 234	49 (71)	8 (67)	93 (36)	18 (46)	142 (43)	26 (51)	
Prior History of Brain Metastases, n (%)							
Yes	15 (19)	2 (17)	8 (3)	2 (5)	23 (6)	4 (8)	NS
No	64 (81)	10 (83)	273 (97)	38 (95)	337 (94)	48 (92	

[1] Two-sided with p-value < 0.05 considered statistically significant; no correction for multiple comparisons.

NS = not significant; NE = not evaluable

Tumor Response

The investigator best response (**Table 4**) and maximal tumor reduction (**Figure 1**) show that trametinib has activity in patients with BRAF V600E and V600K melanoma in both clinical

studies. No complete responses and fewer partial responses were noted in patients with BRAF V600K mutations. Furthermore, trametinib appears to provide minimal activity for patients with either BRAF V600E or V600K melanoma who received prior treatment with a BRAF inhibitor (Cohort A, Study MEK113583). Age, gender and V600 mutation status were not associated with investigator maximal tumor reduction or best response; however, the data suggest a trend in poorer response in patients with V600K mutations. It is possible that no statistically significant differences were identified due to the relatively small sample size.

Table 4. Investigator Best Response [Applicant Data]

Study MEK113583				
	Cohort A Prior Treatment with a BRAF Inhibitor		**Cohort B** No Prior Treatment with a BRAF Inhibitor	
	V600E (n=30)	**V600K** (n=4)	**V600E** (n=45)	**V600K** (n=8)
Complete Response	-	-	1 (2.2%)	-
Partial Response	-	-	11 (24%)	-
Stable Disease	9 (33%)	2 (50%)	24 (53%)	5 (62%)
Progressive Disease	20 (66%)	2 (50%)	8 (18%)	2 (25%)
Not Evaluable	1 (1.0%)	-	1 (2.2%)	1 (12%)
BORR (90% CI)	0%	0%	27% (17%, 39%)	0%
Study MEK114267				
	Trametinib		**Chemotherapy**	
	V600E (n=182)	**V600K** (n=29)	**V600E** (n=90)	**V600K** (n=9)
Complete Response	4 (2.2%)	-	-	-
Partial Response	40 (22%)	3 (10%)	7 (7.8%)	2 (22%)
Stable Disease	97 (53%)	22 (76%)	32 (36%)	2 (22%)
Progressive Disease	35 (19%)	3 (10%)	45 (50%)	5 (56%)
Not Evaluable	6 (3.3%)	1 (3.4%)	6 (6.7%)	-
BORR (90% CI)	24% (19%, 30%)	10% (4.2%, 23%)	7.8% (4.3%, 14%)	22% (7.6%, 50%)

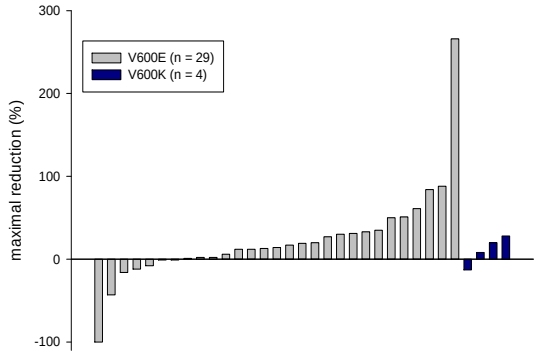
Source: Reviewer's analysis, data from oncttern database;

BORR = best overall response rate, CI = confidence interval

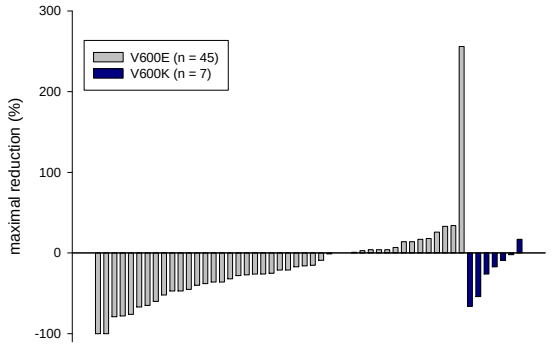
Figure 1. Maximal Reduction in Tumor Response as Documented by Investigator [Applicant Data]

Study MEK113583

Cohort A

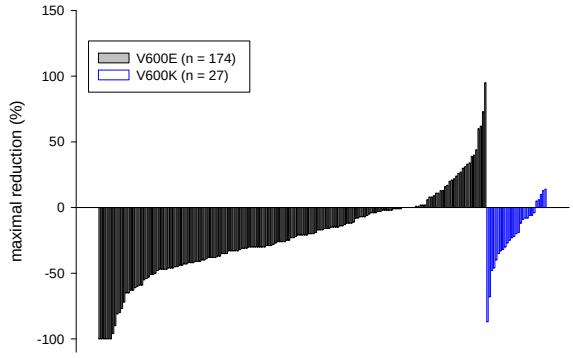


Cohort B

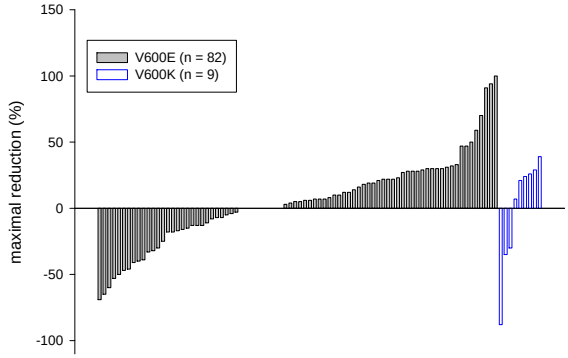


Study MEK 114267

Trametinib



Chemotherapy



Source: Reviewer's analysis, data from oncttern database

4 SUMMARY AND CONCLUSIONS

- In Studies MEK113857 and MEK114267, trametinib demonstrated clinical activity in patients with BRAF V600E or V600K metastatic melanoma without prior treatment with a BRAF inhibitor, supporting its use in this patient population providing that the clinical and statistical review determines a favorable benefit-risk.
- Based on the literature and applicant's clinical trial data, patients with BRAF V600K mutated metastatic melanoma are more likely to be male and older at initial diagnosis compared to patients with the more common V600E mutation. No other clinicopathological features included in our analyses correlated with the V600 mutation.
- Older age, male gender and V600K mutation have been associated with poorer prognosis in patients with melanoma [PMID: 22535154; 2316948; 22039425 22800552] Nonetheless, clinical activity was generally consistent across subgroups including age, gender and V600 mutation based on the applicant's (PFS, Appendix Figure 2) and our analyses. Of note, results for BRAF V600K mutation-positive melanoma, and for patients aged ≥65 years were

not statistically significant possibly due to the smaller sample size of these subgroups (Appendix Figure 2).

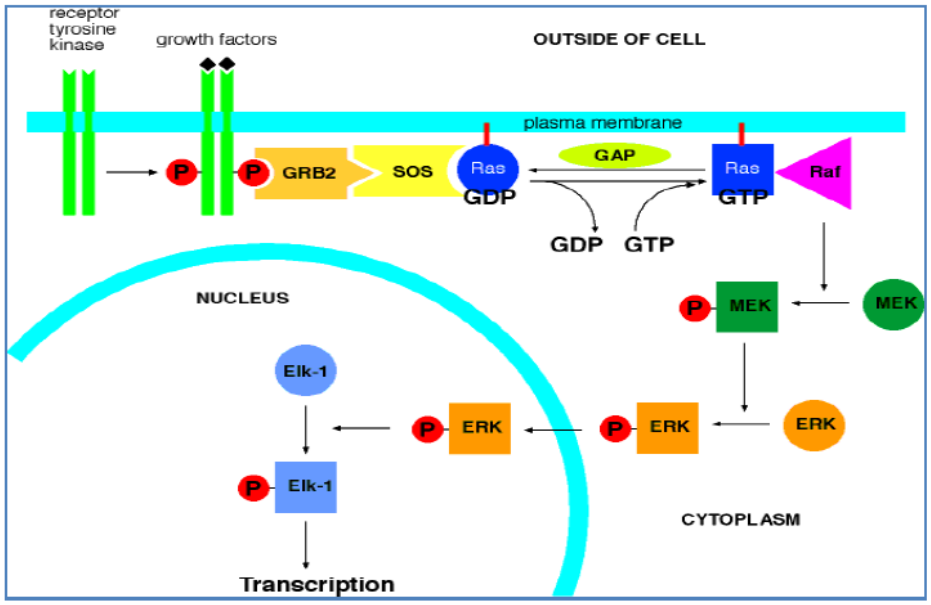
- Our findings support the published literature in that BRAF V600 mutated melanoma may be further categorized based on distinct V600 mutations. Potential differences in clinicopathological features and sensitivity to inhibitors of the MAPK signaling pathway according to the unique V600 mutation should be carefully considered when designing studies and interpreting results and underscores the importance of assessing V600 mutations in more detail. Of note, biological or clinical distinctions based on the underlying mutation are not unique to BRAF in melanoma, as similar findings have been reported for EGFR [PMID: 15118073] and KRAS [PMID: 21169473; 23437064] mutations.

5 RECOMMENDATIONS

The NDA is acceptable from the OCP Genomics Group perspective. No labeling or post-approval actions are proposed at this time.

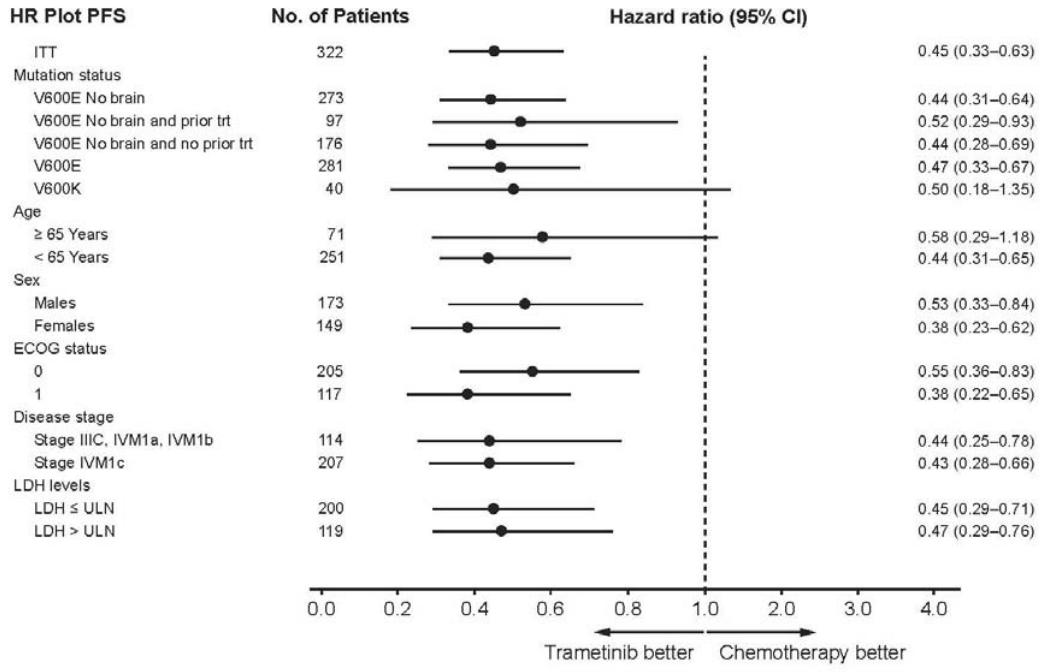
APPENDICES

Appendix Figure 1. MAPK Signaling Pathway



Source: Nonclinical overview

Appendix Figure 2. Hazard Ratios and 95% Confidence Ratios for Investigator Assessed Progression Free Survival observed in Study MEK114267



Source: Summary Clinical Efficacy, Figure 5

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/s/

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BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 204-114	**Reviewer:** Minerva Hughes, Ph.D.	
Submission Date:	3 August 2012		
Division:	Division of Oncology Products 2	**Team Leader:** Angelica Dorantes, Ph.D.	
		Supervisor: Richard Lostritto, Ph.D.	
Sponsor:	GlaxoSmithKline	**Secondary Reviewer:** John Duan, Ph.D.	
Trade Name:	Mekinist (proposed)	**Date Assigned:**	26 July 2012
		GRMP Date: **PDUFA Date:**	8 April 2013 3 June 2013
Generic Name:	Trametinib	**Date of Review:** Revised:	13 March 2013 5 April 2013
Indication:	unresectable or metastatic melanoma with BRAV V600 mutations	**Type of Submission: Original NDA, NME**	
Formulation/ strengths	Film-coated Tablet: 0.5 mg, 1 mg and 2 mg		
Route of Administration	Oral		

Biopharmaceutics Review Focus:

- Suitability of the dissolution test method and acceptance criteria
- Suitability of the dissolution test method or other performance outputs (e.g., disintegration) in QbD considerations
- Dissolution stability
- Defining acceptable DMSO content limits
- Acceptability of the in vitro data bridging the Phase III and commercial product formulation and process changes.

SUBMISSION: NDA 204-114 was submitted in accordance with Section 505(b)1 of the FD&C act for the use of trametinib in the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation. Trametinib (GSK1120212 or JTP-74057) is a novel, reversible, selective, (b) (4) inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2; proteins that are critical for cell proliferation and survival. The drug was developed specifically to address known oncogenic mutations in upstream mitogen-activated protein kinase (MAPK) pathway proteins BRAF and Ras, which signal through MEK1 and MEK2. The drug substance is the dimethyl sulfoxide (DMSO) solvate of trametinib.

The proposed drug product is an immediate-release tablet comprised of the drug substance and the excipients mannitol, microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate (vegetable source), sodium lauryl sulfate, colloidal silicon dioxide. The tablets are available in three strengths (0.5, 1, and 2 mg), which are film-coated with a solution of hypromellose, titanium dioxide, polyethylene glycol, polysorbate 80 (2 mg tablets), iron oxide yellow (0.5 mg tablets), or iron oxide red (2 mg tablets).

NDA 204-114 contains Quality-by-Design (QbD) elements such as the identification of critical

quality attributes (CQAs), risk assessments, proven acceptable ranges (PARs), and design of experiment (DoE) studies. Product dissolution was identified as a CQA, which is affected by formulation components and process parameters (b) (4)

BIOPHARMACEUTICS CONCLUSIONS/ RECOMMENDATION:

1. The following dissolution method and acceptance criterion is recommended for approval.

Dissolution Method	
Apparatus	USP 2
Medium	pH 4.5 Acetate buffer, with 0.75% sodium lauryl sulfate, 500 mL
Agitation Speed	60 rpm
Temperature	37°C
Sampling Times	5, 15, 30, and 45 min
Analytical Method	HPLC
Acceptance Criterion	Q = (b) (4) at 20 minutes

2. The proposed commercial product was adequately bridged to the Phase III product using in vitro dissolution. The minor changes implemented for the commercial product, (b) (4), are not expected to affect bioavailability, provided the in-process and finished product testing controls are met.

3. Dissolution was used a quality output for various manufacturing parameters. From the Biopharmaceutics perspective, the following ranges are acceptable.
   a. Drug substance particle size: (b) (4) (b) (4)
   b. Tablet coating weight gain: (b) (4)
   c. (b) (4)
   d. (b) (4) : (b) (4)
   e. (b) (4) : (b) (4)

All recommendations inconsistent with the Applicant's proposal were communicated to the appropriate Chemistry Reviewer for consideration.

4. Dissolution is not rate limiting for setting a product shelf-life either at room temperature or refrigerated storage.

5. Relying on dissolution data to qualify changes in DMSO content is not recommended. Using clinical exposure data, a DMSO content range of (b) (4) is recommended for approval.

Overall, the NDA is recommended for approval from the Biopharmaceutics perspective. The pending product storage/shelf life items will be addressed by Quality Reviewer Ms. Sue-Ching Lin in her review.

Minerva Hughes, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

John Duan, Ph.D.
Biopharmaceutics Secondary Reviewer
Office of New Drug Quality Assessment

BIOPHARMACEUTICS REVIEW NOTES

1.0 GENERAL INFORMATION

1.1 Relevant Regulatory History

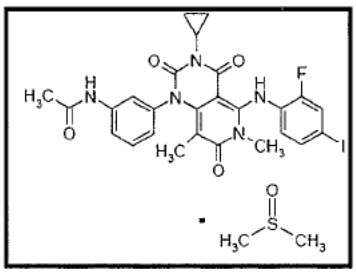
NDA 204-114 was submitted in accordance with Section 505(b)1 of the FD&C Act for the use of trametinib in the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutations in combination with the bioMerieux BRAF THxID companion diagnostic assay (PMA reviewed in parallel with NDA). Trametinib (GSK1120212 or JTP-74057) is a novel, reversible, selective, (b) (4) inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2; proteins that are critical for cell proliferation and survival. The drug was developed specifically to address known oncogenic mutations in upstream mitogen-activated protein kinase (MAPK) pathway proteins BRAF and Ras, which signal through MEK1 and MEK2.

Relevant Biopharmaceutics advice provided under the referenced IND 102,175 is summarized below.

- 9 November 2010, EOP2 CMC Meeting
  - Changes in tablet size for a low dose formulation may preclude the use of dissolution for comparability testing to bridge the Phase 3 and commercial product. Both parties agreed to address the issue under the IND.
  - The proposed dissolution method showed inconsistent data throughout the submission so FDA could not comment on the appropriateness of the method.
- 15 February 2012, pre-NDA CMC Meeting
  - The dissolution method appeared reasonable but the data provided were incomplete to support a full evaluation. Additionally, the data showed that DMSO content was critical for product performance. Therefore, the proposed DMSO range should be supported with in vivo bioavailability data.
    - The Applicant stated that they did not qualify the DMSO limits with bioavailability data. In lieu of this, FDA requested additional information on the clinical trial material and drug-DMSO physico-chemical properties.

1.2 Drug Substance Summary

The proposed drug substance trametinib dimethylsulfoxide (DMSO), is a 1:1 stoichiometric DMSO solvate with the following structure and formula.



Structure of trametinib DMSO, $C_{26}H_{23}FIN_5O_4 \cdot C_2H_6OS$, 693.53 (DMSO solvate)

Trametinib DMSO (GSK1120212B) was selected for clinical development over the nonsolvated parent form based on its desirable solid state properties, higher solubility and improved oral bioavailability. In pre-clinical studies in rats, a suspension of the crystalline trametinib DMSO had an oral bioavailability of 42%, similar to the solution prepared using acetic acid solvate. Trametinib concentrations were not detected after the administration of the free form suspension using the same oral dose of 3 mg/kg. Although trametinib DMSO is claimed to have better solubility than the non-solvated parent form, its solubility in pH 2 to 8 is still very low (see below). (b) (4) of the drug substance was employed to maximize the bioavailability and manufacturability of the dosage form. (b) (4)

(b) (4)

General properties include the following.

- pKa = 0.25 (acetamide, calculated)
- pH = 8.4 (saturated solution)
- LogP = 4.99
- Solubility

Solvent	Solubility[1] (µg/mL)			
	0.5 hour	2 hours	4 hours	24 hours
(b) (4)				

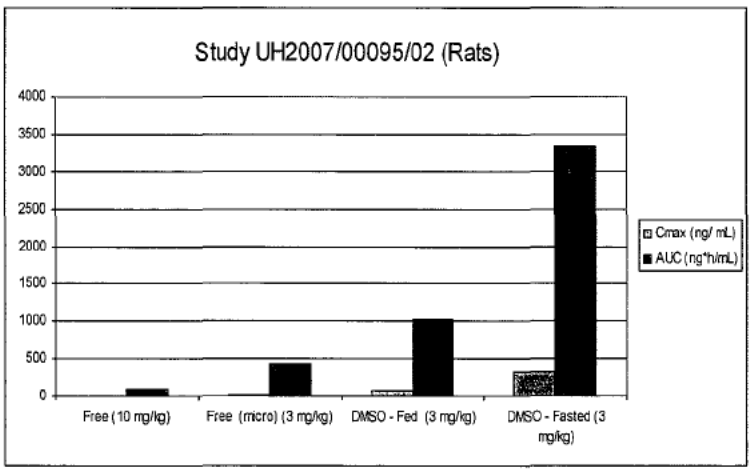
Solvent	Input Form	Solubility at 20°C (mg/mL)
		(b) (4)

Notes
1. Trametinib (non-solvated parent)
2. Trametinib dimethyl sulfoxide

- Polymorphs: (b) (4) is targeted for the DMSO co-solvate.

The drug substance specification includes tests for appearance, identification, crystal structure, purity, DMSO content, residual solvents, (b) (4) heavy metals, and particle size. The proposed particle size acceptance criteria are (b) (4) (b) (4) In silico modeling (Gastroplus) suggested that a median particle size of 10 µm was necessary to maximize in vivo exposure.

Reviewer's Assessment: *The DMSO co-solvate complex is important for clinical performance. A detailed review of the animal pharmacokinetic (PK) studies is not covered by this reviewer. However, the formulation evaluation studies done in animals provide some relevant points regarding the potential impact of DMSO desolvation on bioavailability, especially since clinical studies were not completed using the free base. The mean Cmax and AUC data from one of the rat pre-clinical studies are illustrated in the following figure, generated by the reviewer.*



Particle size and DMSO solvation clearly affected overall drug exposure. The effect of DMSO solvation on drug bioavailability was drastic (compare column 1 and column 4). There was also a negative food effect in rats, which is analogous to the human PK studies. Although particle size and DMSO solvate structure appear to be critical, optimal product performance seems to rely on more than just improving solubility given that the DMSO-cosolvate is almost 5X less soluble in FaSSIF compared with FeSSIF media (depending on time), but drug exposure is greater under fasting conditions.

The CMC package should provide adequate controls for DMSO desolvation at both the drug substance and drug product manufacturing steps. The manufacturing information is reviewed by the assigned Review Chemists.

1.3 Drug Product Summary

The proposed drug product is an immediate release tablet for oral administration containing trametinib DMSO equivalent to 0.5 mg, 1 mg or 2 mg trametinib (non-solvated parent). Different shapes and colors are used to assist in the visual identification of the different strengths. Trametinib Tablets-0.5 mg, are yellow, modified oval, biconvex, film-coated tablets debossed with GS on one face and TFC on the opposing face. Trametinib Tablets-1 mg are white, round, biconvex, film-coated tablets debossed with GS on one face and LHE on the opposing face. Trametinib Tablets-2 mg are pink, round, biconvex, film-coated tablets debossed with GS on one face and HMJ on the opposing face

The compositional formula is summarized in the following table.

Trametinib Tablet Composition

Component	Quantity (mg/tablet)			Function	Reference to Standard[1]
Strength	0.5	1	2		
Trametinib Dimethyl Sulfoxide[2]	(b) (4)			Active	GSK
Mannitol				(b) (4)	USP
Microcrystalline Cellulose					NF
Hypromellose (b) (4)					USP
Croscarmellose Sodium					NF
Sodium Lauryl Sulfate					NF
Colloidal Silicon Dioxide					NF
Magnesium Stearate[3]					NF
(b) (4) Yellow (b) (4)					Supplier
White (b) (4)					Supplier
Pink (b) (4)					Supplier
(b) (4)					USP
Total Tablet Weight	149.35	159.65	169.95	-	-

The proposed commercial formulation is the same as used in clinical studies, except that the film coat color was changed from (b) (4) to yellow for the 0.5 mg tablet. The proposed manufacturing process is a (b) (4)

The finished tablets are packed with desiccant in opaque, white HDPE bottles with a (b) (4) closure that includes a (b) (4) faced foil induction seal liner.

Reviewer's Assessment: *The reviewer has no specific concerns with the proposed formulation. It is noted, however, that the different tablet strengths* (b) (4) *The Phase III study in subjects with metastatic melanoma (MEK114267) used the intended 0.5, 1.0, and 2.0 mg tablets, and a biowaiver is not applicable unless the Phase III product is not representative of the to-be-marketed product. In vitro dissolution data are generally acceptable to qualify the proposed*

change to the 0.5 mg tablet film coat. See Section 2.0 of this review for a detailed discussion of the dissolution method and product bridging studies.

Overall, the comparative dissolution data show that the proposed change to the 0.5 mg film coat is acceptable and bioequivalence studies are not necessary.

1.4 Pharmacokinetic/Clinical Summary

In all clinical studies, trametinib was administered as the DMSO solvate. The oral bioavailability of the 2.0 mg tablet was moderate to high with a geometric mean (90% CI) of 72.3% (50.0, 105). Administration of a single, 2 mg oral tablet dose of trametinib with a high-fat, high calorie meal resulted in a 70% decrease in maximum plasma concentration (Cmax), and a 10% decrease in area under the plasma concentration-time curve from time zero (predose) extrapolated to infinity (AUC(0-∞)), compared with fasted conditions. The Tmax was delayed by approximately 4 hours with food. Under fasting conditions, peak plasma concentrations were observed after 1.5 hours, and exposure was dose proportional between 0.125 and 4 mg.

Trametinib has a long terminal half-live (5.3 days) and accumulates with repeat once daily dosing, with a mean accumulation ratio of 5.97 with 2.0 mg once daily dosing. The Applicant's recommended dose is 2 mg, orally, once daily (b) (4) , at least one hour before or two hours after a meal, with appropriate modifications to manage adverse reactions.

Reviewer's Comment: *See the Clinical Pharmacology and Clinical Reviews for the Agency's recommendation on the PK and clinical data, respectively. The reduced rate of drug absorption under fed conditions does not appear to affect overall exposure in any appreciable way. To the extent that AUC is a better indicator of effectiveness, the data suggest to the reviewer that there is a reduced risk of clinical performance issues under slower uptake conditions.*

1.5 Biopharmaceutics Classification

The Applicant proposed a BCS classification of Class 2 (low solubility, high permeability). The permeability conclusions were based on in vitro permeability studies using MDCKII-MDR1 cells, with appropriate reference compounds for high and low permeability. The Applicant also referenced the Developability Classification System (DCS) and proposed a DCS classification of DCS 1, with the claim that absorption in vivo is not expected to be solubility limited.

Reviewer's Comment: *The drug's low solubility is noted. Since a BCS Class 1 designation is not requested, the proposed designation has no impact on future regulatory actions for biowaivers and is not reviewed in detail. Additionally, the DCS classification system is not used by FDA for classifying drug products. Of note, despite the Applicant's assertion regarding the limited impact of drug solubility on absorption, solubility does appear to play an important role in overall product performance and was the basis for selecting the DMSO solvate as optimal for development.*

The in vitro/in vivo permeability data are not under Biopharmaceutics' purview. However, to this reviewer, a BSC Class II designation seems appropriate.

1.6 Biopharmaceutics Review Focus

This Biopharmaceutics review evaluates the (1) acceptability of the proposed dissolution test method and acceptance criterion, (2) the appropriateness of drug product process controls affecting product dissolution, (3) the appropriateness of the drug product quality attributes affecting the biopharmaceutics properties of the product, (4) product dissolution data supporting any changes between the to-be marketed product and the clinical product, and (5) the dissolution stability data supporting the proposed shelf-life. Review topics 2, 3 and 5 are evaluated in close collaboration with the assigned CMC Reviewer.

2.0 BIOPHARMACEUTICS REVIEW

2.1 Dissolution Method

The proposed dissolution method for Trametinib Tablets is summarized below.

Dissolution Method	
Apparatus	USP 2
Medium	pH 4.5 Acetate buffer, with 0.75% sodium lauryl sulfate, 500 mL
Agitation Speed	60 rpm
Temperature	37°C
Sampling Times	5, 15, 30, and 45 min
Analytical Method	HPLC
Acceptance Criterion	Q = (b) (4)

Note: The reviewer rejected the Applicant's proposed acceptance criterion of Q = (b) (4) (b) (4) The final agreed upon limit is Q (b) (4) at 20 minutes. See subsequent sections for full details.

2.1.1 Dissolution Method Development

(b) (4)

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2.2 Dissolution HPLC Method and Method Validation

The dissolution HPLC instrument parameters are the same as used for drug content and impurities.

Column details	(b) (4)
Column temperature	40°C
Mobile phase A	0.05% v/v TFA in Water
Mobile phase B	0.05% v/v TFA in Acetonitrile
Flow rate	1.0 mL/min
Detector wavelength	UV at 245 nm

The method was validated according to pre-specified criteria for specificity, linearity, accuracy, repeatability, solution stability, filter compatibility and robustness.

Reference was made to the dissolution method DOE studies for robustness assessment. The repeatability, reproducibility, and sample stability results are summarized below since they are most specific to applying the method to dissolution sample analysis.

- Repeatability: the RSD of the 6 standards should be ≤ 1.5%. The RSD of the six 0.5, 1 and 2 mg samples at the Q time point of 30 minutes should (b) (4)
  - (b) (4)
- Reproducibility: the 90% confidence interval for the difference in mean values (percent released) (b) (4) (two different analysts from same site) is completely contained within the bound as determined by the TOST (two one sided t) test alternatively, if the acceptance range calculated for the TOST test is less than 5.0%, the acceptable difference in mean values is ±5.0% released.
  - Result: Pass.
- Sample Stability: 7 days = stock standard; 14 days = working standard; 1 day = sample solution in test tubes; 5 days = sample solution in capped HPLC vials.

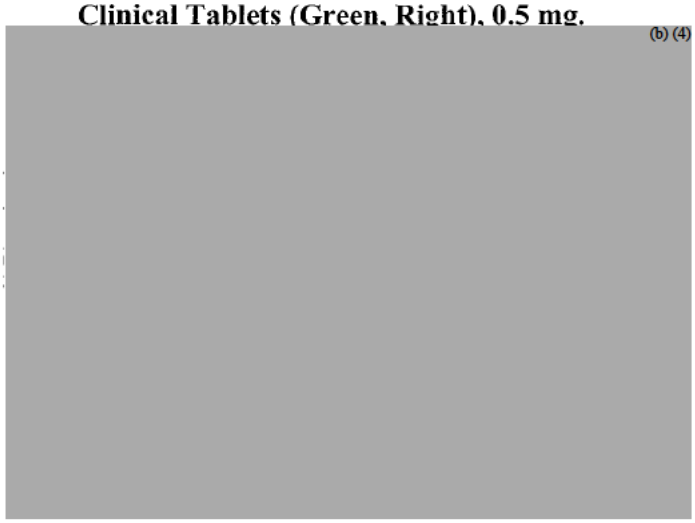
Reviewer's Assessment: *The acceptability of the dissolution HPLC method validation data are handled by the assigned Review Chemist, particularly in this case when the HPLC method is the same as the drug content method. Thus, method validation paralleled the HPLC method for drug content and impurities.*

In response to review concerns about the dissolution acceptance criterion, the Applicant proposed a new limit of Q = (b) (4) *at 20 minutes using statistical modeling. The FDA Method Validation Review Staff was consulted to evaluate the suitability of the dissolution method, with sampling at Q =* (b) (4) *at 20 minutes, to support product testing for regulatory purposes. The Method Validation Review by Michael Trehy, dated 29 March 2013, concludes that the dissolution method is acceptable for regulatory purposes.*

2.3 Dissolution Acceptance Criterion

The proposed acceptance criterion is Q = (b) (4) The proposed limit was based on the observed dissolution profiles for the clinical and Primary Stability batches. The data variability plots for individual tablets generated by the Applicant are illustrated below.

Variability Plot for Dissolution Stability Through 12 months (Red, Left) and Phase III Clinical Tablets (Green, Right), 0.5 mg.



Variability Plot for Dissolution Stability Through 12 months (Red, Left) and Phase III Clinical Tablets (Green, Right), 1 mg.

Variability Plot for Dissolution Stability Through 12 months (Red, Left) and Phase III Clinical Tablets (Green, Right), 2 mg.

FDA requested additional information to justify the proposed limit of Q = (b) (4) in the Information Request letter dated 21 November 2012. Responses were received on 7 December 2012, as summarized below.

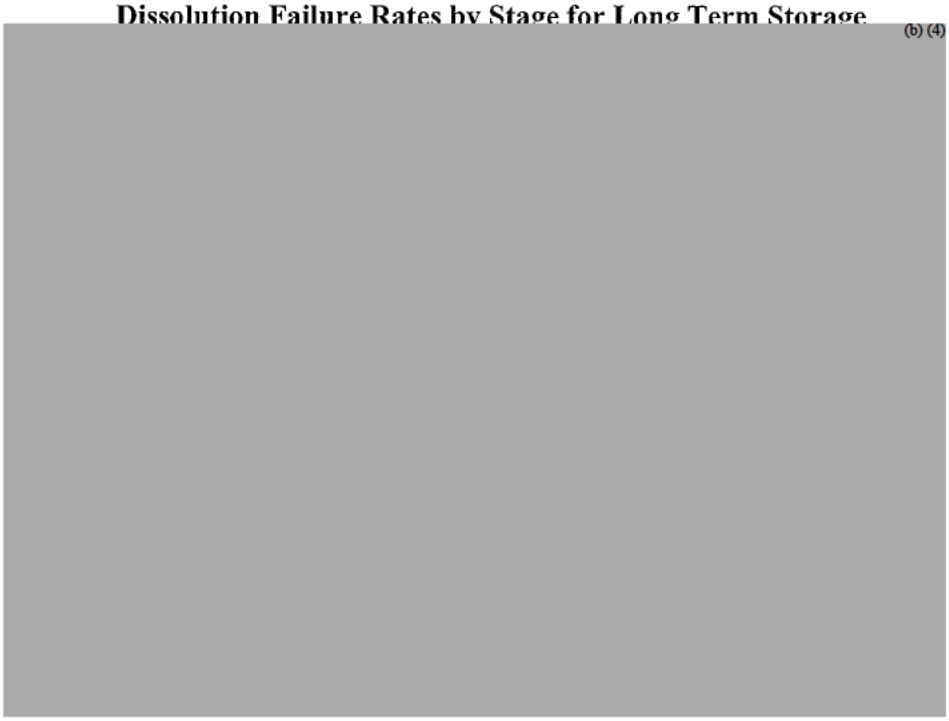
The Applicant proposed an acceptance limit of Q (b) (4) at 20 minutes. Although dissolution data for sampling at the 20 minute time point have not been collected, the Applicant developed a model using the available dissolution data to predict the dissolution at 20 minutes. A Weibull model (as shown in the equation below) was found to be appropriate, with all residuals between +1 and -1% dissolution:

$$\%Released = Max * \left(1 - exp\left(\frac{-(t - T_{lag})^b}{a}\right)\right)$$

Using the model, the predicted mean dissolution at 20 minutes was approximately 3% higher than the (b) (4) time point.

The estimated dissolution stage 1/2/3 failure rates were done using the dissolution data at (b) (4) and estimated 20 minute data (b) (4)

Dissolution Failure Rates by Stage for Long Term Storage



Reviewer's Assessment: *The Applicant's initially proposed acceptance criterion seems to target an individual unit performance of* (b) (4) *however, the dissolution test is a staged test based on mean and individual unit performance. Acceptance limits set to pass all individual units at stage 1 testing is not sufficiently discriminating. After reviewing the individual dissolution stability and batch release data, a limit of Q =* (b) (4) *may be more appropriate if the percentage of stage 2 testing is reasonable (See NDA Section P.5.6). In response to FDA's request for additional information to justify the proposed dissolution acceptance criterion, the Applicant proposed a new limit of Q =* (b) (4) *at 20 minutes based on predicted dissolution at 20 minutes because there is no 20 minute sampling data available. The predicted failure rates show that even at* (b) (4)*, there are no anticipated stage 2 or 3 failures. However, the frequency of stage 2 testing at* (b) (4) *is relatively high, which suggest that* (b) (4) *may be too restrictive. Electronic stability data sets were not available for ease for reanalysis. A visual review of the individual data by the reviewer did note several instance of stage 1 failures at* (b) (4)*, but the reviewer did not anticipate a frequency of* (b) (4) *as noted by be Applicant. Relying on the Applicant's analysis, an acceptance criterion of Q =* (b) (4) *at 20 minutes seems to provide better quality control than the initial limit of Q =* (b) (4) *and is acceptable. During development, the* (b) (4) *sampling time point was the least sensitive to detect product changes.*

The lack of 20 minute dissolution stability data was discussed with the CMC Review team, with regards to setting a shelf-life. The team was in agreement that since the (b) (4) *dissolution stability data suggest product will meet a limit of Q =* (b) (4) *albeit at Stage 2 or 3 through 12 months, it is reasonable to expect satisfactory results at 20 minutes (dissolution stability data* (b) (4) *are summarized in Section 3.2.P.5.6. The Applicant will collect dissolution data at 20 minutes for the post approval stability study and ongoing annual stability studies. Dissolution data did not appear to be rate limiting for defining the product's shelf life. Any future issues will be addressed within the appropriate post-approval regulatory framework.*

A revised drug product specification reflecting a dissolution acceptance criterion of Q= (b) (4) *at 20 minutes was received on 27 February 2013.*

2.4 Formulation Changes and Dissolution Bridging Studies

Tablets used in early clinical studies were qualitatively similar to the Phase III and commercial tablets. The manufacturing (b) (4) was optimized before Phase III studies, which resulted in qualitative changes in various excipients. The Phase III tablets were manufactured at the proposed commercial site using the proposed commercial process. There are two differences between the Phase III and commercial tablets:

1. The 0.5 mg tablet film coat was changed from (b) (4) to yellow (b) (4) (b) (4)

   a. Comparative dissolution data in three different media (0.01N HCl with 0.5% SDS, 50 rpm, 50 mM acetate buffer, pH 4.5 with 0.75% SDS, 60 rpm, 50 mM phosphate buffer, pH 6.8 with 0.5% SDS, 50 rpm) were submitted to qualify the proposed change.

      The results of similarity f1/f2 tests are tabulated below.

Comparative Dissolution Data for Clinical versus Proposed Commercial Trametinib Tablets, 0.5 mg

Media, Paddle Speed	Difference Factor f_1	Similarity Factor f_2	Evaluation
Acceptance Criteria	0 - 15	50 - 100	Profiles Equivalent
0.01 N HCl with 0.5% SDS, 50 rpm	1.8	84.1	Yes
50 mM Acetate Buffer, pH 4.5 with 0.75% SDS, 60 rpm[1]	2.9	78.4	Yes
50 mM Phosphate Buffer, pH 6.8 with 0.5% SDS, 50 rpm	4.2	68.5	Yes

Source: Table 7, Section P.2.2.

2. (b) (4)

   a. Comparative dissolution data in three different media (0.01N HCl with 0.5% SDS, 50 rpm, 50 mM acetate buffer, pH 4.5 with 0.75% SDS, 60 rpm, 50 mM phosphate buffer, pH 6.8 with 0.5% SDS, 50 rpm) were submitted to qualify the proposed change.

      The results of similarity f1/f2 tests are tabulated below.

In-Vitro Dissolution Comparison of Phase III Clinical versus Proposed Commercial Trametinib Tablets, 2 mg

Media, Paddle Speed	Difference Factor f_1	Similarity Factor f_2	Evaluation
Acceptance Criteria	0 - 15	50 – 100	Profiles equivalent
0.01 N HCl with 0.5% SDS[1], 50 rpm	6.9	66.4	Yes
50 mM Acetate Buffer, pH 4.5 with 0.75% SDS[1], 60 rpm[2]	0.6	95.6	Yes
50 mM Phosphate Buffer, pH 6.8 with 0.5% SDS[1], 50 rpm	6.8	65.7	Yes

Source: Table 11, m2.3.P.

Other formulations used during development included a ^{14}C-trametinib oral solution and ^{14}C-trametinib solution for injection, which was used for ADME studies.

The NDA was updated on 7 December 2012 to include the complete comparative dissolution data for the 2 mg tablets (individual values) to allow FDA to verify the similarity conclusions.

Reviewer's Assessment: *The noted differences between the proposed commercial product and Phase III material are not expected to affect bioavailability. Applying SUPAC-IR principles, in vitro dissolution data are sufficient to bridge the clinical and to-be marketed products. The dissolution profiles were similar between the test and reference across the pH range tested, which was independently verified by the reviewer. Thus, additional bioequivalence data are not necessary to qualify the to-be-marketed material.*

Conclusion: A bioequivalence study is not needed. The to-be-marketed material was appropriately linked to the clinical trial material.

2.5 Dissolution and Formulation Development

(b) (4)

[redacted]

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(b) (4)

On 6 February 2013, the Applicant updated the NDA with a request to change the storage conditions from room temperature to refrigerated conditions (b) (4) *FDA requested a complete stability package to support refrigerated storage conditions; however, the Applicant was unable to submit the data before 15 April 2013.*

At the time of this report, a final CMC recommendation on product storage conditions and shelf life was pending.

Overall Conclusion: A DMSO content range of (b) (4) ***is recommended for approval. This change was agreed to by the Applicant (amendment dated 27 February 2013).***

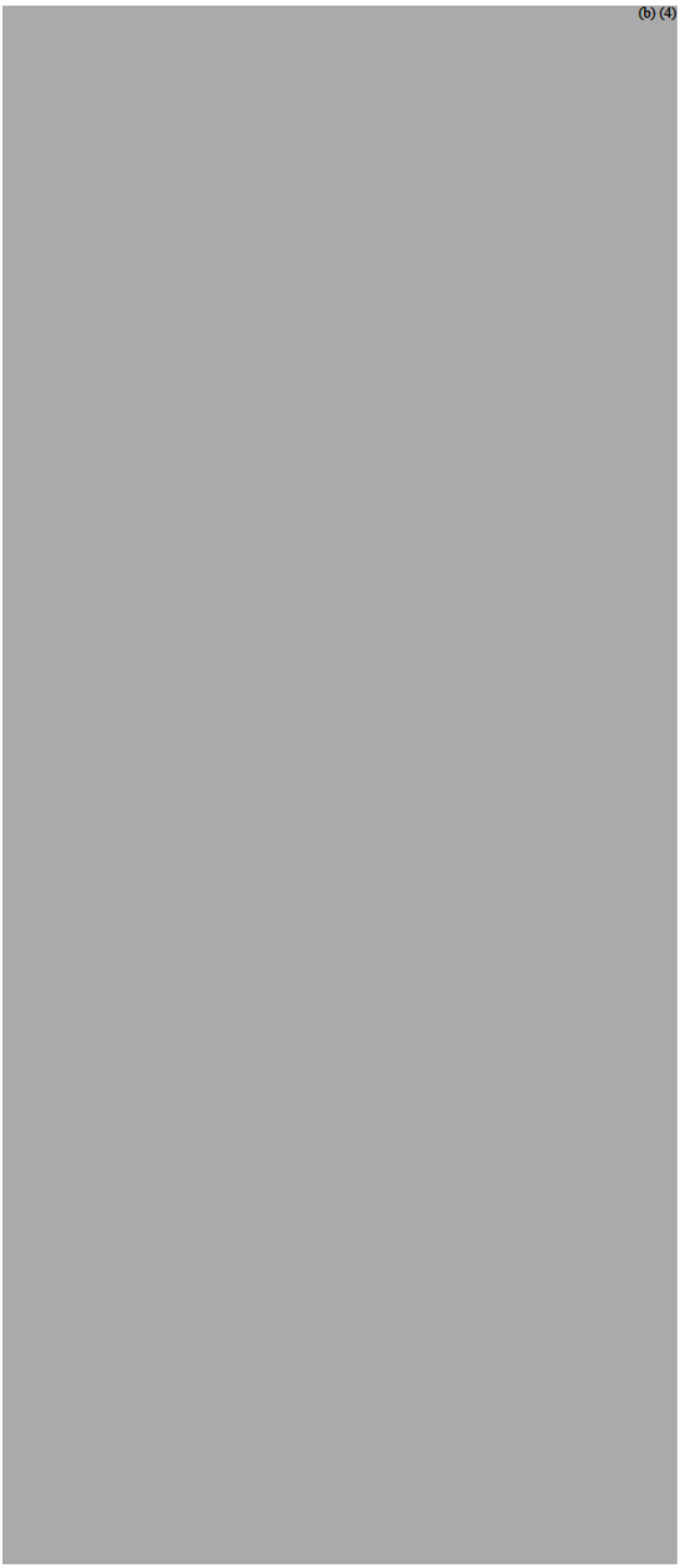
2.8 Product Stability (Dissolution)

Twenty four months primary stability data were submitted for three batches per strength of Trametinib Tablets, 0.5 mg, 1 mg and 2 mg, manufactured on a production-scale at the proposed commercial manufacturing site, GSK Parma. The batches of Trametinib Tablets are representative of those proposed for commercialization except for a (b) (4)

Stability data were also presented for confirmatory batches (one per strength in two different configurations) of Trametinib Tablets, 0.5 mg and 2 mg. At the time of this review, 9 months data were available for review (14 December 2012 update).

The summary dissolution data are illustrated in the following figures.

(b) (4)



The Applicant seeks to change the product storage condition from room temperature to refrigeration. There is limited dissolution stability data at 5°C; 12 – 24 months; three time points for two lots each of the primary stability batches and 0-9 months, one lot each of the confirmatory batches. However, the dissolution data were consistent with the findings at room temperature storage.

Reviewer's Assessment: *The dissolution stability data included only single point sampling at* (b) (4) *The mean dissolution across all samples and times was generally* (b) (4) *There was no consistent trend between the dissolution and DMSO content levels, which was somewhat expected given the method's sensitivity. The Applicant needs to confirm acceptable dissolution stability post marketing at the revised dissolution acceptance criterion of A=* (b) (4) *at 20 minutes. As mentioned previously, dissolution stability data* (b) (4) *sampling did not indicate any product failures, but the level 2 testing frequency was very high, which is why the reviewer accepted the firm's proposal for 20 minutes.*

Overall, dissolution does not appear to be limiting for setting a shelf life. *The DMSO content, however, is another issue, as discussed previously.*

Note on DMSO Stability

(b) (4)

3.0 BIOPHARMACEUTICS INFORMATION REQUESTS DURING THE REVIEW CYCLE

A list of the Information Requests submitted during the review cycle is provided below.

21 November 2012 request, responses received on 7 December 2012

1. Provide the complete dissolution data (individual values, means, and RSD) for all studies completed to support your proposed PAR for the 0.5 mg and 2 mg (b) (4)
2. Provide the complete dissolution data (individual values, means, and RSD) for the study evaluating the effects of the proposed changes to the 2 mg commercial tablet's dimensional attributes (b) (4) compared with the Phase III 2 mg tablet.
3. In vitro dissolution data are not appropriate to justify your proposed DMSO content acceptance range of (b) (4) given the limited discriminating power of your proposed dissolution method (500 mL pH 4.5 acetate buffer with 0.75% SDS, USP 2 at 60 rpm). In the absence of in vivo bioavailability data demonstrating acceptable drug exposure at your proposed DMSO lower limit, clinical study batch data (i.e., Table 2, Section 3.2.P.5.6 may be used to define an

appropriate range. Therefore, FDA recommends that you change your DMSO content lower limit from [redacted] to align with the clinical batch data. Provide a revised specification table that includes the recommended changes.

4. In consideration of the dissolution method's robustness, sensitivity to critical quality attributes and available dissolution stability data for the clinical and registration stability data, FDA believes that an acceptance criterion of Q = [redacted] is more appropriate for your rapidly dissolving immediate release product. Provide a revised specification table with the recommended changes or provide the following additional statistical data to further justify your proposed acceptance criterion of Q = [redacted]

    a. Estimated and predicted stage 1/2/3 testing and batch failure rates at release and after 12 and 24 months long-term storage with an acceptance criterion of Q = [redacted] compared with [redacted] for the pivotal clinical and primary stability lots.

    b. Trend analysis of the mean dissolution stability data at the [redacted] (include the standard deviation) sampling times for all storage conditions.

    c. Provide similar statistical data for sampling at the 20 minute time point, if these data are available.

Follow-up to Question 3 from 21 November 2012 IR and 19 December 2012 teleconference. Responses received on 16 January 2013. Additional information regarding the DMSO limit and product shelf-life was also submitted on 6 February 2013 and 27 February 2013.

1. As discussed during the December 19, 2012 teleconference, your proposal to maintain a DMSO content lower limit of [redacted] in response to FDA Question #3 in the November 21, 2012 information request letter is not acceptable. FDA considers changes in DMSO content to have a high likelihood of impacting clinical performance, and, as we have communicated previously, dissolution data alone are not sufficient to support these changes. We acknowledge your plans to conduct a bioequivalence study to address the effects of DMSO content on bioavailability. In the interim, we recommend a lower limit of not less than [redacted] which aligns with the available clinical batch data. Provide a revised drug product specification table in line with the proposed recommendation. In addition, we acknowledge your proposal to change the dissolution acceptance criterion from Q [redacted] to Q= [redacted] at 20 minutes. Include these changes in your updated specification as well.

The Applicant's responses were incorporated into the previous sections of this review.

SUPPLEMENTAL TABLES AND FIGURES

Table 2 Potential Impact of Drug Substance Attributes on Drug Product Attributes

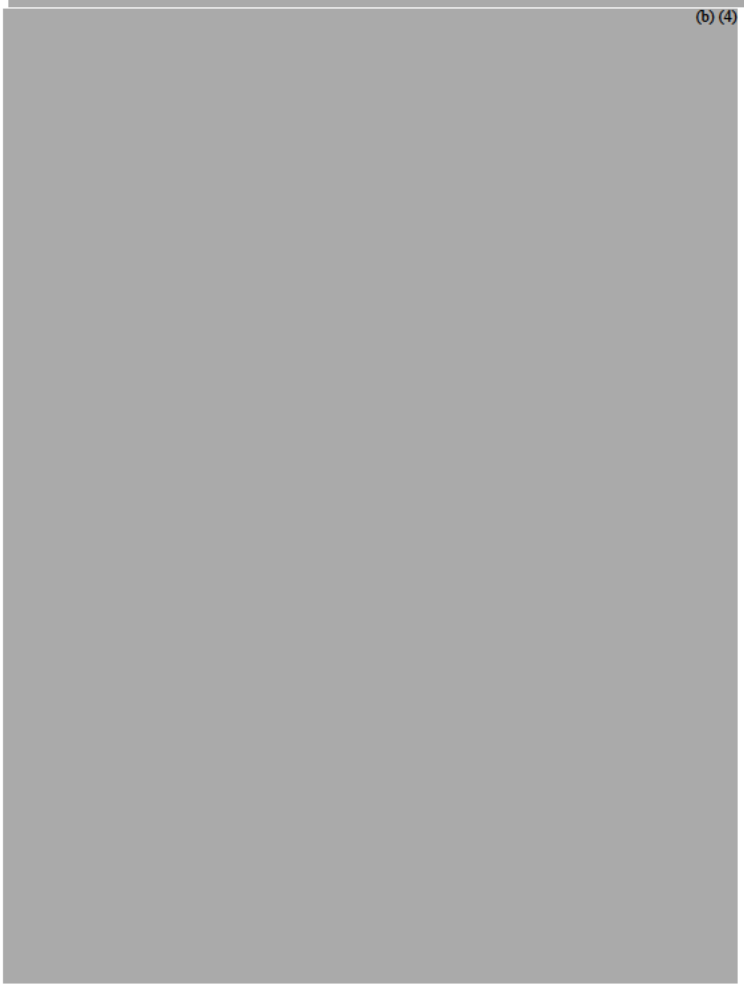
	Drug Product Attributes					
Drug Substance Attributes	Description and Identity	Uniformity of Dosage Units	Trametinib Content	DMSO Content	Dissolution	Impurities
Particle Size	Low	High	Low	Low	Medium	Low
Solid State Form	Low	Low	Low	High	High	Low
Impurities	Low	Low	Low	Low	Low	Medium
(b) (4)	Low	Low	Low	Low	Low	Low
DMSO Content	Low	Low	Low	High	Medium	Low
Residual Solvent Content	Low	Low	Low	Low	Low	Low

Note: The Applicant is not able to monitor solid state changes in the finished tablet and is using DMSO content as a surrogate, to some extent.

Figure 5 Dissolution Profiles of Over-lubricated vs Reference Tablets

(b) (4)


(b) (4)


(b) (4)

DMSO Detection Linear Stats for 50 RPM 0.75% Method

Table 16 Linear Regression Statistics, Dissolution vs. Desolvation by Dissolution Time Point

(b) (4)

DMSO Detection Linear Stats for 60 RPM 0.75% Method

Table 34 Regression Output for DMSO Content Data - Dissolution (% Claim) vs. DMSO Content (%) by Time (min), 2 mg Tablets in 14 Day Accelerated Stability (Exposed) Study

(b) (4)

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/s/

MINERVA HUGHES
04/05/2013

JOHN Z DUAN
04/05/2013

CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR NDA 204114

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	204114	**Brand Name**	MEKINIST
OCP Division (I, II, III, IV, V)	V	**Generic Name**	Trametinib
Medical Division	Division of Oncology Products 2	**Drug Class**	Small molecule; Kinase inhibitor
OCP Reviewer	Ruby Leong, Pharm.D.	**Indication(s)**	Metastatic melanoma with BRAF V600 mutation
OCP Team Leader	Hong Zhao, Ph.D.	**Dosage Form**	0.5, 1, 2 mg tablets
Pharmacometrics Reviewer	Jingyu (Jerry) Yu, Ph.D.	**Dosing Regimen**	2 mg once daily
Pharmacometrics Team Leader	Nitin Mehrotra, Ph.D.		
Pharmacogenomics Reviewer	Stacy Shord, Pharm.D.	**Route of Administration**	Oral
Pharmacogenomics Team Leader	Rosane Charlab Orbach, Ph.D.	**Sponsor**	GlaxoSmithKline
Date of Submission	8/3/2012		
Estimated Due Date of OCP Review	12/17/2012		
Medical Division Due Date	1/6/2013	**Priority Classification**	Priority
PDUFA Due Date	2/3/2013	**eCTD link**	\\Cdsesub1\evsprod\NDA204114\0002

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			Module 5.2
HPK Summary	X			Module 2.7.2
Labeling	X			Module 1.14
Reference Bioanalytical and Analytical Methods	X	6		Report No. CD2008/00957/00, 2010N108094_00, 2011N126160_00, CD2008/00913/00, CD2010/00018/00, CD2010/00125/00
I. Clinical Pharmacology				
Mass balance:	X	1		Study 113708
Isozyme characterization:	X	5		Report No. UH2007/00111/00, CD2008/00864/00, CD2007/00194/00, CD2008/00819/00, 2012N135962_01
Blood/plasma ratio:	X	1		Report No. 2012N133368_00
Plasma protein binding:	X	1		Report No. UH2007/00036/00
Pharmacokinetics -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	X			Study 113708 / ADME Study 113709 / Food effect Study 115064 / Absolute bioavailability

multiple dose:	X	3		Study 111054 / FTIH Study 112111 / Combination with gemcitabine Study BRF113220 / Combination with dabrafenib
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	X			Study 111054 / FTIH Study 112111 / Combination with gemcitabine Study BRF113220 / Combination with dabrafenib
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X			Study BRF113220 / Combination with dabrafenib
In-vivo effects of primary drug:				
In-vitro:	X	9		Report No. UH2007/00111/00, CD2008/00124/00 / CYP inhibition Report No. CD2007/01330/00, 2012N131823_00 / CYP induction Report No. UH2007/00111/00 / P-gp substrate Report No. CD2007/00975/00 / P-gp inhibition Report No. RD2008/00032/01 / BCRP substrate Report No. RD2007/01466/00 / BCRP inhibition Report No. CD2007/01007/00 / OATP1B1, OATP1B3 inhibition
Subpopulation studies -				
ethnicity:				N/A, 97% Caucasian
gender:	X			PopPK
pediatrics:				Requested pediatric waiver
geriatrics:	X			PopPK
renal impairment:	X			PopPK
hepatic impairment:	X			PopPK
PD - QT Study:	X			C-QT analysis using QT data from FTIH Study 111054
Phase 2:	X	1		Study 113583
Phase 3:	X	1		Study 114267
PK/PD -		1		Report No. 2011n130902
Phase 1 and/or 2, proof of concept:	X			Study 113583 / Phase 2
Phase 3 clinical trial:	X			Study 114267 / Phase 3
Population Analyses -		1		Report No. 2011n120486
Data rich:	X			Study 111054 / FTIH
Data sparse:	X			Study 113583 / Phase 2 Study 114267 / Phase 3
II. Biopharmaceutics				
Absolute bioavailability	X	1		Study 115064
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	X	1		Study 113709
Bio-waiver request based on BCS				
BCS class	X	1		Study 2010N104737_00
Dissolution study to evaluate alcohol induced dose-dumping				

III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	X			Requested pediatric waiver
Literature References	X			
Total Number of Studies		33		

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-be-marketed product(s) and those used in the pivotal clinical trials?			X	No major differences between clinical trial formulation and to-be-marketed formulation
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?			X	
	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	X			

	guidance?				
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	Requested pediatric waiver
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	Requested pediatric waiver
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 this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

Yes, the application is fileable from a clinical pharmacology perspective.

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

The following information requests should be forwarded to the Applicant:

Clinical Pharmacology

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

2. *Please propose post marketing requirement (PMR) language and provide milestone timelines for completion of the dedicated QTc study (MEK114655).*

3. *Please propose PMR language and provide milestone timelines for a hepatic impairment study.*

Pharmacometrics

4. *For your report named "POPULATION PHARMACOKINETICS OF TRAMETINIB IN SUBJECTS WITH CANCER (PROTOCOLS MEK111054, MEK113583, AND MEK114267)",*

the data items in NMGSK.XPT (NONMEM data file included in submission) are not consistent with those specified in the NONMEM control stream included in your report (PDF format). Please submit NONMEM dataset, control stream and scripts of exploration/diagnostics for base and final popPK model as TXT format.

Ruby Leong, Pharm.D.	9-26-2012
Clinical Pharmacology Reviewer	**Date**
Hong Zhao, Ph.D.	9-26-2012
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/

RUBY LEONG
09/26/2012

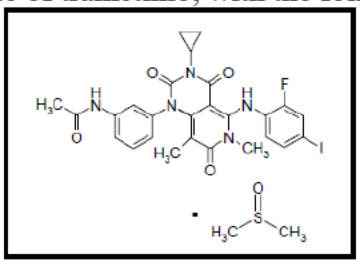
HONG ZHAO
09/27/2012
I concur.

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

NDA Number	204-114
Submission Date	3 Aug 2012
Product name, generic name of the active	Trametinib
Dosage form and strength	Tablet, 0.5, 1 and 2 mg
Applicant	GlaxoSmithKline One Franklin Plaza 200 N. 16th Street Philadephia, PA 19102
Clinical Division	Division of Oncology Products - 2
Type of Submission	Original NDA 505(b)1
Biopharmaceutics Primary Reviewer	Minerva Hughes, Ph.D.
Biopharmaceutics Secondary Reviewer	John Duan, Ph.D.
Biopharmaceutics Team Leader	Angelica Dorantes, Ph.D.
Filing Review Date	17 August 2012

Biopharmaceutics Summary

NDA 204-114 was submitted in accordance with Section 505(b)1 of the FD&C act for the use of trametinib in the treatment of patients with unresectable or metastatic melanoma with BRAFV600 mutation. Trametinib (GSK1120212 or JTP-74057) is a novel, reversible, selective, (b) (4) inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2; proteins that are critical for cell proliferation and survival. The drug was developed specifically to address known oncogenic mutations in upstream mitogen-activated protein kinase (MAPK) pathway proteins BRAF and Ras, which signal through MEK1 and MEK2. The drug substance is the dimethyl sulfoxide (DMSO) solvate of trametinib, with the following chemical structure.



Trametinib DMSO was selected because of its improved aqueous solubility and bioavailability in animal studies relative to the parent compound, which suggests a potentially critical role for DMSO content and product performance. The justification for the selected DMSO content ranges will be closely evaluated in conjunction with the assigned Review Chemist to ensure that clinically relevant ranges are established for product quality.

The proposed drug product is an immediate-release tablet comprised of the drug substance and the excipients mannitol, microcrystalline cellulose, hypromellose, croscarmellose sodium, magnesium stearate (vegetable source), sodium lauryl sulfate, colloidal silicon dioxide. The tablets are available in three strengths (0.5, 1, and 2 mg), which are film-coated with a solution of

Biopharmaceutics Summary

hypromellose, titanium dioxide, polyethylene glycol, polysorbate 80 (2 mg tablets), iron oxide yellow (0.5 mg tablets), or iron oxide red (2 mg tablets).

The Applicant notes that the oral bioavailability of trametinib 2.0 mg tablet was moderate to high with a geometric mean (90% CI) of 72.3% (50.0, 105). Peak plasma concentrations occurred around 1.5 hours under fasting conditions. Administration with a high-fat, high calorie meal resulted in a 70% decrease in Cmax, and a 10% decrease in $AUC_{(0-\infty)}$ compared with fasted conditions. The Tmax was delayed by approximately 4 hours with food. The intended dosing regimen for the proposed indication is 2.0 mg daily (b) (4) The 0.5 mg and 1.0 mg tablets are proposed for dose modifications, where necessary. Clinical studies used all three tablet strengths. The principle differences between the Phase III clinical trial material and the proposed commercial product are:

- (b) (4)

The impact of these changes on in vitro tablet dissolution performance will be evaluated in the Biopharmaceutics review.

NDA 204-114 contains Quality-by-Design (QbD) elements such as the identification of critical quality attributes (CQAs), risk assessments, proven acceptable ranges (PARs), and design of experiment (DoE) studies. Product dissolution was identified as a CQA, which is affected by formulation components and process parameters (e.g., (b) (4)). All aspects of the formulation and process development/controls related to tablet dissolution will be evaluated in the Biopharmaceutics review.

Critical Review Issues

Critical review issues identified during filing are as follows.

- Suitability of the dissolution test method and acceptance criteria to assure product quality
- Suitability of the dissolution test method or other performance outputs (e.g., disintegration) to support design space conclusions
- Defining acceptable DMSO content limits
- Acceptability of the in vitro data bridging the Phase III and commercial product formulation and process changes.

Comments for Day 74-Letter

None.

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

The following parameters for the ONDQA's Product Quality-Biopharmaceutics filing checklist are necessary in order to initiate a full biopharmaceutics review (i.e., complete enough to review but may have deficiencies).

<table>
<tr><th colspan="5">ONDQA-BIOPHARMACEUTICS
<u>A. INITIAL</u> OVERVIEW OF THE NDA APPLICATION FOR FILING</th></tr>
<tr><th></th><th>PARAMETER</th><th>YES</th><th>NO</th><th>COMMENT</th></tr>
<tr><td>1.</td><td>Does the application contain dissolution data?</td><td>x</td><td></td><td></td></tr>
<tr><td>2.</td><td>Is the dissolution test part of the DP specifications?</td><td>x</td><td></td><td><table><tr><th colspan="2">Dissolution Method</th></tr><tr><td>Apparatus</td><td>USP 2</td></tr><tr><td>Medium</td><td>pH 4.5, 50 mM sodium acetate with 0.75% sodium lauryl sulfate (SLS)</td></tr><tr><td>Agitation speed</td><td>60 rpm</td></tr><tr><td>Temperature</td><td>37°C</td></tr><tr><td>Sampling Times</td><td>5, 15, 30, and 45 for profile</td></tr><tr><td>Quantitation</td><td>HPLC</td></tr><tr><td>Acceptance Criterion</td><td>Q = (b) (4)</td></tr></table></td></tr>
<tr><td>3.</td><td>Does the application contain the dissolution method development report?</td><td>x</td><td></td><td>Development report is located in section 3.2.R. The report was updated as per FDA's request (i.e., pre-NDA meeting) to include the complete dissolution data (individual values, mean, min, etc.) for each tested variable.</td></tr>
<tr><td>4.</td><td>Is there a validation package for the analytical method and dissolution methodology?</td><td>x</td><td></td><td></td></tr>
<tr><td>5.</td><td>Does the application include a biowaiver request?</td><td></td><td>x</td><td>The tablet differences between the Phase 3 and proposed commercial product are within the allowable changes for which in vitro test data are sufficient to bridge the products. Comparative dissolution data in three media were submitted to support the 0.5 mg and 2 mg tablets.</td></tr>
<tr><td>6.</td><td>Does the application include a IVIVC model?</td><td></td><td>x</td><td></td></tr>
<tr><td>7.</td><td>Is information such as BCS classification mentioned, and supportive data provided?</td><td></td><td>x</td><td></td></tr>
<tr><td>8.</td><td>Is information on mixing the product with foods or liquids included?</td><td></td><td>x</td><td>The drug is intended to be taken (b) (4)</td></tr>
</table>

PRODUCT QUALITY - BIOPHARMACEUTICS
FILING REVIEW

ONDQA-BIOPHARMACEUTICS **A. INITIAL** OVERVIEW OF THE NDA APPLICATION FOR FILING				
	PARAMETER	**YES**	**NO**	**COMMENT**
9.	Is there any in *vivo* BA or BE information in the submission?	x		In vivo data will be reviewed by the Office of Clinical Pharmacology. All three strengths were used in clinical studies, which included PK assessments for PK/PD analyses. An absolute bioavailability study was also done using the 2 mg strength.
10.	Is there a modified-release claim? If yes, address the following: a.) Is there information submitted to support the claim in accordance with 320.25(f)? b.) Is there information on the potential for alcohol-induced dose dumping?		x	

B. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
11.	**IS THE BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?**	x		
12.	If the NDA is not fileable from the product quality-biopharmaceutics perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			Not applicable.
13.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?		x	

Administrative Block: *{See appended electronic signature page}*

Minerva Hughes, Ph.D.
Biopharmaceutics Primary Reviewer
Office of New Drug Quality Assessment

John Duan, Ph.D.
Biopharmaceutics Secondary Reviewer
Office of New Drug Quality Assessment

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

/s/

MINERVA HUGHES
08/17/2012

JOHN Z DUAN
08/17/2012